Chemistry of Heterocyclic Compounds, Vol. 47, No. 11, February, 2012 (Russian Original Vol. 47, No. 11, November, 2011)

SYNTHESIS AND PROPERTIES OF PYRAZOLE CARBALDEHYDE BIS(2-HYDROXYETHYL)-DITHIOACETAL HYDROCHLORIDES*

L. K. Papernaya[1], A. A. Shatrova[1], A. I. Albanov[1], E. V. Rudyakova[1], and G. G. Levkovskaya[1]**

A simple method has been developed for the synthesis of water-soluble pyrazole derivatives, namely 4-[bis(2-hydroxyethylsulfanyl)methyl]pyrazoles hydrochlorides, by the reaction of a series of pyrazole carbaldehydes with 2-mercaptoethanol in the presence of trimethylchlorosilane. When treated with aqueous ammonia solution the pyrazole-4-carbaldehydes bis(2-hydroxyethyl)dithioacetal hydrochlorides are converted to the 4-[bis(2-hydroxyethylsulfanyl)methyl]pyrazole free bases.

Keywords: bis(2-hydroxyethyl)dithioacetals, 2-mercaptoethanol, 1,3-oxathiolane, pyrazole carbaldehydes, trimethylchlorosilane, acetalization.

Protection of carbonyl compounds by conversion to acetals, thioacetals, and oxathioacetals is a generally used method for the synthesis of important natural and polyfunctional compounds [1-4]. Oxathioacetals and dithioacetals are widely used in synthetic practice in reactions involving ring expansion [5, 6] or opening [7], as generators of an acyl anion [8-11], or in reactions to lengthen a carbon chain [12-14]. Functionalized thioacetals are synthons for preparation of benzofuran and indole classes of compounds which are widely used in medicinal practice [15]. Cyclic thioacetals (oxathiolanes) are efficiently converted to acetals [16] or monosulfoxides [17] and chiral 1,3-oxathiolanes are valuable structural fragments for the enantioselective synthesis of α-hydroxyaldehydes and α-hydroxyacids [8-11].

At the same time many dithiolanes and oxathiolanes are a constituent part of a lipoic acid with characteristic pharmacological properties close to that of the group B vitamins. A five-membered oxathiolane ring appears in the composition of nucleoside analogs having powerful antiviral activity [18-20], in particular in Lamivudine which is primarily used in the treatment of hepatitis B and HIV infections.

Syntheses of open-chain and cyclic oxathioacetals and dithioacetals are based on condensation of carbonyl compounds with thiols, dithiols, and mercaptoalkanols and are catalyzed by protonic acids [21, 22], Lewis acids [23-26], Bu_4NBr_3 [27], SO_2 [28], and Amberlyst-15 ion exchange resin [29]. At the same time

*Dedicated to Academician M. G. Voronkov on his 90th birthday.

**To whom correspondence should be addressed, e-mail: irk_inst_chem@irioch.irk.ru, papern@irioch.irk.ru.

[1]A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky St., Irkutsk 664033, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1680-1690, November, 2011. Original article submitted June 28, 2011.

many of existing methods are of low chemoselectivity [21, 22], demand rigorous reaction conditions [21, 22], use of expensive toxic or poorly available catalysts [27], an inert atmosphere, and are characterized by lengthy processing [21] or additional work up of the reaction mixture in a course of the product separation [24, 25].

Therefore, search for novel and efficient alternative synthetic routes to oxathioacetals and dithioacetals occurring under mild conditions is of current importance.

Along with this there are only isolated evidences for the synthesis of bis(2-hydroxyethyl)dithioacetals from aldehydes and mercaptoethanol. In the study [30] a chemoselective method of synthesis of bis(2-hydroxyethyl)dithioacetal 2,2'-((4-chlorophenyl)methylene)bis(sulfanediyl)diethanol from 4-chlorobenzaldehyde and mercaptoethanol using cerium triflate catalyst has been proposed. In another study [31] acetalyzation of 3-nitrobenzaldehyde by mercaptoethanol to form the corresponding bis(2-hydroxyethyl)-dithioacetal was performed using $NaHSO_4$-SiO_2.

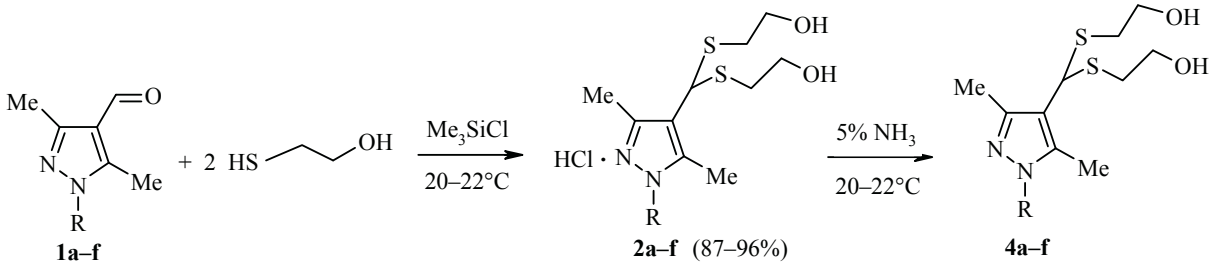
Open-chain or cyclic acetals and thioacetals of the pyrazole series are little known or studied. Pyrazole is an important structural component in the synthesis of current pharmaceutical preparations which possess analgesic, anti-inflammatory, antibacterial, or antidepressant activity [32] and also of insectoacaricides [33], dyes, luminophors, and ligands [34]. It is evident that introduction of acetal function into its structure opens up still more possibilities for preparation of novel, promising pyrazole derivatives. Hence the development of water-soluble pyrazole derivatives is of particular practical value.

We have recently shown that pyrazole carbaldehydes and mercaptoethanol react in the presence of trimethylchlorosilane (Me_3SiCl) to give bis(2-hydroxyethyl)dithioacetals hydrochlorides [35].

Within the scope of these investigations we have examined in detail the acetalyzation reaction of formyl-substituted pyrazoles by mercaptoethanol showing that its course depends on the reaction conditions and the ratio of starting reagents. We have synthesized several pyrazole bis(2-hydroxyethyl)dithioacetals and their hydrochlorides. Condensation of pyrazole carbaldehydes with 2-mercaptoethanol was carried out in the presence of Me_3SiCl which was used as both medium and as catalyst, similarly to previously reported work [35].

