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Simple synthesis of pyrazole-derived dithioethers

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Abstract

A number of pyrazole-derived dithioethers were prepared by the reaction of diisothiuronium salts and 2-(3,5-dimethylpyrazol-1-yl)ethanol tosylate in a basic aqueous solution. Diisothiuronium salts were prepared by the reaction of thiourea with alpha,omega-dibromoalkanes containing from two to nine methylene groups. The use of these salts allowed *in situ* generation ions dithiolate, thus eliminating the need to use hazardous dimercaptans.

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1. Introduction

Compounds with two pyrazole rings linked by an aliphatic spacer act as bidentate chelating ligands forming complexes with most elements of the periodic table¹. Coordinating ability of these ligands can be diversified by introducing additional donor atoms into the spacer between the heterocycles. Ligands with spacers bearing nitrogen, oxygen, and sulfur atoms have been reported, some of them were found to be effective steel corrosion inhibitors², while their chromium(III) and palladium(II) complexes demonstrated catalytic activity in ethylene oligomerization³ and Heck cross-coupling reactions⁴. Recently we and others have reported high superoxide dismutase-like activity of copper(II) complexes with bis(pyrazole) ligands^{5,6}. Copper(II) complexes with azole-derived thioether ligands were

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proposed as models for type I copper proteins⁷. Metal complexes with azole ligands modified by chalcogenide atoms are especially active cross-coupling catalysts⁸⁻¹⁰.

One of the ligands with a well-explored coordination chemistry is 1,5-bis(3,5-dimethylpyrazol-1-yl)-3-thiapentane (**L_S**, Fig.1)^{11,12}. Some of the complexes of dithioethers **1** and **2** with short di- and trimethylene linkers (Fig. 1) were also reported^{11,13-16}.

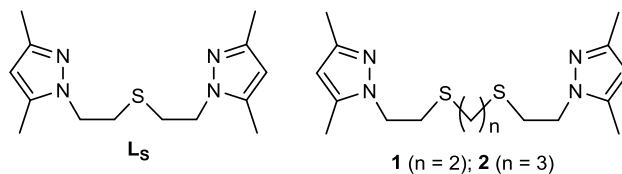


Fig. 1. Structures of previously reported pyrazole-thioether complexes.

Elongation of the spacer between sulfur atoms in dithioether ligands could lead to complexes of new structures and types of activities. Here we present a facile method for the preparation of pyrazole-derived dithioethers with long aliphatic spacers by the reaction of diisothiuronium salts with 1-(2-tosyloxyethyl)-3,5-dimethylpyrazole.

2. Results and discussion

Diisothiuronium salts were prepared by the reaction of α,ω -dibromoalkanes with two equivalents of thiourea in ethanol solution following a literature procedure¹⁷ (Fig. 2).

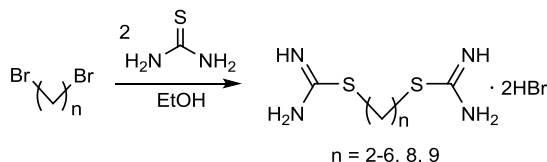


Fig. 2. Synthesis of diisothiuronium salts.

Alkaline hydrolysis of thiuronium salts is known to lead to thiolate ions¹⁸, which in our syntheses then acted as nucleophiles in the reaction with the tosylate (Fig. 3). The proposed method allows to generate dithiolate-ions *in situ* and avoid the use of toxic and malodorous dithiols, which gives it an advantage to the known methods for preparation of similar products¹⁹.

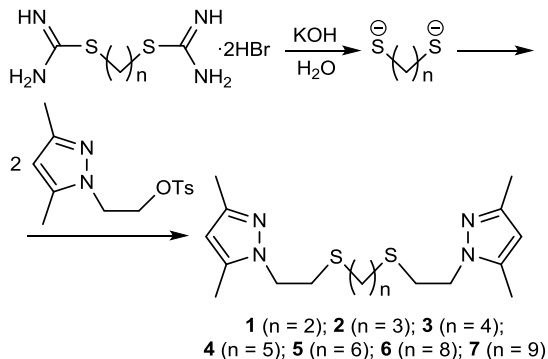


Fig. 3. Synthesis of dithioethers.

