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Synthesis of Polyfunctional β-Ketosulfides and Their Reactions with *m*-Chloroperbenzoic Acid and Chlorine Dioxide

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Abstract—The reaction of bromoacetophenone with various thiols furnished β-ketosulfides: 2-(1-methyl-1*H*-imidazol-2-ylsulfanyl)-1-phenylethanone, 2-(1*H*-imidazol-2-ylsulfanyl)-1-phenylethanone, 2-(2-hydroxyethylsulfanyl)-1-phenylethanone. β-Ketosulfoxides were obtained by the oxidation of β-ketosulfides with *m*-chloroperbenzoic acid and chlorine dioxide.

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Polyfunctional ketosulfoxides alongside two active sites, sulfinyl and carbonyl groups that underlie their reactivity, may have in the molecule the other functional groups providing them with specific properties.

Imidazol-containing sulfides, sulfoxides, and sulfones possess the antimicrobial action [1]. Hydroxyalkyl sulfides are interesting for the production of lubricants, anion exchangers, dyes, organic solvents, polymers, polymer stabilizers, plasticizers, supplying the polymers with stability against heat and freezing, against light [2]. Hydroxysulfoxides are characterized by many typical reactions of the sulfinyl and hydroxy groups. They can be converted into hydroxysulfones, β-oxo- and acetoxysulfoxides [3].

We formerly reported on a chemoselective oxidation with chlorine dioxide of γ-ketosulfides [4] and polyfunctional sulfides containing triazole, tetrazole, or benzimidazole groups [5].

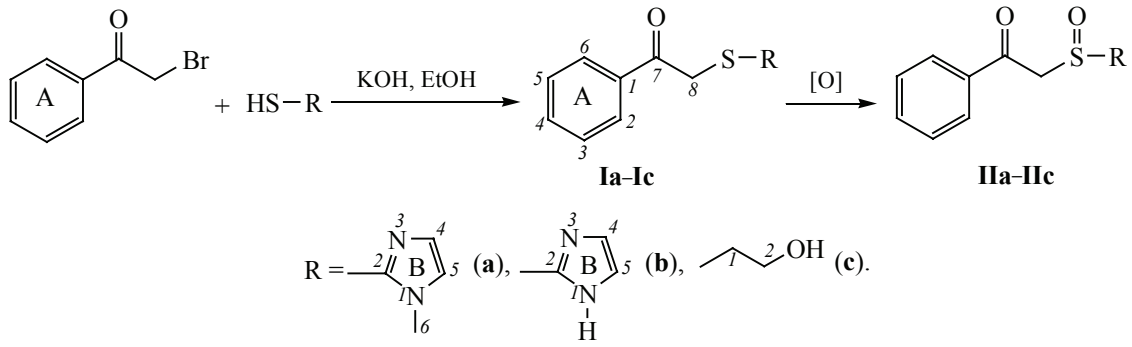
In this article results are presented of the oxidation of polyfunctional β-ketosulfides containing imidazole or hydroxy groups.

Initial β-ketosulfides **Ia–Ic** were obtained in 42–69% yields by the reaction of bromoacetophenone with appropriate thiols in alkaline alcoholic medium (Scheme 1).

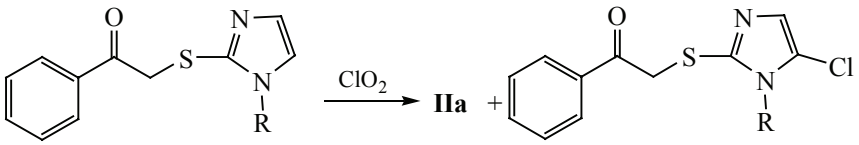
The structure of compounds **Ia–Ic** was established from TR and NMR spectra (see EXPERIMENTAL).

At the oxidation of sulfides **Ia–Ic** with *m*-chloroperbenzoic acid at 20°C, molar ratio sulfide–oxidant 1 : 1, and the complete conversion of the initial sulfides

Scheme 1.



Scheme 2.



Ia **III**

R = Me, H.

β-ketosulfoxides **IIa–IIc** free of sulfones formed in 47–53% yields. Further increase in the proportion of the oxidant resulted in the tarring of the reaction mixture.

^{1}H NMR spectra of compounds **IIa, IIb** contained the proton signals from the imidazole and aromatic fragments. The signals of the diastereotopic protons of the methylene groups in the position *8* are observed as two doublets in the region δ 5.25–5.30 and 5.15–5.20 ppm with the coupling constant of 15.5 Hz characteristic of the geminal protons.