For the first time we have found that acetalyzation of the pyrazole carbaldehydes **1a-f** with a twofold excess of 2-mercaptoethanol readily takes place to form the pyrazole series bis(2-hydroxyethyl)dithioacetal hydrochlorides **2a-f** (Scheme 1).

Scheme 1



1a–f **2a–f** (87–96%) **4a–f**

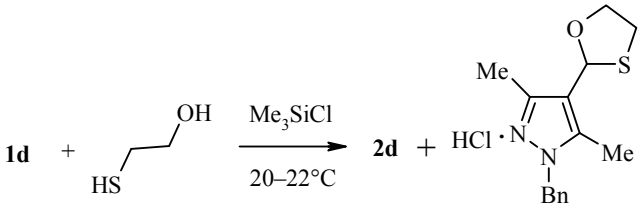
a R = Me, **b** R = Pr, **c** R = All, **d** R = Bn, **e** R = *p*-$NO_2C_6H_4$, **f** R = *i*-Pr

Reaction of equimolar amounts of the pyrazole carbaldehyde **1d** with 2-mercaptoethanol under the optimal conditions for synthesis of aryloxathiolanes from nitrobenzaldehydes [36] gave a mixture of the bis(2-hydroxyethyl)dithioacetal hydrochloride **2d** and 4-(1,3-oxathiolan-2-yl)pyrazole hydrochloride **3d** in the ratio 5:1 as judged by ^{1}H NMR data (Scheme 2). Moreover, unreacted starting aldehyde remained in the reaction mixture (conversion about 60%).

Hence, in contrast to the nitrobenzaldehydes which formed the aryl-(1,3-oxathiolanes) with good selectivity using an equimolar amount of 2-mercaptoethanol without heating, the reaction of pyrazole carbaldehyde **1d** under analogous conditions occurred with primary formation of dithioacetal **2d**, similarly to its reaction with a twofold amount of mercaptoethanol. This observation indicates a major tendency of the carbaldehyde group of 4-formylpyrazoles to react with the thiol fragment of mercapto alcohol according to

principles of hard and soft acids and bases (HSAB) in the presence of the trimethylchlorosilane and this needs further detailed study.

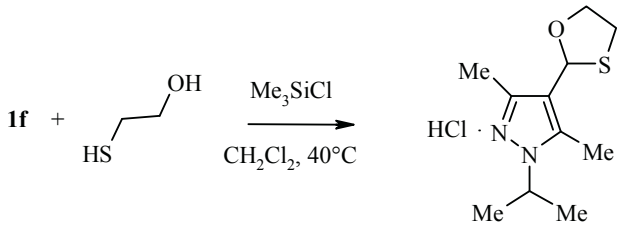
Scheme 2



3d

The 2-(pyrazol-4-yl)-1,3-oxathiolane hydrochloride **3f** was prepared in quantitative yield by heating the pyrazole carbaldehyde **1f** with an equimolar amount of mercaptoethanol (Scheme 3).

Scheme 3



3f

A possible route for formation of the products **2** and **3** is given in Scheme 4. Depending on the reaction conditions, a condensation of one or two of the thiol groups of the mercaptoethanol with the aldehyde function occurs.

The synthesis method (mercapto alcohol being added in small portions to a solution of the aldehyde in excess of Me_3SiCl) allows us to deduce that the Me_3SiCl demonstrates the properties of a Lewis acid [37] rather than a silylating agent in this process. Further, the complex formed is subsequently converted to the addition product of the mercapto alcohol as shown in Scheme 4.

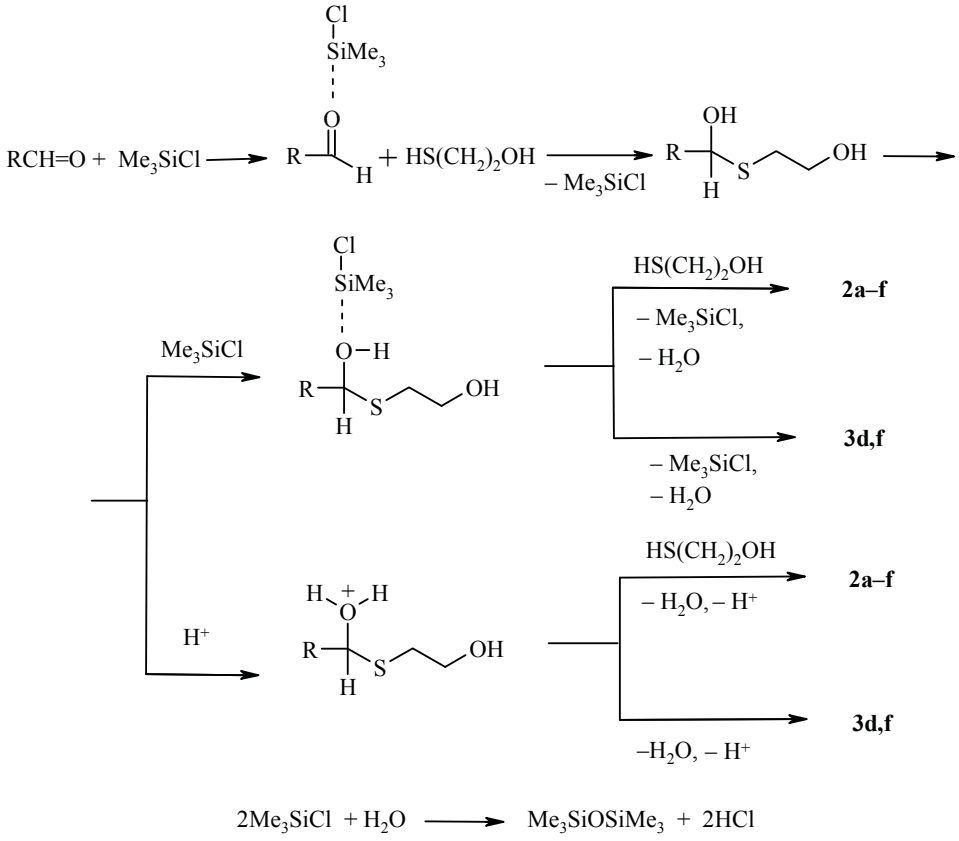
Finally, we do not exclude the possibility of forming the α-chlorothioether $HOCH_2CH_2SCHRCl$, similarly to [38], previously noted for the reaction of formaldehyde with thiols which subsequently react in accordance with the HSAB principle to give the target dithioacetals.