The structures of dithioethers were confirmed by IR and NMR spectra, as well as elemental analysis data.

Using the proposed method we have prepared dithioethers with polymethylene linkers between sulfur atoms (compounds **1-7**) and hybrid ligand **8** with hard oxygen and soft sulfur donor atoms in the linker between pyrazole rings (Fig. 4).

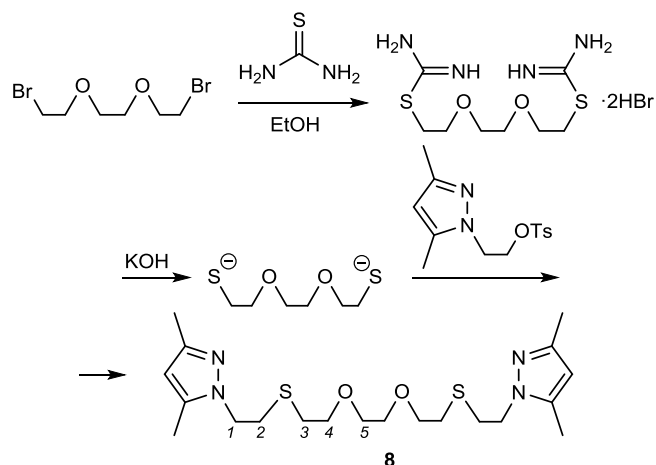


Fig. 4. Synthesis of hybrid diether-dithioether ligand

NMR ^1H spectrum of compound **8** shows three triplets (CH_2 groups 1, 2 and 3) at 4.09, 2.89 and 2.59 ppm correspondingly and a triplet overlapping with a singlet (CH_2 groups 4 and 5) at 3.55 ppm.

In summary, we have developed a facile synthetic protocol for the synthesis of functionalized dithioethers, which does not require the use of free dithiols. Six new pyrazole-derived dithioethers were prepared, which are interesting flexible ligands for coordination chemistry.

3. Experimental part

NMR spectra were recorded on Bruker AV300 instrument operating at 300 MHz for ^1H and 75 MHz for ^{13}C . Elemental analyses were carried out on a Carlo Erba CHNS analyzer. Infrared (IR) spectra of solid samples as KBr disks were recorded on a Nicolet 5700 (4000–400 cm^{-1}) spectrophotometer.

Commercially available α,ω -dibromoalkanes and thiourea were used as received. 1-(2-Tosyloxyethyl)-3,5-dimethylpyrazole was prepared using a reported procedure²⁰. 1,2-Bis(2-bromoethoxy)ethane was prepared by the reaction of triethylene glycol with phosphorus tribromide²¹.

1,8-Bis(3,5-dimethylpyrazol-1-yl)-3,6-dithiooctane (1). A solution of 1,2-dibromoethane diisothiuronium salt (3.46 g, 10 mmol), KOH (5.6 g, 100 mmol) in water (15 ml) were refluxed for 5 hours. Then, 1-(2-Tosyloxyethyl)-3,5-dimethylpyrazole (5.88 g, 20 mmol) was added, refluxing and vigorous stirring continued for 8 hours. After cooling to a room temperature, the precipitate formed, which was filtered and washed with water. Yield 73 %, colorless crystals, m.p. 85–87 °C (*i*-PrOH), lit. m.p. 78 °C¹⁹. IR bands, cm^{-1} : 1549; 1461; 1315 (Pz), 787 (C–S). NMR ^1H (CDCl_3), δ , ppm: 2.18, 2.24 (s, 12H, CH_3), 2.52 (s, 4H, $\text{SCH}_2\text{CH}_2\text{S}$), 2.91 (t, 4H, $\text{PzCH}_2\text{CH}_2\text{S}$, J 6.6 Hz), 4.10 (t, 4H, $\text{PzCH}_2\text{CH}_2\text{S}$, J 6.6 Hz), 5.76 (s, 2H, H^4 (Pz)). NMR ^{13}C (CDCl_3), δ , ppm: 11.0 (5- CH_3), 13.3 (3- CH_3), 32.0 ($\text{SCH}_2\text{CH}_2\text{S}$ and $\text{PzCH}_2\text{CH}_2\text{S}$), 48.5 ($\text{PzCH}_2\text{CH}_2\text{S}$), 104.9 (C^4 (Pz)), 139.1 (C^5 (Pz)), 147.7 (C^3 (Pz)). Found, %: C 56.31; H 7.65; N 16.56; S 18.48. Calculated for $\text{C}_{16}\text{H}_{26}\text{N}_4\text{S}_2$, %: C 56.77; H 7.74; N 16.55; S 18.94.