In the ^{1}H NMR spectrum of compound **IIc** the signals of the protons of the aromatic ring remained. The presence of the chiral sulfur aton in the sulfoxide group affects the methylene protons present in the α-position with respect to the asymmetric center. These protons become nonequivalent and appear in the spectrum as two doublets in the region of 4.66 and 4.70 ppm, analogous to the spectra of compounds **IIa, IIb**.

At the oxidation of N-substituted β-ketosulfide **Ia** with chlorine dioxide the main reaction product was 2-(5-chloro-1-methyl-1*H*-imidazol-2-ylsulfanyl)-1-phenylethanone (**III**) (yield 47%), the yield of sulfoxide (**IIa**) ≤8% (Scheme 2).

The absence in the ^{1}H NMR spectrum of compound **III** of the proton signal in the position *5* of the imidazole fragment indicates its replacement. The proton signals of the methylene group in the ^{1}H NMR spectrum are not shifted downfield showing that the sulfoxide group is absent.

The assignment of the signals in the ^{1}H and ^{13}C NMR spectra was done with the use of 2D spectra HMCC and HSQC. In the heteronuclear HSQC spectrum a cross-peak was observed due to the coupling of the proton with the carbon atom in the position *4,* and no cross-peak existed from the coupling of a proton with a carbon atom in the position *5* indicating that no proton substitution occurred at the atom C^5. In the HMCC spectrum a cross-peak was observed from the coupling of the methyl protons of the NCH_3 group and the quaternary atom C^5.

At the oxidation of β-ketosulfides **Ib, Ic** with ClO_2 under the same conditions the yield of β-ketosulfoxides **IIb, IIc** reached 98 and 54% respectively.

Thus the oxidation of the N-substituted β-ketosulfide with ClO_2 led to the formation of the chlorination products. *m*-Chloroperbenzoic acid is more preferable oxidant for these compounds. ClO_2 is a promising oxidant for the preparation of N-unsubstituted β-ketosulfoxides.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Prestige-21 from pellets with KBr. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance II-300 (300 and 75 MHz respectively) from solutions in deuterated DMSO. Mass spectra were measured on an instrument Thermo DSQ (Direct Probe System), EI ionization, ionizing electrons energy 70 eV. Elemental analysis was carried out on an automatic analyzer EA1110 CHNS-O. Melting points were measured on an instrument Sanyo gallenkamp equipped with a digital thermometer. The reaction products were isolated by column chromatography on silica gel Alfa Aesar 70/230μ. TLC was performed on Sorbfil plates, eluent *tert*-butyl methyl ether, developer 5% solution of potassium permanganate. The ClO_2 solution in organic solvent was prepared by bubbling ClO_2 from the water solution (*c* 7 g L^{-1}) through the organic solvent cooled to 0°C.

β-Ketosulfides. General procedure. To a solution of 5.6 g (0.1 mol) of KOH in 30 ml of ethanol heated to 50°C was added at stirring 1.14 g (0.1 mol) of 1-methyl-1*H*-imidazole-2-thiol and 19.9 g (0.1 mol) of bromoacetophenone. The reaction mixture was stirred for 3 h. The solution was cooled and water was added till the precipitate dissolved. The reaction product was extracted with *tert*-butyl methyl ether, the extract was washed with 5% NaOH solution (50 × 2 ml), and dried with Na_2SO_4. The solvent was evaporated, the reaction products were isolated by chromatography.

2-(1-Methyl-1*H*-imidazol-2-ylsulfanyl)-1-phenyl-

ethanone (Ia). Yield 51%. Light-yellow crystals, mp 65–66°C. IR spectrum, ν, cm^{-1}: 1678 (C=O), 686 (C–S). ^1H NMR spectrum, δ, ppm: 3.57 s (3H, $C^{6C}H_3$), 4.65 s (2H, C^8H_2), 6.90 s (1H, $C^{4C}H$), 7.23 s (1H, $C^{5C}H$), 7.54 t (2H, $C^{3A}H$, $C^{5A}H$, *J* 7.3 Hz), 7.68 t (1H, $C^{4A}H$, *J* 7.3 Hz), 7.97 d (2H, $C^{2A}H$, $C^{6A}H$, *J* 7.1 Hz). ^{13}C NMR spectrum, δ, ppm: 33.35 (C^{6C}), 41.48 (C^8), 123.89 (C^{5C}), 128.88 (C^{3A}, C^{5A}), 129.09 (C^{4C}), 129.22 (C^{2A}, C^{6A}), 134.01 (C^{4A}), 135.81 (C^{1A}), 139.59 (C^{2C}), 194.50 (C^7). Found, %: C 62.12; H 5.21; N 11.97; S 13.86. $C_{12}H_{12}N_2OS$. Calculated, %: C 62.07; H 5.17; N 12.07; S 13.79.