Continuation of our work will be directed to identifying methods of acetals formation in these processes.

The advantage of using Me_3SiCl in the aldehydes acetalyzation reaction includes a possibility of performing the reaction in mild reaction conditions. A further useful attribute of Me_3SiCl is that no any hygroscopic agents are needed since the water evolved in the synthetic process binds with the Me_3SiCl to give hexamethyldisiloxane and hydrogen halide which promotes formation of the products **2** and **3**. The hydrogen halide formed in the hydrolysis of Me_3SiCl then increases the catalytic activity of the system. In turn, the hexamethyldisiloxane and excess of Me_3SiCl are readily removed from the reaction products after its completion.

It should be particularly noted that all of the studied reactions of the 4-formylpyrazoles with mercaptoethanol in the presence of Me_3SiCl lead to formation of the pyrazole carbaldehyde dithioacetal hydrochlorides **2a-f** or to 4-(1,3-oxathiolan-2-yl)pyrazoles **3d,f**. The ability of the pyrazoles to form hydrohalides is determined by the presence in their structures of "pyridine" type nitrogen atoms with increased nucleophilicity [39].

Scheme 4



It is known that pyrazole hydrochlorides are unstable but, with the presence of another nucleophilic center in the pyrazole structure (e.g. a double bond), the reaction can occur by two routes. Thus, for example, hydrochlorination of alkenyl- or allyl pyrazoles with hydrogen chloride occurs at the N-2 atom only upon cooling (-70ºC). At room temperature the process takes place with participation of the alkenyl substituent [40].

For the studied pyrazole with allyl substituent at position 1 of the pyrazole ring (as for other pyrazole carbaldehydes) we have obtained a stable hydrochloride by quaternization at the N-2 atom and this was identified by ^{1}H, ^{13}C, and ^{15}N NMR methods.

The synthesized pyrazole hydrochlorides **2a-f** are oily substances which are stable to storage for several months at 5-6ºC. They are readily soluble in water.

We have prepared the free bases of the 4-[bis(2-hydroxyethylsulfanyl)methyl]pyrazoles **4a-f** (Scheme 1) by treating the hydrochlorides **2a-f** with a diluted aqueous ammonia solution. The bis(2-hydroxyethyl)-dithioacetals **4a-f** can also be prepared by a one-pot method from the starting compounds **1a-f** by treatment of the products **2a-f** with 5-7% aqueous ammonia solution without isolation from the reaction mixture.

Structures of the synthesized compounds **2a-f**, **4a-f** were determined by IR, ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy and confirmed by elemental analysis and mass spectrometric data.

Hydrochlorides of all of the studied compounds **2a-f** are characterized by a low-field shift of the resonance for the methyl groups protons in positions 3 and 5 of the ring (0.16-0.27 ppm) relative to the free bases **4a-f**. In addition, the ^{1}H NMR spectra of compounds **2a-f** show a low-field shift of the resonance for the SCHS group proton (0.17-0.23 ppm). The shift of the α-carbon atom protons signals of the alkyl substituent at position N-1 when going to the hydrochlorides **2a-f** depends on the R substituent. Hence, for compound **2a** (R = Me) the value of the low-field shift is 0.27 ppm while for the hydrochloride **2f** (R = *i*–Pr) this value is 0.43 ppm.

The ^{13}C NMR spectra of compounds **2a-f** show deshielding of the carbon atom at the position 4 of the ring (~ 3-4.4 ppm) and at ring position 3 (~ 5-6.5 ppm). There are also observed shielding of the C-5 atom (1.5-2.2 ppm) and shielding of the carbon atom of the methyl group on C-5. These changes in chemical shifts of the ring carbons do not correspond to those observed by Grant and Pugmire for symmetrically unsubstituted pyrazole [41]. With protonation the chemical shifts of the C-3 and C-5 carbon atoms are shifted by 0.5 ppm to low field and the chemical shift of the C-4 atom by 3.6 ppm. This conflict can be explained both by a greater degree of localization of the positive charge on the pyridine N-2 atom and by the electronic effect of methyl substituents on the ring carbon atoms.

Protonation at the "pyridine" nitrogen atom (N-2) is unambiguously indicated by 2D ^{15}N–^{1}H HMBC correlation spectra for the *N*-propyl-substituted pyrazole **4b** and its hydrochloride **2b**. In the neutral molecule chemical shifts in the ^{15}N NMR spectrum are -177.5 (N-1) and -110.7 ppm (N-2). Protonation leads to a substantial high-field shift for atom N-2 of 70 ppm but a relatively small shielding of the N-1 atom by 10 ppm. Such changes in chemical shifts are also characteristic for other *N*-1-substituted pyrazoles [42]. The presence of a broad NH^+ stretching band at 2500-2800 cm^{-1} in the IR spectra also points to protonation of the N atom of the heterocycle.

Thus for the first time we have found mild and convenient conditions for preparation of water-soluble pyrazole derivatives which are stable under usual conditions. Reaction of pyrazole carbaldehydes with a twofold excess of 2-mercaptoethanol in the presence of trimethylchlorosilane leads to a chemoselective formation of the water-soluble pyrazole bis(2-hydroxyethyl)dithioacetals hydrochlorides. For an equimolar ratio of reagents at room temperature the process is also principally directed to formation of the dithioacetal hydrochlorides. When treated with aqueous ammonia solution (5-7%) the quaternized pyrazole derivatives form the corresponding pyrazolylbis(2-hydroxyethyl)dithioacetal free bases.

EXPERIMENTAL

IR spectra were recorded on a Bruker Vertex 70 spectrometer and ^{1}H, ^{13}C, and ^{15}N NMR spectra on a Bruker DPX-400 (400, 100, and 40 MHz respectively) with TMS as internal standard. Electron impact mass spectra (70 eV) were recorded on a Shimadzu GCMS-QP5050A quadrupole mass analyzer (mass detection range 34-650 Da) using direct introduction of the sample into the ion source. The output temperature was varied from 30 to 200ºC depending on the volatility of the sample. Melting points were determined on a Boetius block. Monitoring of a reaction course and obtained compounds purity was carried out on Merck Silica Gel 60 F254 plates in the system chloromethylene–methanol (95:5) and revealed using 0.5-1.0% aqueous $KMnO_4$ solution.

