Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2018, **28**, 524–526
Mendeleev Communications

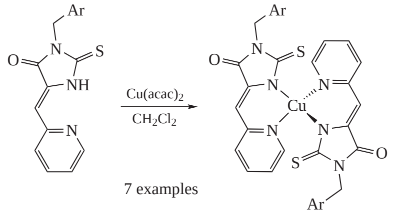
A convenient synthesis of copper(II) bis[5-(pyridin-2-ylmethylidene)-2-thiohydantoin] complexes

Irina A. Salimova, Anna V. Yudina, Andrei V. Mironov, Alexander G. Majouga, Nikolai V. Zyk and Elena K. Beloglazkina*

Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation.
E-mail: bel@org.chem.msu.ru

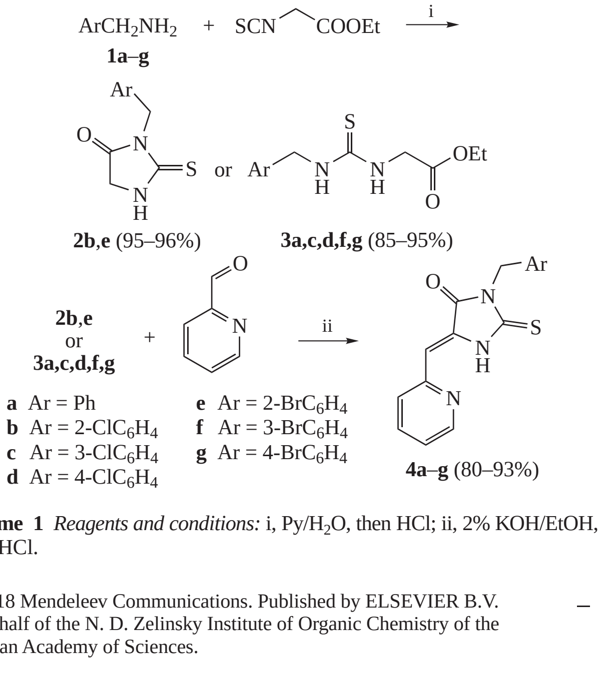
DOI: 10.1016/j.mencom.2018.09.025

A treatment of the ligands, 3-benzyl-substituted 5-(pyridin-2-ylmethylidene)-2-thioxoimidazolidin-4-ones, with Cu(acac)$_2$ in CH$_2$Cl$_2$ affords the mononuclear bis-ligand copper(II) complexes of the corresponding thiohydantoins.



Thiohydantoins and their hetarylmethylidene-substituted derivatives form with copper(II) ions complexes of various ligand coordination and denticity.[1–5] In particular, these ligands coordinate metal atoms in the form of monoanions formed upon deprotonation of the NH group.[6] If 5-positioned substituents in the thiohydantoin ring contain additional donor atoms, the metal coordination usually gives chelate six-membered metallacycles.[3,4,7–10] Such copper coordination compounds are of considerable interest as cytotoxic agents[11–13] and catalysts of redox reactions.[14–16] The coordination chemistry of heterocyclic thioamides has become topical in recent years because of their relevance to biological systems.[17–19] However, complexation with thiohydantoin ligands are often complicated by side reactions such as ligand transformation[9,19–21] or Cu^{II} reduction.[12–14,22]

Here, we describe a simple and convenient synthesis of copper(II) bis[5-(pyridin-2-ylmethylidene)-2-thiohydantoin] complexes depriving hydrolysis of the thiohydantoin moiety to hydantoin and reduction of Cu^{II} into Cu^{I}. The procedure is based on the interaction of the corresponding ligands with Cu(acac)$_2$ in CH$_2$Cl$_2$.



1a–g

2b,**e** (95–96%) or **3a**,**c**,**d**,**f**,**g** (85–95%)

2b,**e** or **3a**,**c**,**d**,**f**,**g**

4a–g (80–93%)

a Ar = Ph
b Ar = 2-ClC$_6$H$_4$
c Ar = 3-ClC$_6$H$_4$
d Ar = 4-ClC$_6$H$_4$
e Ar = 2-BrC$_6$H$_4$
f Ar = 3-BrC$_6$H$_4$
g Ar = 4-BrC$_6$H$_4$

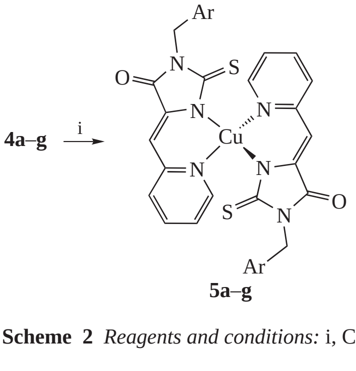
Scheme 1 *Reagents and conditions:* i, Py/H$_2$O, then HCl; ii, 2% KOH/EtOH, then HCl.

