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Unusual complexation of 1-phenylthiocarbamoyl-3-(pyridin-2-yl)pyrazoline with copper(II) chloride

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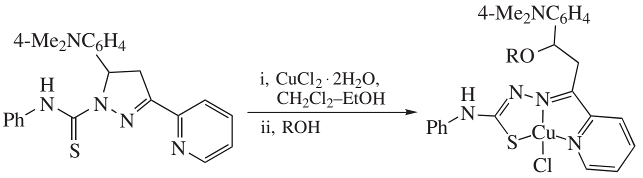
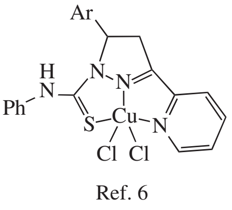
Complexation of 5-(4-dimethylaminophenyl)-1-phenylthiocarbamoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole with $CuCl_2$ followed by recrystallization from alcohols as external nucleophiles affords the products of pyrazoline ring opening by thiosemicarbazone moiety. The structure of the obtained complex was confirmed by X-ray diffraction data.



Keywords: copper(II) complexes, thiosemicarbazone complexes, pyrazolines, ring opening, alcohols, X-ray.

N-Thiocarbamoylpyrazolines are interesting due to their pharmacological properties, including antitumor, antimicrobial and other activities.[1] Coordination of organic compounds with transition metal ions can increase their bioactivity. For instance, an antiamoebic action of palladium thiocarbamoylpyrazoline complexes,[2] antifungal effect of nickel and copper thiocarbamoylpyrazoline coordination compounds[3] as well as antitumor activity of ruthenium[4] and gold[5] complexes of 3-pyridylpyrazolines have been reported.

We have demonstrated previously, that 3-pyridyl-1-thiocarbamoylpyrazolines readily form copper complexes with 1 : 1 ligand to metal ratio upon reaction with $CuCl_2{\cdot}2H_2O$ in CH_2Cl_2–EtOH.[6] Such complexes displayed an antiproliferative activity in the micromolar range against different tumor cell lines.



Ref. 6

However, in this work the similar reactions of 5-(4-dimethylaminophenyl)-1-phenylthiocarbamoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole **1** with $CuCl_2{\cdot}2H_2O$ with subsequent recrystallization of the obtained solid from ROH surprisingly afforded coordination compounds **3** deprived of pyrazoline cycle (Scheme 1 and Figure 1). Detailed examination of these reactions revealed, that the intermediate product of the complexation of ligand **1** with copper(II) chloride at room temperature was the expected complex **2**, however when heated in a nucleophilic solvent like alcohol or aqueous EtOH, it was completely converted into the ring-opened complexes **3a–c**.

The synthesis of ligand **1** was performed according to our reported procedure[6] in 53% yield. Complex **2** was obtained as the single product from equivalent amounts of $CuCl_2{\cdot}2H_2O$ and ligand **1** in ethanol–CH_2Cl_2 at room temperature.[†] Pyrazoline-opened coordination compounds **3a–c** were obtained *via* reflux of complex **2** in an alcohol solvent.[‡]

Compound **3a** was characterized by X-ray diffraction data (Figure 1).[§] The C(8)–S(3) bond length of 1.760 (5) Å in the ligand fragment corresponds to a single bond, while the

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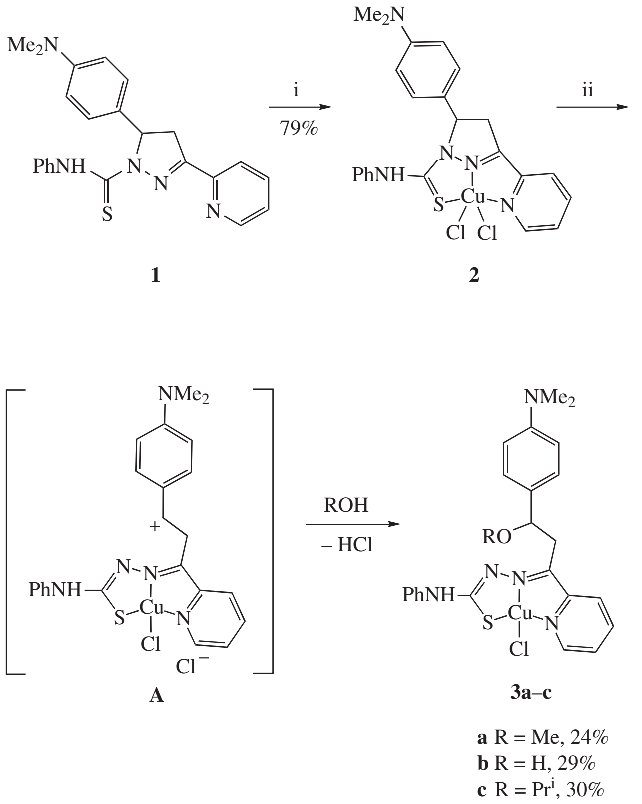
[†] *[5-(4-Dimethylaminophenyl)-1-phenylthiocarbamoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole-*N,N,S*]copper(II) dichloride* **2**. To a solution of ligand **1** (0.5 mmol) in CH_2Cl_2 (1 ml), ethanol (0.5 ml) was added affording a two-phase system. Then the solution of $CuCl_2{\cdot}2H_2O$ (0.5 mmol) in ethanol (1 ml) was slowly added. The reaction mixture was sealed and left until the precipitation occurred. The precipitate was filtered off, washed with water, diethyl ether, benzene and dried *in vacuo* with heating. Yield 79%, brown powder, mp 183–185 °C (decomp.). Found (%): C, 51.20; H, 4.28; N, 12.94; Cl, 11.62. Calc. for $C_{23}H_{22}N_4O_2SCuCl_2$ (%): C, 51.54; H, 4.33; N, 13.07; Cl, 11.86.