The aldehydes **1a-f** were prepared by Vilsmeier-Haack formylation [43] of the corresponding 1,3,5-trisubstituted pyrazoles synthesized from 3,5-dimethylpyrazole, alkyl halides, allyl bromide, or 4-fluoronitrobenzene under indole alkylation conditions [44] and characterized in the report [45].

Commercial 1,2-mercaptoethanol and Me_3SiCl from the Aldrich company were used without additional purification.

Pyrazole Series Dithioacetal Hydrochlorides 2a-f (General Method). 2-Mercaptoethanol (0.156 g, 2 mmol) was added dropwise with stirring to a mixture of the aldehyde **1a-f** (1 mmol) and Me_3SiCl (0.77 ml, 6 mmol). The reaction is accompanied by spontaneous heating and the reaction mixture separated into two layers. After 15-20 min stirring at room temperature the upper layer was separated and the viscous residue was washed with hexane, then with ether, and dried *in vacuo*.

2,2'-{[(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol Hydrochloride (2a). Yield 0.304 g (97%). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 2.50 (3H, s, CH_3); 2.51 (3H, s, CH_3); 2.69 (2H, dt, ^{2}J = 13.7, ^{3}J = 6.3) and 2.81 (2H, dt, ^{2}J = 13.7, ^{3}J = 6.3, 2 CH_2S); 3.78 (4H, m, $2CH_2O$); 3.95 (3H, s, NCH_3); 5.42 (1H, s, SCHS). ^{13}C NMR spectrum, δ, ppm: 10.3 (CH_3); 10.6 (CH_3); 35.8 (NCH_3); 36.2 (CH_2S); 43.5 (SCHS); 62.8 (CH_2O); 119.8 (C-4); 144.2 (C-3); 145.8 (C-5). Found, %: C 42.08; H 6.74; Cl 11.29; N 8.91; S 20.43. $C_{11}H_{20}N_2O_2S_2 \cdot HCl$. Calculated, %: C 42.23; H 6.77; Cl 11.33; N 8.95; S 20.50.

2,2'-{[(3,5-Dimethyl-1-propyl-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol Hydrochloride (2b). Yield 0.315 g (92%). IR spectrum (thin film), ν, cm^{-1}: 3334 (OH), 2850-2300 (NH^+). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 0.90 (3H, t, $CH_2C\underline{H}_3$); 1.85 (2H, m, $C\underline{H}_2CH_3$); 2.48 (3H, s, CH_3); 2.50 (3H, s, CH_3); 2.64 (2H, m) and 2.79 (2H, m, $2CH_2S$); 3.69 (4H, m, $2CH_2O$); 4.25 (2H, s, NCH_2); 5.39 (1H, s, SCHS). ^{13}C NMR spectrum, δ, ppm: 10.3 (CH_3); 10.6 (CH_3); 10.8 ($CH_2\underline{C}H_3$); 23.6 ($\underline{C}H_2CH_3$); 36.0 (CH_2S); 43.4 (SCHS); 51.2 (NCH_2); 62.6 (CH_2O); 119.6 (C-4); 144.6 (C-5); 145.0 (C-3). ^{15}N NMR spectrum, δ, ppm: -167.5 (N-1); -40.7 (N-2). Found, %: C 45.64; H 7.37; Cl 10.44; N 8.19; S 18.74. $C_{13}H_{24}N_2O_2S_2 \cdot HCl$. Calculated, %: C 45.80; H 7.39; Cl 10.40; N 8.22; S 18.81.

2,2'-{[(3,5-Dimethyl-1-(prop-2-en-1-yl)-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol Hydrochloride (2c). Yield 0.350 g (95%). IR spectrum (thin film), ν, cm^{-1}: 3341 (OH), 2840-2500 (NH^+). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 2.52 (3H, s, CH_3); 2.53 (3H, s, CH_3); 2.69 (2H, dt, ^2J = 14.2, ^3J = 6.1) and 2.82 (2H, dt, ^2J = 14.2, ^3J = 6.1, $2CH_2S$); 3.71 (2H, dt, ^2J = 11.1, ^3J = 6.3) and 3.76 (2H, dt, ^2J = 11.1, ^3J = 6.3, $2CH_2O$); 4.96 (2H, d, ^3J = 5.6, NCH_2); 5.12 (1H, d, J_{trans} = 17.4) and 5.38 (1H, d, J_{cis} = 10.4, CH_2=); 5.45 (1H, s, SCHS); 6.00 (1H, d, CH=). ^{13}C NMR spectrum, δ, ppm: 10.2 (CH_3); 10.7 (CH_3); 36.2 (CH_2S); 43.5 (SCHS); 51.7 (NCH_2); 62.8 (OCH_2); 120.2 (C-4, CH_2=); 131.0 (CH=); 145.2 (C-3); 145.6 (C-5); Found, %: C 46.01; H 6.88; Cl 10.45; N 8.25. S 18.89. $C_{13}H_{22}N_2O_2S_2 \cdot HCl$. Calculated, %: C 46.07; H 6.84; Cl 10.46; N 8.27; S 18.92.

2,2'-{[(1-Benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol Hydrochloride (2d). Yield 0.373 g (96%). IR spectrum (thin film), ν, cm^{-1}: 3351 (OH), 2826-2507 (NH^+). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 2.52 (6H, s, $2CH_3$); 2.70 (2H, dt, ^2J = 13.8, ^3J = 6.3) and 2.83 (2H, dt, ^2J = 13.8, ^3J = 6.3, $2CH_2S$); 3.71 (2H, dt, ^2J = 11.0, ^3J = 6.3) and 3.76 (2H, dt, ^2J = 11.0, ^3J = 6.3, $2CH_2O$); 5.45 (1H, s, SCHS); 5.54 (2H, s, NCH_2); 7.23 (2H, m, H-2',6'); 7.38 (1H, m, H-4'); 7.42 (2H, m, H-3',5'). ^{13}C NMR spectrum, δ, ppm: 10.6 (CH_3); 11.0 (CH_3); 36.2 (CH_2S); 43.7 (SCHS); 53.1 (NCH_2); 62.7 (OCH_2); 120.1 (C-4); 128.1 (C-2',6'); 129.9 (C-4'); 130.4 (C-3',5'); 134.9 (C-1'); 145.0 (C-5); 145.7 (C-3). Found, %: C 52.45; H 6.46; Cl 9.10; N 7.19; S 16.50. $C_{17}H_{24}N_2O_2S_2 \cdot HCl$. Calculated, %: C 52.49; H 6.48; Cl 9.11; N 7.20; S 16.49.