Analogously to published data,[23,24] addition of benzylic amines **1a–g** at ethyl isothiocyanatoacetate (Scheme 1) afforded thiohidantoins **2b**,**e** or thioureas **3a**,**c**,**d**,**f**,**g**, depending on the substituent in the benzylic moiety. 5-(Pyridin-2-ylmethylidene)-2-thiohydantoins **4a–g** were accessed *via* a base-catalyzed condensation of pyridine-2-carbaldehyde with 2-thiohydantoins **2** or thioureas **3**. Compounds **4a–g** were isolated as single *Z*-isomers whose configuration was derived from the chemical shift values of vinylic protons in ^{1}H NMR spectra.[23] The preferential formation of *Z*-isomers may result from the intramolecular hydrogen bond between the pyridine nitrogen atom and the N–H fragment of the thiohydantoin cycle. The *Z* configuration of ligand **4e** in its copper complex **5e** was ultimately confirmed by X-ray diffraction data (see below).

Copper complexes **5a–g** were prepared upon slow diffusion of diethyl ether into a dichloromethane solution of ligand **4a–g** and copper(II) acetylacetonate (Scheme 2). All coordination compounds were obtained as almost black microcrystals in yields not exceeding 60%.

Complexes **5** were characterized by UV-VIS spectroscopy and elemental analysis; the structure of complex **5e** was also confirmed by X-ray diffraction study.

The UV-VIS spectra of complexes **5** contain intensive broad adsorption bands in the UV region, which are similar to those in the UV spectrum of the corresponding ligands **4** and refer, most likely, to the π–π* and *n*–π* transitions in the organic fragment.[25,26] The peaks of the complexes are shifted relatively to the corresponding



4a–g

5a–g

5a Ar = Ph (20%)
5b Ar = 2-ClC$_6$H$_4$ (56%)
5c Ar = 3-ClC$_6$H$_4$ (46%)
5d Ar = 4-ClC$_6$H$_4$ (54%)
5e Ar = 2-BrC$_6$H$_4$ (20%)
5f Ar = 3-BrC$_6$H$_4$ (24%)
5g Ar = 4-BrC$_6$H$_4$ (20%)

Scheme 2 *Reagents and conditions:* i, Cu(acac)$_2$/CH$_2$Cl$_2$, then Et$_2$O.

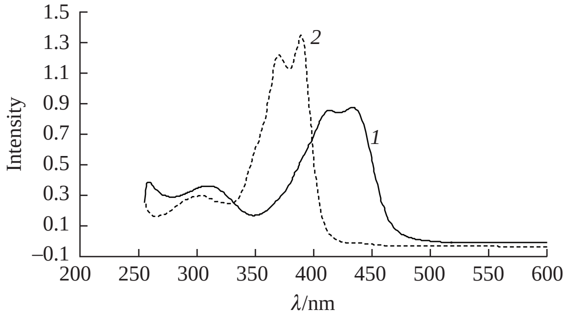


Figure 1 Electronic spectra of (*1*) complex **5e** and (*2*) corresponding ligand **4e** in 5×10^{-5} M DMF solutions.

peaks of their free ligands, and their intensity is decreased (Figure 1). The spectra of the complexes also contain very low-intensive absorption bands of *d*–*d* transitions in the visible spectral region at ~700–850 nm.

Such electronic spectra agree with the distorted tetrahedral coordination environment of copper(II) ions and are consistent with the X-ray data for complex **5e** (Figure 2).[†] The coordination geometry of the copper(II) atom represents the distorted tetrahedron. The metal atom is surrounded by four nitrogen atoms from two distinct ligand molecules which utilize their pyridine and thiohydantoin nitrogen atoms for coordination. Sulfur atoms of thiohydantoin ligands do not participate in the metal coordination. Both pyridylmethylidene-imidazolone moieties are coordinated to the metal atom through their nitrogen atoms with a formation of six-membered metallacycles. Pyridine and imidazole rings of the organic ligands are nearly coplanar.

