Preparation of Heterocyclic Thiolato Ligands and their Copper(II) Complexes

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Abstract

A number of different heterocyclic aldehydes substituted in the β-position with the t-butylthio moiety were converted into new S_2N_2 ligands containing protected thiol groups. Reaction of the protected ligands 2 with copper(II) salts resulted in elimination of isobutene and formation of copper(II) complexes of mercaptoimines 3.

Introduction

In a preliminary note [1] we described the versatility of the 2-methyl-2-propanethiolate anion in the preparation of heterocyclic ligands with protected thiolato groups. A review including a discussion of the physicochemical properties of copper(II) S_2N_2 complexes as models for the study of copper enzymes has recently been published [2].

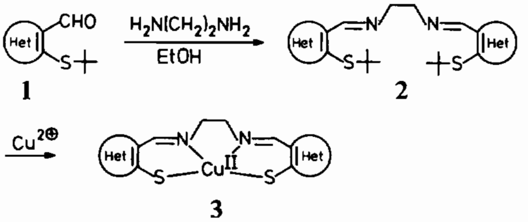
In the present account we describe the preparative aspects of this method, which have been found to be quite general.

Results and Discussion

Ligands

The protected thiolato ligands were all prepared from the appropriate heterocyclic β-S-t-butyl aldehydes [3].

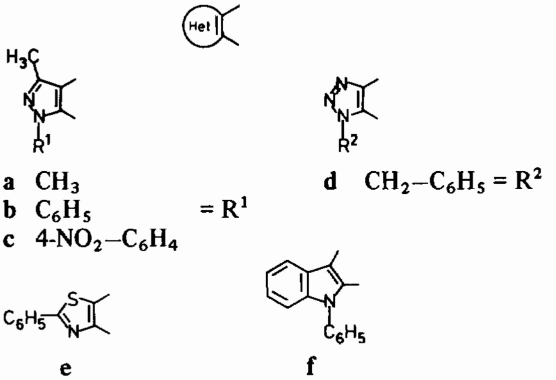
Reaction of aldehydes **1** with the required diamine was carried out in ethanol, in most cases the resulting bis-imines **2** crystallized out after 24–48 h in good yields. The bis-imines (protected ligands) **2** are all stable, crystalline, colourless compounds:



1 2

3

with the heterocyclic part:



a CH_3
b C_6H_5 $= R^1$
c $4\text{-}NO_2\text{-}C_6H_4$

d $CH_2\text{-}C_6H_5 = R^2$

e **f**

The mass spectra of the compounds demonstrated the facile loss of isobutene, as in most cases the molecular ion was <5% abundant. For ligand **2f** no molecular ion was seen in the mass spectrum, since isobutene was already lost in the inlet system. However in a FAB (Fast Atom Bombardment) spectrum the expected $M^+ + 1$ peak for **2f** was clearly seen. The structures of the protected ligands **2** were further assigned on the basis of analytical and spectroscopic data.

In the IR spectra of the protected ligands **2a–f** C=N (imine) absorptions were found at 1640 cm^{-1} in all cases. In the ^1H-NMR spectra of t-butyl protons were observed at $\delta = 1.0–1.3$ ppm, the methylene protons at $\delta = 3.8–4.1$ ppm and the imine protons at $\delta = 8.3–8.5$ ppm.

Syntheses of Copper(II) Complexes

The t-butyl group has been used previously* as a protecting group for thiols, and in some cases conversion to the thiols required rather drastic reaction conditions. We have previously [5] demonstrated that Lewis acids such as aluminium chloride can act as a catalyst in the deprotection reaction. However other metal ions such as copper(II) can also function as Lewis acids. Thus when the protected ligands **2** were refluxed in an appropriate solvent such as

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*For a recent discussion of the use of the S-t-butyl group in cystein chemistry see ref. 4.