2,2'-{[(3,5-Dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol Hydrochloride (2e). Yield 0.378 g (90%). IR spectrum (thin film), ν, cm^{-1}: 3346 (OH), 2750-2300 (NH^+). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 2.41 (3H, s, CH_3); 2.47 (3H, s, CH_3) 2.69 (2H, dt, ^2J = 13.7, ^3J = 6.4) and 2.82 (2H, dt, ^2J = 13.7, ^3J = 6.4, $2CH_2S$); 3.69 (2H, dt, ^2J = 11.0, ^3J = 6.4) and 3.74 (2H, dt, ^2J = 11.0, ^3J = 6.4, $2CH_2O$); 5.35 (1H, s, SCHS); 7.75 (2H, d, ^3J = 9.0, H-2',6'); 8.39 (2H, d, *J* = 9.0, H-3',5'). ^{13}C NMR spectrum, δ, ppm: 11.8 (CH_3); 12.7 (CH_3); 36.1 (CH_2S); 44.8 (SCHS); 62.7 (CH_2O); 119.8 (C-4); 125.8; 126.6 (C-2',3',5',6'); 143.0 (C-1' Ar); 144.6 (C-5); 144.7 (C-3); 150.5 (C-4'). Found, %: C 45.62; H 5.31; Cl 8.48; N 9.98; S 15.34. $C_{16}H_{21}N_3O_4S_2 \cdot HCl$. Calculated, %: C 45.76; H 5.28; Cl 8.44; N 10.01; S 15.27.

2,2'-{[(3,5-Dimethyl-1-(1-methylethyl-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol Hydrochloride (2f). Yield 0.315 g (93%). IR spectrum (thin film), ν, cm^{-1}: 3339 (OH), 2715-2450 (NH^+). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.57 (6H, d, ^3J = 6.7 $CH(C\underline{H}_3)_2$); 2.55 (3H, s, CH_3); 2.56 (2H, s, CH_3); 2.69 (2H, dt, ^2J = 14.1, ^3J = 6.3) and 2.82 (2H, dt, ^2J = 14.1, ^3J = 6.3, $2CH_2S$); 3.70 (2H, dt, ^2J = 11.3, ^3J = 6.3) and 3.76 (2H, dt, ^2J = 11.3, ^3J = 6.3, $2CH_2O$); 4.91 (1H, m, NCH); 5.44 (1H, s, SCHS). ^{13}C NMR spectrum, δ, ppm: 10.4 (CH_3); 10.6 (CH_3); 21.5 ($CH(\underline{C}H_3)_2$); 36.2 (CH_2S); 43.5 (SCHS); 53.7 (NCH); 62.8 (CH_2O); 120.0 (C-4); 144.7 (C-3); 145.6 (C-5). Found, %: C 45.76; H 7.38; Cl 10.38; N 8.21; S 18.85. $C_{13}H_{24}N_2O_2S_2 \cdot HCl$. Calculated, %: C 45.80; H 7.39; Cl 10.40; N 8.22. S 18.81.

3,5-Dimethyl-1-(1-methylethyl)-4-(1,3-oxathiolan-2-yl)-1*H*-pyrazole Hydrochloride (3f). A syringe was used to introduce 2-methylmercaptoethanol (0.156 g, 2 mmol) and then Me_3SiCl (1.54 ml, 12 mmol) to a stirred solution of aldehyde **1f** (0.332 g, 2 mmol) in dichloromethane (2 ml) with heating to 35-40ºC. After stirring for 0.5 h at 40ºC the reaction mixture was evacuated in vacuum without heating, the residue was dried over P_2O_5. Yield 0.505 g (96%). White crystals, mp 94-96ºC (hexane). IR spectrum (oil), ν, cm^{-1}: 2719-1871 br. (NH^+). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.75 (3H, d, ^3J = 6.4) and 1.76 (3H, d, ^3J = 6.4,

($C\underline{H}_3)_2CH$); 2.44 (3H, s, 3-CH_3); 2.59 (3H, s, 5-CH_3); 3.27 (2H, m, SCH_2); 3.82 (1H, ddd, ^2J = 9.4, ^3J = 9.0, ^3J = 6.8) and 4.57 (1H, ddd, ^2J = 9.4, ^3J = 5.7, ^3J = 3.0, CH_2O); 4.73 (1H, sept., ^3J = 6.4, CHN); 5.95 (1H, s, SCHO). ^{13}C NMR spectrum, δ, ppm: 10.0 (5-CH_3); 10.1 (3-CH_3); 21.6 ($CH(C\underline{H}_3)_2$); 34.1 (CH_2S); 52.8 (Me_2CHN); 71.9 (CH_2O); 77.8 (OCHS), 115.3 (C-4); 141.2 (C-5); 144.9 (C-3). Mass spectrum, *m/z* (I_{rel}, %): 227 $[M+1]^+$ (6), 226 $[M]^+$ (36), 167 (19), 166 (61), 165 (14), 151 (53), 137 (11), 125 (11), 124 (58), 123 (100). Found, %: C 50.08; H 7.31; Cl 13.44; N 10.61; S 12.25. $C_{11}H_{18}N_2OS\cdot HCl$. Calculated, %: C 50.27; H 7.29; Cl 13.49; N 10.66; S 12.20.

Preparation of a Mixture of 2,2'-{[(1-Benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol Hydrochloride (2d) and 1-Benzyl-3,5-dimethyl-4-(1,3-oxathiolan-2-yl)-1*H*-pyrazole Hydrochloride (3d) by Reaction of Aldehyde (1d) with an Equivalent Amount of Mercaptoethanol. 2-Mercaptoethanol (0.234 g, 3 mmol) was added dropwise with stirring to a mixture of aldehyde **1d** (0.643 g, 3 mmol) and Me_3SiCl (3.08 ml, 24 mmol). The reaction was accompanied by spontaneous heating and formation of a white, viscous precipitate. After 15 min stirring at room temperature the upper layer was separated and the oily residue was washed three times with ether, dried in vacuum to give 0.53 g of a 5:1 mixture of the products **2d** and **3d**.