1,9-Bis(3,5-dimethylpyrazol-1-yl)-3,7-dithianonane (2) was prepared similarly to compound **1**. Yield 80 %, m.p. 36–37 °C (*i*-PrOH). NMR ^1H (CDCl_3), δ , ppm: 1.73 q (2H, $\text{CH}_2\text{CH}_2\text{CH}_2$, J 7 Hz), 2.16 s (6H, 3- CH_3 -Pz), 2.22 s

(6H, 5-CH₃-Pz), 2.41 t (4H, CH₂SCH₂CH₂Pz, *J* 7 Hz), 4.08 t (4H, PzCH₂CH₂S, *J* 7 Hz), 5.76 s (2H, H⁴-Pz). NMR ¹³C (CDCl₃), δ, ppm: 11.1 (5-CH₃), 13.4 (3-CH₃), 29.2 (CH₂CH₂CH₂), 30.7, 31.9 (SCH₂CH₂S, PzCH₂CH₂S), 48.7 (PzCH₂CH₂S), 104.9 (C⁴ (Pz)), 139.0 (C⁵ (Pz)), 147.6 (C³ (Pz)). Found, %: C 57.56; H 7.68; N 15.43; S 17.75. Calculated for C₁₇H₂₆N₄S₂, %: C 57.92; H 8.01; N 15.89; S 18.19.

1,10-Bis(3,5-dimethylpyrazol-1-yl)-3,8-dithiadecane (3) was prepared similarly to compound **1**. Yield 68 %, m.p. 50–52 °C (EtOH). IR bands, cm⁻¹: 1661; 1461; 1441 (Pz), 772 (C–S). NMR ¹H (DMSO-*d*₆), δ, ppm: 1.52 q (4H, PzCH₂CH₂SCH₂CH₂, *J* 6 Hz), 2.06 s (6H, 3-CH₃-Pz), 2.20 s (6H, 5-CH₃-Pz), 2.40 t (4H, PzCH₂CH₂SCH₂CH₂, *J* 6 Hz), 2.80 t (4H, PzCH₂CH₂S, *J* 7 Hz), 4.05 t (4H, PzCH₂CH₂S, *J* 7 Hz), 5.76 s (2H, H⁴-Pz). NMR ¹³C (DMSO-*d*₆), δ, ppm: 10.4 (5-CH₃), 13.5 (3-CH₃), 38.7 (SCH₂CH₂CH₂CH₂S, PzCH₂CH₂S), 40.3 (PzCH₂CH₂S), 104.9 (C⁴ (Pz)), 139.1 (C⁵ (Pz)), 146.0 (C³ (Pz)).

1,11-Bis(3,5-dimethylpyrazol-1-yl)-3,9-dithiaundecane (4) was prepared similarly to compound **1**. Yield 85 %, m.p. 32–33 °C (EtOH). IR bands, cm⁻¹: 1661; 1461; 1441 (Pz), 773 (C–S). NMR ¹H (DMSO-*d*₆), δ, ppm: 1.35 q (4H, SCH₂CH₂CH₂CH₂CH₂S, *J* 7 Hz), 1.43 q (4H, PzCH₂CH₂SCH₂CH₂CH₂, *J* 7 Hz), 2.06 s (6H, 3-CH₃-Pz), 2.21 s (6H, 5-CH₃-Pz), 2.38 t (4H, PzCH₂CH₂SCH₂CH₂CH₂, *J* 7 Hz), 2.81 t (4H, PzCH₂CH₂S, *J* 7 Hz), 4.05 t (4H, PzCH₂CH₂S, *J* 7 Hz), 5.76 s (2H, H⁴-Pz). NMR ¹³C (DMSO-*d*₆), δ, ppm: 10.6 (5-CH₃), 13.5 (3-CH₃), 38.7 (SCH₂CH₂CH₂CH₂CH₂S, PzCH₂CH₂S), 40.3 (PzCH₂CH₂S), 104.4 (C⁴ (Pz)), 138.8 (C⁵ (Pz)), 145.9 (C³ (Pz)).

