Complexation *versus* thiadiazole formation for reactions of thiosemicarbazides with copper(II)

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Received 24th November 2006, Accepted 7th February 2007
First published as an Advance Article on the web 20th February 2007
DOI: 10.1039/b617186a

The reactions of *N*,*N*-substituted thiosemicarbazides with copper salts have been investigated and either copper(II) thiosemicarbazide complexes, 1,3,4-thiadiazolium salts or 1,3,5-thiadiazoles are obtained depending on the Cu(II) salt and solvent used.

The coordination chemistry of copper with N,S-donor ligands has been widely studied, as the complexes can serve as models for enzymes such as galactose oxidase and superoxide dismutase.[1] Copper complexes of N,S donors also have potential biomedical applications and thiosemicarbazide and thiosemicarbazone complexes have been investigated as antiviral, antibacterial and anticancer chemotherapeutic agents.[2] However it is their use as ligands for radioactive copper complexes in hypoxic selective radiopharmaceuticals that has created the most recent interest.[3] Although many structures of thiosemicarbazone complexes have been reported,[4] there are few for complexes of the precursor thiosemicarbazides. There is also a report of the use of Cu(II) salts for the oxidation of thiosemicarbazones to thiazoles,[5] but the conditions which determine coordination *versus* oxidative cyclisation have not yet been established.

Reaction of 1,1-dimethyl-4-phenyl-thiosemicarbazide (HL^1, Fig. 1) (synthesised from dimethylhydrazine and phenylisothiocyanate in diethyl ether[6]) with copper acetate (2 : 1) in methanol leads to the formation of a red copper(II) complex (**1**) with two monodeprotonated ligands in good yield. The mass spectrum shows a peak at *m*/*z* 452.1 corresponding to the ion $[Cu(L^1)_2 + H]^+$, consistent with the loss of a proton from each ligand. This peak has an appropriate isotope distribution pattern for the proposed structure. Analytical data are also in agreement with this formulation.† Recrystallisation from methanol gave single crystals suitable for X-ray structure analysis. ‡§§

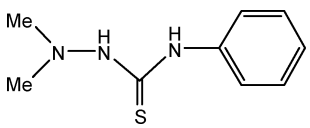

Fig. 1 Structure of thiosemicarbazide HL^1.

The X-ray crystal structure shows the Cu(II) ion to be four-coordinate with the two monodeprotonated ligands in a N_2S_2 *trans* square-planar arrangement (Fig. 2). The complex is centrosymmetric with the inversion point located at the copper ion. The phenyl rings are more or less coplanar to the rest of the ligand

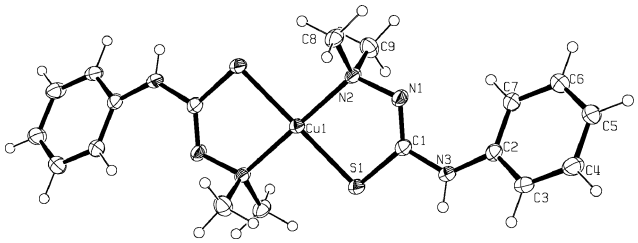

Fig. 2 Representation of the structure of $[Cu(L^1)_2]$,**1**. Selected bond distances (Å) and angles (°): C(2)–N(3) 1.416(3), N(3)–C(1) 1.381(3), C(1)–N(1) 1.284(3), N(1)–N(2) 1.454(2), C(1)–S(1) 1.753(2), Cu(1)–S(1) 2.2419(6), Cu(1)–N(2) 2.0526(18). C(2)–N(3)–C(1) 127.6(2), N(3)–C(1)–S(1) 114.33(16), N(3)–C(1)–N(1) 119.7(2), C(1)–S(1)–Cu(1) 96.14(7), C(1)–N(1)–N(2) 114.38(18), N(1)–N(2)–Cu(1) 116.53(13), N(2)–Cu(1)–S(1) 85.41(5).

chain (dihedral angle 30.10°) and they are parallel to each other. Although the ligand is deprotonated there is not a great deal of electronic delocalisation and this is reflected in the bond distances.[5] The values of the C(1)–N(1) and C(1)–S(1) bonds lengths indicate that the ligand is in its thiolic form. The ligand is close to planar, as found with thiosemicarbazone complexes, although deprotonated thiosemicarbazones are more extensively delocalised.[4] There are no hydrogen bonds and the molecules are held together in the crystal packing by π–π interactions with a distance of 3.521 Å, which leads to the formation of infinite chains running in the *b* direction.