1-Benzyl-3,5-dimethyl-4-(1,3-oxathiolan-2-yl)-1*H*-pyrazole Hydrochloride (3d). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 2.46 (3H, s, CH_3); 2.47 (3H, s, CH_3); 3.32 (2H, m, SCH_2); 3.86 (1H, ddd, ^2J = 9.2, ^3J = 8.9, ^3J = 6.7) and 4.59 (1H, ddd, ^2J = 9.2, ^3J = 5.6, ^3J = 2.9, CH_2O); 5.55 (2H, s, NCH_2); 6.14 (1H, s, SCHO); 7.23 (2H, m, H-3',5); 7.42 (3H, m, H-2',4',6'). ^{13}C NMR spectrum, δ, ppm: 10.1 (5-CH_3); 10.3 (3-CH_3); 34.9 (CH_2S); 53.0 (NCH_2); 73.2 (CH_2O); 79.1 (OCHS); 117.8 (C-4); 120.2, 128.1, 129.8, and 131.3 (C Ph); 141.2 (C-5); 144.9 (C-3).

Dehydrochlorination of the Pyrazole Dithioacetal Series Salts (General Method). The hydrochlorides **2a-f** (with the exception of hydrochloride **2e**) were dissolved in a small amount of water and a dilute aqueous ammonia solution (5-7%) was added dropwise until weakly basic to litmus. The oily precipitate as a lower layer was separated and dissolved in methanol. The aqueous solution was additionally washed with ether and the combined ether extract and methanol solution were dried in vacuum over P_2O_5. The hydrochloride **2e** was poorly soluble in water and was treated by dissolving in methanol, addition of a very dilute solution of NH_4OH to a weakly basic medium, extraction with dichloromethane, removal of the organic layer, evacuation, and drying over P_2O_5. The freshly prepared 4-[bis(2-hydroxyethylsulfanyl)methyl]pyrazoles **4a-f** are oils but compounds **4b-e** crystallize upon storage.

2,2'-{[(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol (4a). Yield 0.255 g (92%). IR spectrum (thin film), ν, cm^{-1}: 3308 (OH). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 2.25 (3H, s, CH_3); 2.32 (3H, s, CH_3); 2.61 (2H, dt, ^2J = 13.6, ^3J = 6.6) and 2.73 (2H, dt, ^2J = 13.6, ^3J = 6.6, $2CH_2S$); 3.64 (2H, dt, ^2J = 11.0, ^3J = 6.6) and 3.69 (2H, dt, ^2J = 11.0, ^3J = 6.6, $2CH_2O$); 3.68 (3H, s, NCH_3); 5.19 (1H, s, SCHS). ^{13}C NMR spectrum, δ, ppm: 10.2 (CH_3); 12.3 (CH_3); 35.8 (NCH_3); 35.9 (CH_2S); 44.9 (SCHS); 62.6 (CH_2O); 114.9 (C-4); 138.5 (C-3); 145.7 (C-5). Mass spectrum, *m/z* (I_{rel}, %): 277 $[M+1]^+$ (< 1), 276 $[M]^+$ (< 1), 78 (12), 66 (14), 60 (32), 59 (18), 56 (33), 48 (15), 47 (24), 46 (12), 45 (34). Found, %: C 47.75; H 7.27; N 10.11; S 23.25. $C_{11}H_{20}N_2O_2S_2$. Calculated, %: C 47.80; H 7.29; N 10.13; S 23.20.

2,2'-{[(3,5-Dimethyl-1-propyl-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol (4b). Yield 0.259 g (85%). Mp 71-74ºC. IR spectrum (thin film), ν, cm^{-1}: 3305 (OH). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 0.87 (3H, t, ^3J = 7.3, $CH_2C\underline{H}_3$); 1.75 (2H, m, $C\underline{H}_2CH_3$); 2.28 (3H, s, CH_3); 2.34 (3H, s, CH_3); 2.62 (2H, dt, ^2J = 13.7, ^3J = 6.6) and 2.74 (2H, dt, ^2J = 13.7, ^3J = 6.6, $2CH_2S$); 3.64 (2H, dt, ^2J = 11.0, ^3J = 6.6) and 3.68 (2H, dt, ^2J = 11.0, ^3J = 6.6, $2CH_2O$); 3.97 (2H, t, ^3J = 7.1, NCH_2); 5.22 (1H, s, SCHS). ^{13}C NMR spectrum, δ, ppm: 10.3 (CH_3); 12.3 (CH_3); 11.2 ($CH_2\underline{C}H_3$); 24.4 ($\underline{C}H_2CH_3$); 36.0 (CH_2S); 44.9 (SCHS); 51.0 (NCH_2); 62.6 (CH_2O); 116.4 (C-4); 139.9 (C-5); 146.8 (C-3). ^{15}N NMR spectrum, δ, ppm: -177.5 (N-1); -110.7 (N-2). Mass spectrum, *m/z* (I_{rel}, %): 305 $[M+1]^+$ (6), 304 $[M]^+$ (< 1), 228 (15), 227 (100), 226 (38), 167 (19), 166 (19), 165 (14), 151 (22), 138 (17), 137 (37), 124 (52), 123 (38), 61 (13), 60 (21), 59 (12), 48 (10), 47 (16), 45 (19). Found, %: C 51.25; H 7.92; N 9.18; S 21.14. $C_{13}H_{24}N_2O_2S_2$. Calculated, %: C 51.28; H 7.95; N 9.20; S 21.06.

2,2'-{[(3,5-Dimethyl-1-(prop-2-en-1-yl)-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol (4c). Yield 0.278 g (92%). Mp 76-78ºC. IR spectrum (thin film), ν, cm^{-1}: 3338 (OH). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3); 2.31 (3H, s, CH_3); 2.62 (2H, dt, ^2J = 14.7, ^3J = 6.7) and 2.75 (2H, dt, ^2J = 13.7, ^3J = 6.7, $2CH_2S$); 3.64 (2H, dt, ^2J = 10.9, ^3J = 6.5) and 3.69 (2H, dt, ^2J = 10.9, ^3J = 6.5, $2CH_2O$); 4.65 (2H, dt, ^3J = 4.8, ^4J = 1.5, NCH_2); 4.87 (1H, dt, J_{trans} = 17.2, ^4J = ^2J = 1.5) and 5.17 (1H, dt, J_{cis} = 10.5, ^4J = ^2J = 1.5, CH_2=); 5.22 (1H, s, SCHS); 5.92 (1H, m, CH=). ^{13}C NMR spectrum, δ, ppm: 10.2 (CH_3); 12.4 (CH_3); 36.0 (CH_2S); 44.9 (SCHS); 52.0 (NCH_2); 62.6 (CH_2O); 116.8 (C-4); 117.4 (CH_2=); 134.0 (CH=); 140.2 (C-3); 147.3 (C-5). Mass spectrum, *m/z* (I_{rel}, %): 303 $[M+1]^+$ (1), 302 $[M]^+$ (< 1), 226 (12), 225 (72), 224 (63), 223 (11), 165 (32), 164 (71), 163 (100), 149 (27), 137 (15), 135 (16), 123 (18), 121 (10), 94 (11), 78 (12), 61 (16), 60 (37), 59 (22), 48 (16), 47 (26), 45 (34). Found, %: C 51.60; H 7.29; N 9.22; S 21.25. $C_{13}H_{22}N_2O_2S_2$. Calculated, %: C 51.62; H 7.33; N 9.26; S 21.20.