2-(1*H*-Imidazol-2-ylsulfanyl)-1-phenylethanone (Ib). Yield 42–50%. Light-yellow crystals, mp 158–159°C. IR spectrum, ν, cm^{-1}: 1686 (C=O), 694 (C–S). ^1H NMR spectrum, δ, ppm: 4.70 s (2H, C^8H_2), 7.04 s (2H, $C^{4C}H$, $C^{5C}H$), 7.55 t (2H, $C^{3A}H$, $C^{5A}H$, *J* 7.5 Hz), 7.68 t (1H, $C^{4A}H$, *J* 7.5 Hz), 8.01 d (2H, $C^{2A}H$, ^{6A}H, *J* 9 Hz), 12.30 s (1H, $N^{1C}H$). ^{13}C NMR spectrum, δ, ppm: 40.88 (C^8), 126.58 (C^{4C}, C^{5C}), 128.90 (C^{3A}, C^{5A}), 129.22 (C^{2A}, C^{6A}), 133.65 (C^{4A}), 135.82 (C^{1A}), 138.37 (C^{2C}), 194.55 (C^7). Found, %: C 60.63; H 4.65; N 12.91; S 14.60. $C_{11}H_{10}N_2OS$. Calculated, %: C 60.55; H 4.59; N 12.84; S 14.68.

2-(2-Hydroxyethylsulfanyl)-1-phenylethanone (Ic). Yield 49–60%. Brown oily fluid, bp 134°C. IR spectrum, ν, cm^{-1}: 1672 (C=O), 690 (C–S). ^1H NMR spectrum, δ, ppm: 2.78 t (2H, C^1H_2, *J* 5.8 Hz), 3.77 t (2H, C^2H_2, *J* 5.9 Hz), 3.89 s (2H, C^8H_2), 7.48 t (2H, $C^{3A}H$, $C^{5A}H$, *J* 7.3 Hz), 7.59 t (1H, $C^{4A}H$, *J* 7.3 Hz), 7.96 d (2H, $C^{2A}H$, $C^{6A}H$, *J* 7.2 Hz). ^{13}C NMR spectrum, δ, ppm: 35.42 (C^1), 37.13 (C^8), 60.70 (C^2), 128.76 (C^{2A}, C^{3A}, C^{5A}, C^{6A}), 133.62 (C^{4A}), 135.14 (C^{1A}), 195.14 (C^7). Found, %: C 61.18; H 6.17; S 16.30. $C_{10}H_{12}O_2S$. Calculated, %: C 61.22; H 6.12; S 16.33.

Oxidation of β-ketosulfides Ia–Ic to β-ketosulfoxides. General procedure. *a.* To s solution of 0.232 g (1 mmol) of compound **Ia–Ic** in 10 ml of CH_2Cl_2 was added at stirring 0.173 g (1 mmol) of *m*-chloroperbenzoic acid at 20°C within 1 h. The sulfoxide was extracted with *tert*-butyl methyl ether, the extract was washed with saturated Na_2CO_3 solution, with brine and water, dried with Na_2SO_4. The solvent was evaporated, the reaction products were isolated by chromatography.

b. To a solution of 0.116 g (0.5 mmol) of compound **Ia–Ic** in 10 ml of CH_2Cl_2 was added at stirring 11 ml (0.5 mmol) of ClO_2 solution in CH_2Cl_2 at 20°C within 30 min. The sulfoxide was extracted with *tert*-butyl methyl ether, the extract was washed with saturated Na_2CO_3 solution, with brine and water, dried with Na_2SO_4. The solvent was evaporated, the reaction products were isolated by chromatography.

2-(1-Methyl-1*H*-imidazol-2-sulfinyl)-1-phenylethanone (IIa). Yield 0.124 g (50%) (*a*), 0.021 g (8%) (*b*). White crystals, mp 102°C. IR spectrum, ν, cm^{-1}: 1044 (S=O). ^1H NMR spectrum, δ, ppm: 3.93 s (3H, $C^{6C}H_3$), 5.25 d (1H, C^8H_2, *J* 15.5 Hz), 5.30 d (1H, C^8H_2, *J* 15.5 Hz), 7.13 s (1H, $C^{4C}H$), 7.45 s (1H, $C^{5C}H$), 7.58 t (2H, $C^{3A}H$, $C^{5A}H$, *J* 7.5 Hz), 7.73 t (1H, $C^{4A}H$, *J* 7.4 Hz), 8.02 d (2H, $C^{2A}H$, $C^{6A}H$, *J* 7.5 Hz). ^{13}C NMR spectrum, δ, ppm: 33.66 (C^{6C}), 61.46 (C^8), 126.09 (C^{5C}), 129.02 (C^{4C}, C^{3A}, C^{5A}), 129.38 (C^{2A}, C^{6A}), 134.66 (C^{4A}), 135.91 (C^{1A}), 146.08 (C^{2C}), 193.45 (C^7). Found, %: C 57.98; H 4.87; N 11.35; S 12.96. $C_{12}H_{12}N_2O_2S$. Calculated, %: C 58.06; H 4.84; N 11.29; S 12.90.