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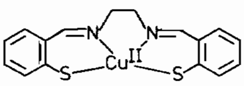
ethanol or 2-methoxyethanol with copper(II) chloride or trifluoroacetate, isobutene was evolved resulting in the formation of complexes **3**. The range of different heterocyclic systems used, **2a–f**, demonstrated the generality of the method. Formation of by-products such as Cu(I) species was not seen and this is another advantage of the method described here.

Previous attempts used in the preparation of related Cu(II)–S_2N_2 complexes [6] usually resulted in redox processes with formation of unwanted by-products (such as disulfides) as well as condensation products.

The copper(II) complexes **3a–f** described here are quite similar to the complex **4** previously investigated by Murray *et al.* [7]



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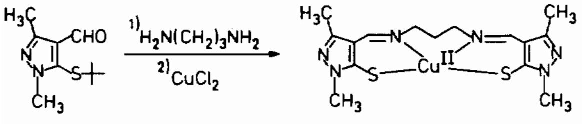
Thus the inner-complexes **3a–f** were all dark-brown, crystalline compounds which could readily be characterized by mass spectrometry. The mass spectra of **3a–f** all showed a molecular ion of large intensity, which in the cases **3a–c** was the base peak. The isotopic pattern found for all of the M^+ ions for complexes **3a–f** in each case confirmed the presence of one copper atom. Furthermore the UV, visible and ESR spectral data for complexes **3a–f** were all similar to the values previously found for the related complex **4** [6].

Thus all the systems **3** derived from 1,2-diaminoethane show weak (ϵ = 100) d–d bands in the region 770–870 nm. In addition the spectra show bands at 475–530 and 410–490 nm of medium intensity (ϵ = 500–2000). These bands are assigned as Cu $\leftarrow$ RS(σ or π) ligand to metal charge transfer (LMCT) bands. The positions of these bands are typical for CuN_2S_2 systems close to square planar geometry [2].

The frozen-glass ESR spectra of the complexes **3** are mainly axial, although with a small rhombic splitting. The $g_\parallel$ values are in the range 2.11–2.16 and $A_\parallel$ in the range 17–19 mK, which is typical for other similar CuN_2S_2 systems [2].

Complex **5** was made in a one pot reaction without isolating the corresponding ligand:



1a **5**

The spectra of **5** showed quite different values [1, 2] from the corresponding ethylene bridged complex **3a**. These differences are due to distortion away from the square planar configuration around the central copper atom [2].

Experimental

Microanalyses were carried out at NOVO A/S, Copenhagen. The ^1H NMR spectra were recorded on a JEOL-FX 60 spectrometer, IR spectra on a Perkin-Elmer 580 spectrometer (KBr used in all cases), UV spectra on a Varian CARY 219 spectrometer (abs. ethanol in all cases) and mass spectra on a Varian MAT 311 A spectrometer. Melting points (uncorrected) were obtained on a Büchi apparatus.

Preparation of Ligands 2a–c, General Method 4,4′-Ethylenebis(nitrilomethylene)bis(1-substituted-3-methyl-5-S-t-butylpyrazole)

The required protected β-mercaptoaldehyde **1a–c** (0.01 mol) was dissolved in dry ethanol (50 ml).

1,2-Diaminoethane (0.005 mol, 0.33 ml) was added and the reaction mixture stirred at 50 °C for 1 h. After storing the solution at 5 °C for 1–2 days ligands **2b** and **2c** crystallized out and were isolated. Ligand **2a** was isolated by concentration of the reaction mixture *in vacuo.*

Preparation of Ligands 2d–f, General Method

The required protected β-mercaptoaldehyde [8] **1d–f** (0.01 mol) was dissolved in dry ethanol (50 ml).

1,2-Diaminoethane (0.005 mol, 0.33 ml) was added and the mixture refluxed for 1 h. The ligands **2d–f** precipitated from the reaction mixture after storing at 5 °C for 1–2 days.

Preparation of Complexes 3a–c, General Method

The appropriate protected ligands **2a–c** were dissolved in ethanol or 2-methoxyethanol (50 ml), copper(II) chloride was then added and the reaction mixture heated under reflux according to the terms given in Table II. The resulting crystalline products were isolated and recrystallized from 2-metoxyethanol. The solubilities generally are quite low (less than 0.1 g per 100 ml solvent). Complexes **3d–f** were prepared by variations of the above described method, as described in Table II.