Complex **1** is sparingly soluble in water and hexane, but quite soluble in a wide range of common solvents, such as methanol, diethyl ether, toluene and acetonitrile giving red solutions. The cyclic voltammogram measured in DMF (Pt working and auxiliary electrodes, standard calomel reference electrode, scan rate 100 mV s^{-1}) shows one quasireversible process corresponding to the oxidation of Cu(II) to Cu(III) at $E_{1/2} = +0.213$ V (*vs* SCE) and another irreversible process attributable to the reduction of Cu(II) to Cu(I) at −0.727 V.

Reaction of the same ligand with copper(II) chloride in methanol (1 : 1) yields a green solution, the ESMS(+) of which shows four peaks at *m*/*z* 192.1, 311.1, 353.2 and 453.1. These correspond to the formation of three species: one copper complex and two different new heterocycles identified below. The peak at *m*/*z* 453.1 corresponds to the Cu(I) species $[Cu(L^1H)_2]^+$ with two neutral thiosemicarbazide ligands. This shows the appropriate isotopic pattern.

If the reaction is carried out in THF the mass spectrum of the solution displays only the peak at *m*/*z* 192.1. After one day in the freezer, green crystals of **2** suitable for X-ray structure determination were obtained from the mother liquor in good

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yield.† The paramagnetism of the complex precluded NMR studies. Compound **2** consists of a copper(II) salt containing one $[CuCl_4]^{2-}$ anion and two positively charged 3-methyl-1,3,4-thiadiazolium cations (Fig. 3), which are formed by the oxidation and cyclisation of the thiosemicarbazide, *via* the formation of a bond between sulfur and a deprotonated methyl group. The asymmetric unit contains two independent molecules of the cation and a single molecule of the anion, none of which have any crystallographic symmetry. The geometry of the $CuCl_4^{2-}$ ion is intermediate between square planar and tetrahedral and all the Cu–Cl distances are different. The cations are both linked to the anion by N–H···Cl hydrogen bonds (N(3)···Cl(1) 3.378(2) Å, N(6)···Cl(6) 3.266(2) Å). The hydrogen-bonded assembly has an approximately twofold axis of rotation. Bond distances and angles in both heterocyclic rings are not identical but are very similar. The N(2)–C(8) and N(5)–C(17) and N(1)–C(1) and N(4)–C(10) bond distances correspond to double bonds, while the remaining C–N, the N–N and the C–S bond distances are close to the value expected for single bonds.[3] The thiadiazolium rings are virtually planar and they are coplanar with the phenyl groups. The molecules are linked together by π–π interactions involving the phenyl groups with a distance between centroids of 3.645 Å.

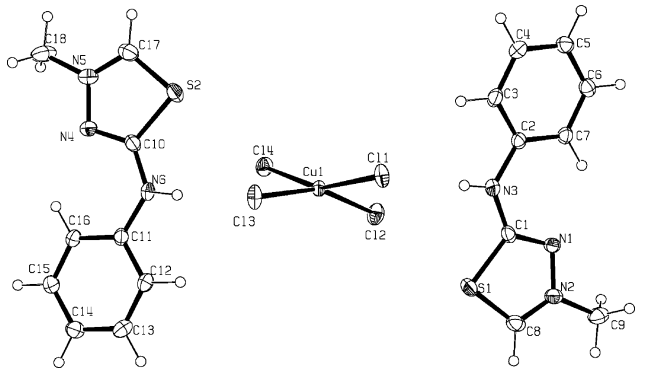

Fig. 3 Thermal ellipsoid plot (ORTEP-3) at 40% probability for compound $[(C_9H_{10}N_3S)_2]^{2+}[CuCl_4]^{2-}$ **2**. Selected bond distances and angles: N(3)–C(1) 1.339(3), C(1)–N(1) 1.313(3), N(1)–N(2) 1.376(3), N(2)–C(8) 1.466(3), C(8)–S(1) 1.694(3), S(1)–C(1) 1.759(2), C(10)–N(6) 1.341(3), C(10)–N(4) 1.317(3), N(4)–N(5) 1.374(3), N(5)–C(17) 1.303(3), C(17)–S(2) 1.688(3), S(2)–C(10) 1.760(2). C(2)–N(3)–C(1) 128.9(2), N(3)–C(1)–N(1) 126.2(2), N(3)–C(1)–S(1) 119.48(17), C(1)–N(1)–N(2) 108.13(19), N(1)–N(2)–C(8) 118.0(2), N(2)–C(8)–S(1) 111.64(18), S(1)–C(1)–N(1) 114.36(18), C(11)–N(6)–C(10) 128.8(2), N(6)–C(10)–N(4) 126.4(2), N(6)–C(10)–S(2) 119.32(17), C(10)–N(4)–N(5) 108.28(19), N(4)–N(5)–C(17) 117.6(2), N(5)–C(17)–S(2) 111.97(18), S(2)–C(10)–N(4) 114.25(17).