1,12-Bis(3,5-dimethylpyrazol-1-yl)-3,10-dithiadodecane (5) was prepared similarly to compound **1**. Yield 87 %, m.p. 61–62 °C (EtOH). IR bands, cm⁻¹: 1649; 1461; 1442 (Pz), 772 (C–S). NMR ¹H (DMSO-*d*₆), δ, ppm: 1.28 q (4H, PzCH₂CH₂SCH₂CH₂CH₂, *J* 7 Hz), 1.45 q (4H, PzCH₂CH₂SCH₂CH₂CH₂, *J* 7 Hz), 2.06 s (6H, 3-CH₃-Pz), 2.21 s (6H, 5-CH₃-Pz), 2.38 t (4H, PzCH₂CH₂SCH₂CH₂CH₂, *J* 7 Hz), 2.81 t (4H, PzCH₂CH₂S, *J* 7 Hz), 4.05 t (4H, PzCH₂CH₂S, *J* 7 Hz), 5.76 s (2H, H⁴-Pz). NMR ¹³C (DMSO-*d*₆), δ, ppm: 10.6 (5-CH₃), 13.3 (3-CH₃), 38.7 (SCH₂CH₂CH₂CH₂CH₂CH₂S, PzCH₂CH₂S), 40.3 (PzCH₂CH₂S), 104.4 (C⁴ (Pz)), 138.7 (C⁵ (Pz)), 145.9 (C³ (Pz)).

1,14-Bis(3,5-dimethylpyrazol-1-yl)-3,12-dithiatetradecane (6) was prepared similarly to compound **1**. Yield 74 %, m.p. 37–38 °C (EtOH). IR bands, cm⁻¹: 1661; 1462; 1442 (Pz), 772 (C–S). NMR ¹H (DMSO-*d*₆), δ, ppm: 1.1–1.4 q (4H, PzCH₂CH₂SCH₂CH₂CH₂CH₂, *J* 7 Hz), 1.46 q (4H, PzCH₂CH₂SCH₂CH₂CH₂CH₂, *J* 7 Hz), 2.06 s (6H, 3-CH₃-Pz), 2.21 s (6H, 5-CH₃-Pz), 2.38 t (4H, PzCH₂CH₂SCH₂CH₂CH₂CH₂, *J* 7 Hz), 2.81 t (4H, PzCH₂CH₂S, *J* 7 Hz), 4.05 t (4H, PzCH₂CH₂S, *J* 7 Hz), 5.77 s (2H, H⁴-Pz). NMR ¹³C (DMSO-*d*₆), δ, ppm: 10.6 (5-CH₃), 13.2 (3-CH₃), 38.6 (PzCH₂CH₂SCH₂CH₂CH₂CH₂CH₂S), 40.3 (PzCH₂CH₂S), 104.5 (C⁴ (Pz)), 138.9 (C⁵ (Pz)), 146 (C³ (Pz)).

1,15-Bis(3,5-dimethylpyrazol-1-yl)-3,13-dithiapentadecane (7) was prepared similarly to compound **1**. Yield 70 %, oil. IR bands, cm⁻¹: 1553; 1461; 1443 (Pz), 775 (C–S). NMR ¹H (DMSO-*d*₆), δ, ppm: (1.2–1.4) m (6H, S(CH₂)₂CH₂CH₂CH₂(CH₂)₂), 1.46 q (4H, SCH₂CH₂(CH₂)₅CH₂CH₂S, *J* 7 Hz), 2.06 s (6H, 3-CH₃-Pz), 2.21 s (6H, 5-CH₃-Pz), 2.38 t (4H, SCH₂(CH₂)₇CH₂S, *J* 7 Hz), 2.80 t (4H, PzCH₂CH₂S, *J* 7 Hz), 4.05 t (4H, PzCH₂CH₂S, *J* 7 Hz), 5.76 c (2H, H⁴-Pz). NMR ¹³C (DMSO-*d*₆), δ, ppm: 10.6 (5-CH₃), 13.2 (3-CH₃), 38.6 (PzCH₂CH₂SCH₂CH₂CH₂CH₂CH₂S), 104.9 (C⁴ (Pz)), 139.0 (C⁵ (Pz)), 146.0 (C³ (Pz)).