Preparation of Complex 5

2,3-Dimethyl-4-formyl-5-(S-t-butyl)pyrazole (0.002 mol) and 1,3-diaminopropane (0.001 mol) was heated in ethanol (50 ml, 60 °C) for 30 min, whereupon copper chloride (0.17 g, 0.001 mol) was added followed by reflux under nitrogen for 0.5 h. Cooling and filtration gave the copper complex **5** as a dark crystalline powder 0.3 g (73%). UV(ethanol) 950(70), 580sh(1104), 486(2676), 329(9860), 281(19550). ESR (in a frozen glass of a 1:1:5 mixture of DMF, H_2O, CH_3OH at liquid nitrogen temp.): $g_\parallel = 2.149$, $g_\perp = 2.025$, $A_\parallel = 15.6$ mK, $A_\parallel N = 1.40$ mK. Mass spectra: 413(29%), 411(54%), 276(27%), 274(60%), 118(100%). The isotopic pattern in the molecular ion was in accordance with the elemental composition

TABLE I. Spectroscopic and Analytical Data for the S_2N_2 Ligands.

Compound No.	% Yield	m.p. (°C) [Solvent]	Molecular formula (Molecular mass)	Analyses				IR(KBr) C=N (cm^{-1})	^{1}H-NMR($CDCl_3$) δ (ppm)	MS (m/e)
					C	H	N			
2a	74	110–111 [Ethanol–water]	$C_{22}H_{36}N_6S_2$ (448.70)	Calcd. Found	58.89 58.34	8.09 8.25	18.73 18.34	1645	1.23(s,18H,CH_3)2,45(s,6H,CH_3) 3.88(s,3H,CH_2,CH_3),8.30(s,2H,CH)	448(7%),392(2%), 335(7%),239(100%)
2b	78	175–177 [Ethanol]	$C_{32}H_4ON_6S_2$ (572.82)	Calcd. Found	67.10 66.87	7.04 6.91	14.67 14.61	1640	1.00(s,18H,CH_3)2.57(s,6H,CH_3), 3.95(s,4H,CH_2),7.48(m,10H,Ph) 8.46(s,2H,CH)	572(19%),516(4%), 459(16%),301(75%), 245(100%)
2c	72	218–220 d [2-Methoxyethanol]	$C_{32}H_38N_8O_4S_2$ (662.84)	Calcd. Found	57.99 57.36	5.78 5.62	16.91 17.08	1640	1.03(s,18H,CH_3),2.57(s,6H,CH_3), 3.96(s,4H,CH_2),7.87(d,4H,J = 9.5H_z) 8.32(d,4H,J = 9.5H_z),8.47(s,2H,CH)	662(11%),606(2%), 549(9%),346(57%), 290(86%),275(34%), 41(100%)
2d	61	161–163 [Ethanol]	$C_{30}H_{38}N_8S_2$ (574.82)	Calcd. Found	62.69 62.20	6.66 6.74	19.49 19.07	1660	1.15(s,18H,CH_3),4.09(s,4H,CH_2), 5.63(s,4H,CH_2),7.27(s,10H,Ph), 8.36(s,2H,CH)	574(1%),518(5%), 462(2%),91(100%)
2e	73	143–145 [Ethanol]	$C_{30}H_{34}N_4S_2$ (578.89)	Calcd. Found	62.25 62.07	5.92 5.94	9.68 9.56	1622	1.38(s,18H,CH_3),3.98(s,4H,CH_3), 1.38(s,18H,CH_3),3.98(s,4H,CH_2),	578(3%),561(100%), 465(15%)
2f	81	222–223 d [Dioxan]	$C_{40}H_{42}N_4S_2$ (642.94)	Calcd. Found	74.72 74.24	6.58 6.63	8.71 8.33	1622	1.00(s,18H,CH_3),4.12(s,4H,CH_2), 7.2–7.5(m,16H,Ph,),8.5–8.7(m,2H,Ph), 8.90(s,2H,CH)	644(2%),587(1%), 531(4%),352(82%), 296(100%[a])

[a] The FAB (fast atom bombardment) technique was used.