Thiadiazoles have attracted interest due to their wide spectra of biological activities[7] and have usually been prepared *via* oxidative reactions. 3,5-Diamino-1,2,4-thiadiazoles (Fig. 4, structure A) can be prepared by oxidative coupling of thioureas with reagents such as acidic DMSO[8] or bis(acyloxyiodo)arenes.[9] Analogous oxidation of aldehyde thiosemicarbazones RCH=NNHCSNHR′ using $Cu(II)(ClO_4)_2$ is reported to give 1,3,4-thiadiazoles of structure B below.[5] Methylation of the 5-amino-1,3,4-thiadiazole C with MeI gives the neutral methylated thiadiazole D.[10] The oxidation of alkylated thiosemicarbazides such as Me_2NNHCSNHPh has not previously been described, and we here report that reaction

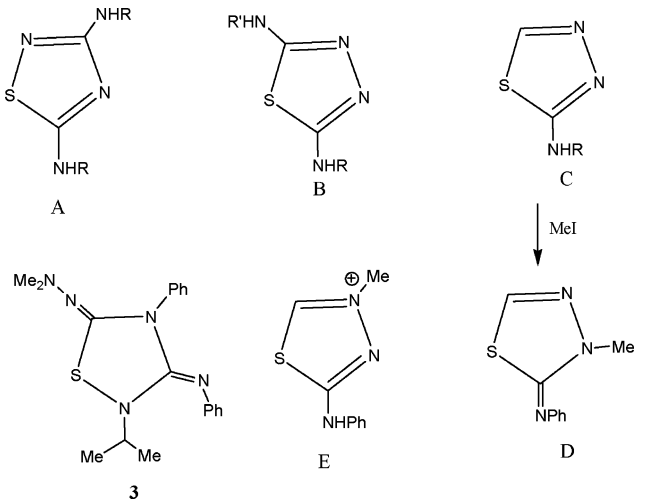

Fig. 4 Thiadiazoles and thiadiazolium salts.

with $CuCl_2$ in THF exclusively gives the previously unreported 3-methyl-5-aminophenyl-1,3,4-thiadiazolium salt (E); the X-ray crystal structure of which is outlined above.

The use of THF as solvent permits the fully selective synthesis of **2**. However, if the filtrate from the synthesis of **2** in methanol is allowed to evaporate slowly white crystals of **3**, are obtained. This was unambiguously identified by an X-ray crystal structure determination. This species results from another oxidative cyclisation reaction, but now involving linking of two thiosemicarbazide ligands with elimination of elemental sulfur to give 2-dimethylhydrazido-3-phenyl-4-phenylimino-5-dimethylamino-1,3,5-thiadiazole (**3**) (Fig. 3). The weak peak described earlier at *m/z* 355.2 corresponds to the molecular ion $[C_{18}H_{22}N_6S + H]^+$ and the most intense peak at *m/z* 311.1 is assigned to the fragment $[C_{16}H_{16}N_5S]^+$, corresponding to the loss of a NMe_2 group. The ^1H and ^{13}C NMR spectra are consistent with the determined structure. Further details of the X-ray crystal structure of **3** will be reported elsewhere.

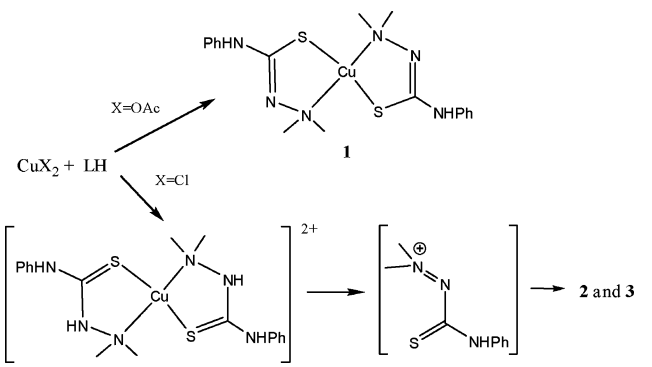

Fig. 5 Reaction scheme with proposed mechanism.