2,2'-{[(1-Benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol (4d). Yield 0.268 g (76%). Mp 84-86ºC. IR spectrum (thin film), ν, cm^{-1}: 3393 (OH). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3); 2.33 (3H, s, CH_3); 2.64 (2H, dt, ^2J = 13.7, ^3J = 6.7) and 2.77 (2H, dt, ^2J = 13.7, ^3J = 6.7, $2CH_2S$); 3.66 (2H, dt, ^2J = 11.0, ^3J = 6.7) and 3.71 (2H, dt, ^2J = 11.0, ^3J = 6.7, $2CH_2O$); 5.26 (1H, s, SCHS); 5.26 (2H, s, NCH_2); 7.06 (2H, m, H-2',6'); 7.27 (1H, m, H-4'); 7.32 (2H, m, H-3',5'). ^{13}C NMR spectrum, δ, ppm: 10.4 (CH_3); 12.4 (CH_3); 36.0 (CH_2S); 44.9 (SCHS); 53.2 (NCH_2); 62.6 (CH_2O); 117.2 (C-4); 127.5 (C-2',6'); 128.8 (C-4'); 129.8 (C-3',5'); 137.9 (C-1'); 140.3 (C-3); 147.3 (C-5). Mass spectrum, *m/z* (I_{rel}, %): 352 $[M]^+$ (< 1), 275 (84), 274 (100), 215 (11), 214 (56), 213(75), 199 (29), 185 (10), 91 (100), 78 (13), 65 (28), 61 (14), 60 (14), 59 (11), 45 (18). Found, %: C 57.85; H 6.76; N 7.93; S 18.23. $C_{17}H_{24}N_2O_2S_2$. Calculated, %: C 57.92; H 6.86; N 7.95; S 18.19.

2,2'-{[(3,5-Dimethyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol (4e). Yield 0.368 g (96%). Mp 58-60ºC. IR spectrum (thin film), ν, cm^{-1}: 3341 (OH). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 2.39 (3H, s, CH_3); 2.46 (3H, s, CH_3); 2.69 (2H, dt, ^2J = 13.7, ^3J = 6.9) and 2.82 (2H, dt, ^2J = 13.7, ^3J = 6.9 $2CH_2S$); 3.70 (2H, dt, ^2J = 11.1, ^3J = 6.9) and 3.75 (2H, dt, ^2J = 11.1, ^3J = 6.9, $2CH_2O$); 5.32 (1H, s, SCHS); 7.73 (2H, d, ^3J = 9.1, H-2',6'); 8.39 (2H, d, *J* = 9.1, H-3',5'). ^{13}C NMR spectrum, δ, ppm: 11.9 (CH_3); 12.9 (CH_3); 36.1 (CH_2S); 45.0 (SCHS); 62.7 (CH_2O); 119.6 (C-4); 125.8; 126.2 (C-2',3',5',6'); 139.9 (C-1'); 145.5 (C-3); 147.8 (C-5); 150.9 (C-4'). Found, %: C 50.08; H 5.47; N 10.94; S 16.75. $C_{16}H_{21}N_3O_4S_2$. Calculated, %: C 50.11; H 5.52; N 10.96; S 16.72.

2,2'-{[(3,5-Dimethyl-1-(1-methylethyl)-1*H*-pyrazol-4-yl)methanediyl]disulfanediyl}diethanol (4f). Yield 0.240 g (79%). IR spectrum (thin film), ν, cm^{-1}: 3350 (OH). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.40 (6H, d, ^3J = 6.7, $CH(C\underline{H}_3)_2$); 2.28 (3H, s, CH_3); 2.33 (3H, s, CH_3); 2.63 (2H, dt, ^2J = 13.8, ^3J = 6.7) and 2.75 (2H, dt, ^2J = 13.8, ^3J = 6.7, $2CH_2S$); 3.62 (2H, dt, ^2J = 10.6, ^3J = 6.7) and 3.64 (2H, dt, ^2J = 10.6, ^3J = 6.7, $2CH_2O$); 4.48 (1H, m, NCH), 5.21 (1H, s, SCHS). ^{13}C NMR spectrum, δ, ppm: 10.1 (CH_3); 12.6 (CH_3); 22.5 ($CH(\underline{C}H_3)_2$); 36.0 (CH_2S); 45.1 (SCHS); 50.6 (NCH), 62.6 (CH_2O); 115.7 (C-4); 138.3 (C-3); 147.1 (C-5). Mass spectrum, *m/z* (I_{rel}, %): 305 $[M+1]^+$ (9), 304 $[M]^+$ (< 1), 228 (14), 227 (100), 226 (18), 185 (10), 166 (11), 151 (18), 124 (21), 123 (28), 61 (10), 45 (22). Found, %: C 51.26; H 7.92; N 9.18; S 21.0. $C_{13}H_{24}N_2O_2S_2$. Calculated, %: C 51.28; H 7.95; N 9.20; S 21.06.

This work was carried out with the financial support of the Russian Foundation for Fundamental Investigations (grant 10-03-00256a).

REFERENCES

1. T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd Edition, Wiley, New York (1991).
2. S. Oh, I. H. Jeong, C. M. Ahn, V. S. Shin, and S. Lee, *Bioorg. Med. Chem.*, **12**, 3783 (2004).