1,14-Bis(3,5-dimethylpyrazol-1-yl)-6,9-dioxo-3,12-dithiotetradecane (8) was prepared similarly to compound **1**. NMR ¹H (CDCl₃), δ, ppm: 2.06 s (6H, 3-CH₃-Pz), 2.21 s (6H, 5-CH₃-Pz), 2.59 t (4H, 3-CH₂), 2.89 t (4H, 2-CH₂), 4.09 t (4H, 1-CH₂), 3.55 m (8H, 4-CH₂, 5-CH₂). Found, %: C 56.85; H 7.94; N 13.18; S 14.21. Calculated for C₂₀H₃₄N₄O₂S₂, %: C 56.31; H 8.03; N 13.13; S 15.03.

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References

- Pettinari C, Pettinari R. Metal derivatives of poly(pyrazolyl)alkanes: II. Bis(pyrazolyl)alkanes and related systems. *Coord Chem Rev* 2005;249:663-91.

- Tebbjji K, Bouabdellah I, Aouniti A, Hammouti B, Oudda H, Benkaddour M, Ramdani A. N-benzyl-N,N-bis[(3,5-dimethyl-1H-pyrazol-1-yl)methyl]amine as corrosion inhibitor of steel in 1 M HCl. *Materials Letters* 2007;**61**:799-804.
- Junges F, Kuhn MCA, Santos AHDPd, Rabello CRK, Thomas CM, Carpentier J-F, Casagrande JOL. Chromium Catalysts Based on Tridentate Pyrazolyl Ligands for Ethylene Oligomerization. *Organometallics* 2007;**26**:4010-4.
- Guerrero M, Pons J, Ros J. Effect of N1-substituted pyrazolic hybrid ligands on palladium catalysts for the Heck reaction. *J. Organomet. Chem* 2010;**695**:1957-60.
- Potapov AS, Nudnova EA, Domina GA, Kirpotina LN, Quinn MT, Khlebnikov AI, Schepetkin IA. Synthesis, characterization and potent superoxide dismutase-like activity of novel bis(pyrazole)-2,2'-bipyridyl mixed ligand copper(II) complexes. *Dalton Trans* 2009:4488-98.
- Lupidi G, Marchetti F, Masciocchi N, Reger DL, Tabassum S, Astolfi P, Damiani E, Pettinari C. Synthesis, structural and spectroscopic characterization and biomimetic properties of new copper, manganese, zinc complexes: identification of possible superoxide-dismutase mimics bearing hydroxyl radical generating/scavenging abilities. *J Inorg Biochem* 2010;**104**:820-30.
- Bowman E, Driessen WL, Reedijk J. Model systems for type I copper proteins: structures of copper coordination compounds with thioether and azole-containing ligands. *Coord Chem Rev* 1990;**104**:143-72.
- Kumar A, Rao GK, Kumar S, Singh AK. Formation and Role of Palladium Chalcogenide and Other Species in Suzuki-Miyaura and Heck C-C Coupling Reactions Catalyzed with Palladium(II) Complexes of Organochalcogen Ligands: Realities and Speculations. *Organometallics* 2014;**33**:2921-43.
- Kelly ME, Gómez-Ruiz S, Schmidt J, Wagner C, Schmidt H. Platinum(IV) complexes with α,ω -bis(pyrazol-1-yl) alkanediyl and diethyl ether/thioether ligands. Crystal structures of dibromodimethyl[1,2-bis(pyrazol-1-yl)ethane]platinum(IV) and trimethyl-bis[2-(pyrazol-1-yl)ethyl]etherplatinum(IV) tetrafluoroborate. *Polyhedron* 2008;**27**:3091-6.