The formation of the Cu(II) complex **1** occurs with Cu(II) acetate where acetate is sufficiently basic to deprotonate the thiosemicarbazide to give a stable Cu(II) complex. When Cu(II) chloride is used ligand deprotonation does not occur and an internal redox process occurs for the dicationic complex to give presumably Cu(I) and a diazenium cation which then cyclises to give **2** or couples with elimination of sulfur to give **3** (see Fig. 5). As

expected the reduction of the positively charged complex occurs more readily than for neutral **1**. The Cu(II) anion arises from adventitious oxidation during crystallisation which was carried out in air. The formation of **2** cannot occur while the copper is bound as the N-methyl groups and sulfur atoms are held too far apart.

These investigations show that the products of the reactions of Cu(II) with this type of thiosemicarbazide can in part be controlled by selection of the appropriate metal salt and reaction solvent. This has permitted the isolation of a new Cu(II) complex together with a previously unreported 3-methyl-1,3,4-thiadiazolium cation and a very unusual 1,3,5-thiadiazole.

Notes and references

† Compound **1**: Found: C, 47.35; H, 5.35; N, 18.65; S, 14.22; Cu, 14.09. $C_{18}H_{24}N_6S_2Cu$ requires C, 47.84; H, 5.31; N, 18.66; S, 14.17; Cu, 14.06. HPLC: R_t 10.44 min. λ_{max}(DMF)/nm 288 (ε/dm^3 mol^{-1} cm^{-1} 4972), 353 (4674) and 394sh (4177). Compound **2**: Found: C, 36.91; H, 3.58; N, 14.31; S, 10.94; Cl, 23.92; Cu, 10.71. $C_{18}H_{20}N_6S_2CuCl_4$ requires C, 36.63; H, 3.39; N, 14.25; S, 10.86; Cl, 24.06; Cu, 10.71. HPLC: R_t 11.15 min. λ_{max}(DMF)/nm 407sh (ε/dm^3 mol^{-1} cm^{-1} 870), 640 (100). Compound **3**: δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.2 (6H, s, Me), 2.5 (6H, s, Me), 6.79–6.84 (2H, t, Ph), 7.09–7.14 (2H, t, Ph), 7.39–7.48 (6H, m, Ph). δ_C(300 MHz, $CDCl_3$, Me_4Si) 42.6 (Me), 47.2 (Me), 120.5 (Ph), 120.9 (Ph), 127.8 (Ph), 128.0 (Ph), 128.6 (Ph), 129.0 (Ph), 136.4 (NNC=N), 149,2 (NSC=N).

‡ **X-Ray crystallography** Crystals were mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius Kappa CCD diffractometer (graphite-monochromated Mo-Kα radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package.[11] The structures were solved using the direct-methods program SIR92,[12] which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite.[13] Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The NH hydrogen atoms were located in a difference Fourier map and their coordinates and isotropic thermal parameters subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Representations of the structures were produced using ORTEP-3.[14] **Crystal structure determination of complex 1 Crystal data**. $C_{18}H_{24}CuN_6S_2$, M = 452.11, monoclinic, a = 11.8923(4), b = 5.5608(2), c = 15.7983(5) Å, β = 99.3695(14), U = 1030.81(6) Å^3, T = 150 K, space group $P\,2_1/c$, Z = 2, μ(Mo-Kα) = 1.277 mm^{-1}, 10012 reflections measured, 2578 unique (R_{int} = 0.040) which were used in all calculations. The final $wR(F_2)$ was 0.0379. **Crystal structure determination of complex 2 Crystal data**. $C_{18}H_{20}Cl_4CuN_6S_2$, M = 589.89, triclinic, a = 7.3900(2), b = 9.9448(2), c = 16.1842(3) Å, α = 80.9969(10), β = 88.6086(10), γ = 85.1073(9) U = 1170.40(5) Å^3, T = 150 K, space group $P\bar{1}$, Z = 2, μ(Mo-Kα) = 1.588 mm^{-1}, 17872 reflections measured, 5319 unique (R_{int} = 0.039) which were used in all calculations. The final $wR(F_2)$ was 0.0357.

§ CCDC reference numbers 623527 and 623528. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b617186a

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