2-(1*H*-Imidazol-2-sulfinyl)-1-phenylethanone (IIb). Yield 47% (*a*), 98% (*b*). White crystals, mp 108°C. IR spectrum, ν, cm^{-1}: 1026 (S=O). ^1H NMR spectrum, δ, ppm: 5.15 d (1H, C^8H_2, *J* 15.5 Hz), 5.20 d (1H, C^8H_2, *J* 15.5 Hz), 7.17 s (1H, $C^{4C}H$), 7.47 s (1H, $C^{5C}H$), 7.59 t (2H, $C^{3A}H$, $C^{5A}H$, *J* 7.5 Hz), 7.73 t (1H, $C^{4A}H$, *J* 7.4 Hz), 8.01 d (2H, $C^{2A}H$, $C^{6A}H$, *J* 7.7 Hz), 13.44 s (1H, $N^{1C}H$). ^{13}C NMR spectrum, δ, ppm: 62.04 (C^8), 121.78 (C^{5C}), 129.08 (C^{3A}, C^{5A}), 129.37 (C^{4C}, C^{2A}, C^{6A}), 134.65 (C^{4A}), 136.08 (C^{1A}), 146.64 (C^{2C}), 193.01 (C^7). Found, %: C 56.45; H 4.32; N 12.03; S 13.71. $C_{11}H_{10}N_2O_2S$. Calculated, %: C 56.41; H 4.27; N 11.96; S 13.67.

2-(2-Hydroxyethylsulfinyl)-1-phenylethanone (IIc). Yield 53% (*a*), 54% (*b*). White crystals, mp 106°C. IR spectrum, ν, cm^{-1}: 1028 (S=O). ^1H NMR spectrum, δ, ppm: 3.04 m (2H, C^1H_2), 3.84 m (2H, C^2H_2), 4.66 d (1H, C^8H_2, *J* 15.5 Hz), 4.70 d (1H, C^8H_2, *J* 15.5 Hz), 7.59 t (2H, $C^{3A}H$, $C^{5A}H$, *J* 7.5 Hz), 7.72 t (1H, C^4H, *J* 7.4 Hz), 8.03 d (2H, $C^{2A}H$, $C^{6A}H$, *J* 7.5 Hz). ^{13}C NMR spectrum, δ, ppm: 54.30 (C^1), 55.15 (C^2), 60.72 (C^8), 129.19 (C^{3A}, C^{5A}), 129.30 (C^{2A}, C^{6A}), 134.48 (C^{4A}), 136.60 (C^{1A}), 194.04 (C^7). Found, %: C 56.67; H 5.71; S 15.12. $C_{10}H_{12}O_3S$. Calculated, %: C 56.60; H 5.66; S 15.09.

2-(5-Chloro-1-methyl-1*H*-imidazol-2-ylsulfanyl)-1-phenylethanone (III). Yield 47%. Yellow crystals, mp 82–83°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 804 (C–Cl), 690 (C–S). ^1H NMR spectrum, δ, ppm: 3.53 s (3H, $C^{6C}H_3$), 4.68 s (2H, C^8H_2), 7.04 s (1H, $C^{4C}H$), 7.55 t (2H, $C^{3A}H$, $C^{5A}H$, *J* 7.6 Hz), 7.69 t (1H, $C^{4A}H$, *J* 7.2 Hz), 7.98 d (2H, $C^{2A}H$, $C^{6A}H$, *J* 7.7 Hz). ^{13}C NMR spectrum, δ, ppm: 31.51 (C^{6C}), 41.38 (C^8), 126.21 (C^{5C}), 128.90 (C^{4C}, C^{3A}, C^{5A}), 129.23 (C^{2A}, C^{6A}), 134.11 (C^{4A}), 135.71 (C^{1A}), 140.03 (C^{2C}), 194.28 (C^7). MaCC-Cпeqtp, *m/z* ($I_{OtH.}$, %):

268 (10.5) $[M+2]^+$, 266 (27.5) $[M]^+$. Found, %: C 54.09; H 4.11; Cl 13.32; N 10.54; S 11.94. $C_{12}H_{11}ClN_2OS$. Calculated, %: C 54.03; H 4.13; Cl 13.31; N 10.51; S 12.01. *M* 266.7.

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