- Sharma KN, Joshi H, Singh VV, Singh P, Singh AK. Palladium(II) complexes of pyrazolated thio/selenoethers: syntheses, structures, single source precursors of Pd₄Se and PdSenano-particles and potential for catalyzing Suzuki-Miyaura coupling. *Dalton Trans* 2013;**42**:3908-18.
- León Ad, Antonio Ayllón J, Pons J. Tuning the hemilabile behaviour of a thioether-pyrazole ligand on Pd(II) complexes with diphosphines. *J Organomet Chem* 2012;**696**:4275-80.
- de Leon A, Garcia-Anton J, Ros J, Guirado G, Gallardo I, Pons J. Environmentally benign and selective synthesis of hybrid pyrazole sulfoxide and sulfone ligands. *New J Chem* 2013;**37**:1889-94.
- de Leon A, Pons J, García-Antón J, Solans X, Font-Bardia M, Ros J. Synthesis of new platinum(II) complexes containing hybrid thioether-pyrazole ligands: Structural analysis by ¹H and ¹³C{¹H} NMR spectroscopy and X-ray crystal structures. *Inorg Chim Acta* 2007;**360**:2071-82.
- Haanstra WG, van der Donk WAJW, Driessen WL, Reedijk J, Drew MGB, Wood JS. Coordination behavior of the ligand 1,9-bis(3,5-dimethyl-1-pyrazolyl)-3,7-dithianone (bddn) towards first-row transition metals. X-ray structure of [Cu(bddn)(H₂O)](BF₄)₂. *Inorg Chim Acta* 1990;**176**:299-305.
- Garcia-Anton J, Mathieu R, Luga N, Pons Picart J, Ros J. Coordination properties of N₂S (1,5-bis(3,5-dimethyl-1-pyrazolyl)-3-thiapentane) or N₂S₂ (1,8-bis(3,5-dimethyl-1-pyrazolyl)-3,6-dithiaoctane or 1,2-bis[3-(3,5-dimethyl-1-pyrazolyl)-2-thiapropryl]benzene) donor ligands toward Rh(I). *J Organomet Chem* 2004;**689**:1599-608.
- Garcia-Anton J, Pons J, Solans X, Font-Bardia M, Ros J. Synthesis of new Pd(II) complexes containing thioether-pyrazole hemilabile ligands - Structural analysis by ¹H and ¹³C NMR spectroscopy and crystal structures of [PdCl₂(bddo)] and [Pd(bddo)](BF₄)₂ [bddo = 1,8-Bis(3,5-dimethyl-1-pyrazolyl)-3,6-dithiaoctane]. *Eur J Inorg Chem* 2002:3319-27.
- Reger DL, Pascui AE, Smith MD, Jezierska J, Ozarowski A. Halide and Hydroxide Linearly Bridged Bimetallic Copper(II) Complexes: Trends in Strong Antiferromagnetic Superexchange Interactions. *Inorg Chem* 2012;**51**:7966-8.
- Grogan CH, Leonard MR, Emmet R. Dithiols and derivatives. *J Org Chem* 1955;**20**:50-9.
- Haanstra WG, Driessen WL, Reedijk J, Turpeinen U, Hamalainen R. Unusual Chelating Properties of the Ligand 1,8-Bis(3,5-dimethyl-1-pyrazolyl)-3,6-dithiaoctane (bddo). Crystal Structures of Ni(bddo)(NCS)₂, Zn(bddo)(NCS)₂ and Cd₂(bddo)(NCS)₄. *J Chem Soc, Dalton Trans* 1989:2309-14.
- Potapov AS, Chernova NP, Ogorodnikov VD, Petrenko TV, Khlebnikov AI. Synthesis and oxidation of some azole-containing thioethers. *Beilstein J Org Chem* 2011;**7**:1526-32.
- De S, Aswal VK, Goyal PS, Bhattacharya S. Novel Gemini Micelles from Dimeric Surfactants with Oxyethylene Spacer Chain. Small Angle Neutron Scattering and Fluorescence Studies. *J Phys Chem B* 1998;**102**:6152-60.