[‡] *General procedure for the synthesis of complexes* **3a–c**. Complex **2** (0.1 mmol) was refluxed in MeOH, EtOH–H_2O (1 : 1) or Pr^iOH for 4 h, then the reaction mixture was cooled, the formed precipitate was filtered off, washed with water, diethyl ether, benzene and dried *in vacuo* with heating affording complexes **3** as red-black crystalline powders. For **3a**. Found (%): C, 54.10; H, 5.21; N, 12.90. Calc. for $C_{24}H_{26}N_5OS{\cdot}CuCl$ (%): C 54.23, H 4.93, N 13.18. For **3b**. Found (%): C, 52.98; H, 4.81; N, 13.31; Cl, 6.78. Calc. for $C_{23}H_{24}N_5OS{\cdot}CuCl$ (%): C, 53.38; H, 4.67; N, 13.53; Cl, 6.85. For **3c**. Found (%): C, 55.44; H, 5.39; N, 12.86; Cl, 6.63. Calc. for $C_{26}H_{30}N_5OS{\cdot}CuCl$ (%): C, 55.80; H, 5.40; N, 12.51; Cl, 6.33.

[§] *Crystal data for* **3a**. $C_{24}H_{26}ClCuN_5OS$ (M = 531.55), monoclinic, space group $P2_1/n$, a = 8.3788(3), b = 11.9966(3) and c = 23.8255(8) Å, V = = 2378.01(13) Å^3, Z = 4, d_{calc} = 1.485 g cm^{-3}, μ = 3.368 mm^{-1}, $F(000)$ = = 1096, the final R = 0.0721, wR = 0.1875 and S = 0.994 for 2496 observed reflections with $I > 2\sigma(I)$. Data were collected using a STOE diffractometer (STOE & Cie GmbH, Germany) with Pilatus100K detector (DECTRIS, USA), focusing mirror collimation and CuKα (1.54086 Å) radiation in rotation method mode. STOE X-Area software was employed for cells refinement and data editing. Data collection and image processing was performed with X-Area 1.67 (2013). Intensity data were scaled with LANA as a part of X-Area to minimize differences of intensities for symmetry-equivalent reflections (multi-scan method).



Scheme 1 *Reagents and conditions:* i, $CuCl_2 \cdot 2H_2O$, CH_2Cl_2–EtOH; ii, recrystallization from ROH.

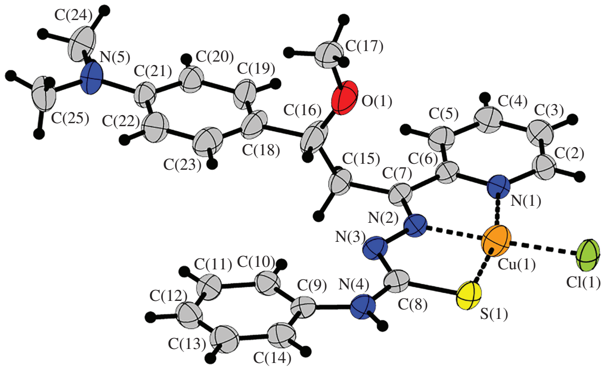


Figure 1 Molecular structure of compound **3a**. Selected bond lengths (Å): Cu–S 2.246(2), Cu–N(1) 2.010(5), Cu–N(2) 1.970(4), Cu–Cl 2.216(2).

C(8)–N(3) bond length of 1.301(8) Å corresponds to a double bond. The presence of Cu^{2+} ion is confirmed by strong line broadening in the NMR spectra of complexes **3**, as well as by results of electrochemical investigation of complex **3a** in DMF (see Online Supplementary Materials, Figure S2), which reveals $Cu^{2+} \rightarrow Cu^{1+}$ reduction peak at 0.39/0.52 V.

Pyrazoline ring opening during the complex formation with transition metal ions has been reported for ligands with tautomeric equilibrium of closed pyrazoline and opened bis(thiosemicarbazone) forms.[7–9] In our case, pyrazoline ring opening of copper(II) thiosemicarbazone complex induced by alcohols as exogenous nucleophiles is observed for the first time, according to our knowledge. Apparently, the initial copper complex **2**, generated from ligand **1** reaction with $CuCl_2$ (see Scheme 1), is converted into another complex with the acyclic product resulting from nucleophilic opening of the pyrazoline ring. At the first step of this transformation, cyclic form of the ligand can undergo an equilibrium transformation into stabilized benzylic cation **A**, which is attacked by alcohol as a nucleophile. Then the final product **3** is formed as a result of HCl elimination. The presence of dimethylamino group as a strong mesomeric donor at the *para*-position of benzene ring in ligand **1** is critical for this reaction to occur, since it stabilizes benzylic cation **A**.

In summary, we have revevaled pyrazoline ring opening upon treatment of copper(II) complexes of pyrazoline-containing ligand by external O-nucleophiles. This reaction may be of interest for the preparation of bioactive copper(II) coordination compounds with hydroxy- or alkoxy-containing *N*-phenylthiosemicarbazone ligands.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.039.

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CCDC 1852723 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.