3. K. Benda, W. Regenhardt, E. Shaumann, and G. Adiwidjaja, *Eur. J. Org. Chem.*, 1016 (2009).
4. K. C. Golden, B. T. Gregg, and J. F. Quinn, *Tetrahedron Lett.*, **51**, 4010 (2010).
5. T. Mori, Y. Sawada, and A. Oku, *J. Org. Chem.*, **65**, 3620 (2000).
6. M. Ioannou, M. J. Porter, and F. Saez, *Chem. Commun.*, 346 (2002).
7. K. Krohn and S. Cludius-Brandt, *Synthesis*, 1344 (2010).
8. K. Utimoto, A. Nakamura, and S. Matsubara, *J. Am. Chem. Soc.*, **112**, 8189 (1990).
9. J. E. Lynch and E. L. Eliel, *J. Am. Chem. Soc.*, **106**, 2943 (1984).
10. E. L. Eliel and S. Morris-Natschke, *J. Am. Chem. Soc.*, **106**, 2937 (1984).
11. S. Dei, P. Angeli, C. Bellucci, M. Buccioni, F. Gualtieri, G. Marrucci, D. Manetti, R. Matucci, M. N. Romanelli, S. Scapecchi, and E. Teodori, *Biochem. Pharmacol.*, **69**, 1637 (2005).
12. P. C. Bulman Page, M. B. van Niel, and J. C. Prodger, *Tetrahedron*, **45**, 7643 (1989).
13. A. T. Khan, E. Mondal, S. Ghosh, and S. Islam, *Eur. J. Org. Chem.*, 2002 (2004).
14. S. Ter-Sarkisyan, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988 (1960).
15. C. Macleod, G. J. McKiernan, E. J. Guthrie, L. J. Farrugia, D. W. Hamprecht, J. Macritchie, and R. C. Hartley, *J. Org. Chem.*, **68**, 387 (2003).
16. B. Karimi, H. Seradj, and J. Maleki, *Tetrahedron*, **58**, 4513 (2002).
17. K. Krohn and S. Cludius-Brandt, *Synthesis*, 2369 (2008).
18. Y. Wang, G. Inguaggiato, M. Jasamai, M. Shah, D. Hughes, M. Slater, and C. Simons, *Bioorg. Med. Chem.*, **7**, 481 (1999).
19. A. Martinez, A. I. Esteban, A. Herrero, C. Ochoa, G. Andrei, R. Snoeck, J. Balzarini, and E. De Clercq, *Bioorg. Med. Chem.*, **7**, 1617 (1999).
20. M. Camplo, A. S. Charvet-Faury, C. Borel, F. Turin, O. Hantz, V. Trabaud, C. Niddam, N. Mourier, J. C. Graciet, J. C. Chermann, and J. L. Kraus, *Eur. J. Med. Chem.*, **31**, 539 (1996).
21. J. W. Ralls, R. M. Dodson, and B. Riegel, *J. Am. Chem. Soc.*, **71**, 3320 (1949).
22. C. Djerassi and M. Gorman, *J. Am. Chem. Soc.*, **75**, 3704 (1953).
23. G. E. Wilson Jr., M. G. Huang, and W. W. Schloman Jr., *J. Org. Chem.*, **33**, 2133 (1968).
24. V. Kumar and S. Dev, *Tetrahedron Lett.*, **24**, 1289 (1983).
25. J. S. Yadav, B. V. S. Reddy, and S. K. Pandey, *Synth. Commun.*, **32**, 715 (2002).
26. V. K. Yadav and A. G. Fallis, *Tetrahedron Lett.*, **29**, 897 (1988).
27. E. Mondal, P. R. Sahu, G. Bose, and A. Khan, *Tetrahedron Lett.*, **43**, 2843 (2002).
28. B. Bogdan and Z. Kortylewicz, *Synthesis*, 831 (1982).
29. K. Manabe, S. Iimura, X-M. Sun, and S. Kobayashi, *J. Am. Chem. Soc.*, **124**, 11971 (2002).
30. A. Kumar, M. S. Rao, and V. K. Rao, *Aust. J. Chem.*, **63**, 135 (2010).
31. D. Azarifar and A. Forghaniha, *J. Chin. Chem. Soc. (Taipei, Taiwan)*, **53**, 1189 (2006).
32. P. Elguero, N. Goya, N. Jagerovic, and A. M. S. Silva, in: A. Attanasi and D. Spinelli (editors), *Targets in Heterocyclic Systems. Chemistry and Properties*, Vol. 6, Italian Chemical Society, Rome (2002), p. 53.
33. A. F. Grapov, *Russ. Chem. Rev.*, **68**, 697 (1999).
34. E. S. Domina, L. A. Es'kova, E. V. Petrova, N. N. Chipanina, V. K. Voronov, A. V. Afonin, and G. G. Skvortsova, *Zh. Neorg. Khim.*, **32**, 1523 (1987).
35. L. K. Papernaya, A. A. Shatrova, A. I. Albanov, E. V. Rudyakova, and G. G. Levkovskaya, *Zh. Org. Khim.*, **47**, 467 (2011).
36. L. K. Papernaya, A. A. Shatrova, A. I. Albanov, and G. G. Levkovskaya, *Zh. Org. Khim.*, **47**, 305 (2011).
37. Z.-Y. Peng, F.-F. Ma, L.-F. Zhu, X.-M. Xie, and Z. Zhang, *J. Org. Chem.*, **74**, 6855 (2009).
38. L. P. Turchaninova, N. A. Korchevin, A. T. Shipov, E. N. Deryagina, Yu. I. Baukov, and M. G. Voronkov, *Zh. Obshch. Khim.*, **59**, 722 (1989).
39. M. Kamiya, *Bull. Chem. Soc. Jpn.*, **43**, 3344 (1970).

40. I. A. Zyryanova, L. V. Baikalova, O. A. Tarasova, A. V. Afonin, V. A. Kukhareva, M. A. Maksimova, and B. A. Trofimov, *Zh. Obshch. Khim.*, **75**, 1353 (2005).
41. R. J. Pugmire and D. M. Grant, *J. Am. Chem. Soc.*, **90**, 4232 (1968).
42. I. I. Schuster and J. D. Roberts, *J. Org. Chem.*, **44**, 3864 (1979).
43. A. Pawer and A. A. Patil, *Indian J. Chem. Sect. B*, **33**, 156 (1994).
44. A. F. Pozharskii, V. A. Anisimova, and E. B. Tsupak, *Practical Work on Heterocyclic Chemistry* [in Russian], Rostov on Don Publishing House (1988), p. 22.
45. E. V. Rudyakova, V. A. Savosik, L. K. Papernaya, A. I. Albanov, I. T. Evstaf'eva, and G. G. Levkovskaya, *Zh. Org. Khim.*, **45**, 1053 (2009).