TABLE II. Spectroscopic and Mass Spectroscopic Data for Cu(II) Complexes.

Compound No.	Yield[a] %	Molecular formula (molecular mass)	UV(abs. ethanol) λ_{max} (nm) (lgϵ)	ESR[b]	MS(m/e) Peak matching[c] [Calcd./Found][d]
3a	50 40 min, A, C	$C_{14}H_{18}CuN_6S_2$ (398.00)	829(150)520sh(690), 441(1835),336(10000), 314(12300),284(19260)	$g_\parallel$ = 2.139 $g_\perp$ = 2.020 $A_\parallel^{Cu}$ = 18.4 mK $A_\parallel^{N}$ = 1.0 mK	401(5%),400(10%),399(55%), 398(19%),397(100%),232(20%), 230(41%) [397.03303/397.0334]
3b	79 30 min, A, C	$C_{24}H_{22}CuN_6S_2$ (521.14)	808(130),503sh(1015), 413(2330),314(11250), 272(40640)	$g_\parallel$ = 2.139 $g_\perp$ = 2.020 $A_\parallel^{Cu}$ = 17.6 mK $A_\parallel^{N}$ = 1.0 mK	522(31%),521(100%),294(52%), 525(7%),524(16%),523(56%), 292(14%) [521.06433/521.0672]
3c	98 30 min, A, C	$C_{24}H_{20}CuN_8O_4S_2$ (613.15)	772(50),510sh(340) 430sh(1140),322sh(11330), 312(12240)	$g_\parallel$ = 2.170 $g_\perp$ = 2.020 $A_\parallel^{Cu}$ = 17.0 mK	615(7%),614(17%),613(57%), 612(32%),609(111%),609(11%),339(16%), 337(28%) [6.11.044/611.0331]
3d	21 1 h, B, D	$C_{22}H_{20}CuN_8S_4$ (524.13)	530sh(77),439(2200) 346(11800),312(19469)	$g_\parallel$ = 2.158 $g_\perp$ = 2.019 $A_\parallel^{Cu}$ = 17.9 mK	526(5%),525(19%),524(9%), 523(29%),91(100%) [523.05483/523.0570]
3e	45 15 min, A, C,	$C_{22}H_{16}CuN_4S_2$ (528.18)	830(200),507sh(835), 409(7965),345sh(16700) 326sh(25700),307(35300)	$g_\parallel$ = 2.135 $g_\perp$ = 2.020 $A_\parallel^{Cu}$ = 17.5 mK	529(30%),528(15%),527(50%) 525(5%),103(100%) [526.95538/526.9565]
3f	47 1 h, A, C	$C_{32}H_{24}CuN_4S_2$ (592.21)	870(192),457(1865), 340sh(16300),302(45400)	$g_\parallel$ = 2.130 $g_\perp$ = 2.015 $A_\parallel^{Cu}$ = 18.1 mK	595(7%),594(18%),593(49%), 592(15%),591(100%),590(17%), 589(27%),329(31%),327(64%) [591.07383/591.0743]

[a] Reflux time in: A, 2-methoxyethanol; B, ethanol. Copper salt: C, cupric chloride; D, cupric trifluoroacetate.

[b] ESR measured in a frozen glass at liquid nitrogen temp. prepared from a 1:1:5 mixture of DMF, H_2O and CH_3OH.

[c] Reference for compounds **3a**, b, c, d and f: Heptacosafluorotributylamine, for compound 3e Perfluorokerosene.

[d] The isotropic patterns of the molecular ions are in accordance with the elemental composition in all cases. Reference 413.97755[411.04868/411.0480].

$C_{15}H_{20}CuN_6S_2$ (412.0). Peak match calcd. 411.0487, found 411.0188.

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