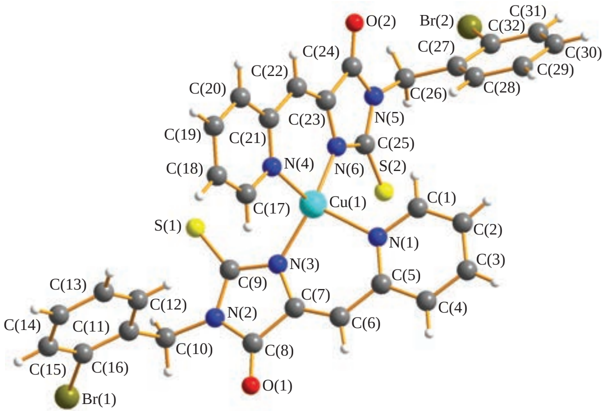


Figure 2 Molecular structure of compound **5e**. Relevant interatomic distances are given in Table S2 (see Online Supplementary Materials).

Table 1 Electrochemical potentials of compounds **4** and **5** *vs.* Ag/AgCl/KCl (aq., sat.), DMF, 0.1 M Bu_4NClO_4, glassy carbon electrode, potential scan rate 100 mV s^{-1}.

Compound	E_{pc}/V	$E_{1/2}^{Red}$/V	E_{pa}/V	$E_{1/2}^{Ox}$/V
Ligand **4b**	–1.07 –1.63 –1.84/–1.77	–0.77 –1.04 –1.69 –1.83	1.19 1.46 1.58	1.09 1.48
Complex **5b**	–0.12/+0.08, +0.13 –1.12 –1.28/–1.22 –1.86	–0.01 –1.11 –1.30 –1.52 –1.84	1.27	1.21
Ligand **4c**	–1.20 –1.92 –1.99	–1.12 –2.01	1.28 1.37	1.26
Complex **5c**	–0.40/–0.33 –1.31/–1.29 –1.46/–1.42 –1.92 –2.05/–1.81	–0.37 –1.28 –1.45 –1.66 –2.05	1.05 1.16 1.30 1.45	1.06 1.46
Ligand **4e**	–1.03 –1.78	–0.99 –1.77	1.05 1.14	1.11
Complex **5e**	–0.08/–0.08, +0.17 –1.10 –1.22/–1.16 –1.80/–1.70	–0.05 –1.19 –1.46 –1.80	1.11 1.49	1.11
Ligand **4f**	–1.08 –1.63 –1.84	–1.04 –1.68 –1.83	1.09 1.14	1.09
Complex **5f**	–0.09/–0.02, +0.18 –1.15 –1.26 –1.65 –1.84	–0.04 –1.23 –1.43 –1.80	1.17 1.52	1.08

Ligands **4b**,**c**,**e**,**f** and their complexes **5b**,**c**,**e**,**f** were studied by cyclic voltammetry (CV) and rotating disk electrode (RDE) voltammetry in DMF in the presence of 0.05 M Bu_4NClO_4 as the supporting electrolyte (Table 1, Figure 3, and Online Supplementary Materials). Ligands **4** undergo a two or three step reduction at the potentials from –1.07 to –1.99 V and are oxidized irreversibly at 1.06–1.48 V. Copper complexes **5** undergo a quasi-reversible two-electron cathodic redox transition at the potentials from –0.08 to –0.40 V; these processes are apparently copper based and correspond to $Cu^{II} \rightarrow Cu^{I}$ reduction [see Figure 3(*b*), peak 1]:

$$L_2Cu^{II} \xrightarrow[\text{peak 1}]{+\,e} L_2Cu^{I}$$

The subsequent peaks in cathodic region at the potentials from –1.10 to –2.05 V apparently correspond to the reduction of organic ligand fragment [see Figure 3(*b*), peaks 2 and 3]:

$$L_2Cu^{I} \xrightarrow[\text{peak 2}]{+\,e} L(L^{-\bullet})_2Cu^{I} \xrightarrow[\text{peak 3}]{+\,e} (L^{-\bullet})_2Cu^{I^{\cdot}}$$

This fact is supported by the absence of peaks of Cu^0 reductive desorption during the reverse anodic scans after the potential of second and third cathodic peaks. Importantly, copper precipitation on the electrode surface was never observed.

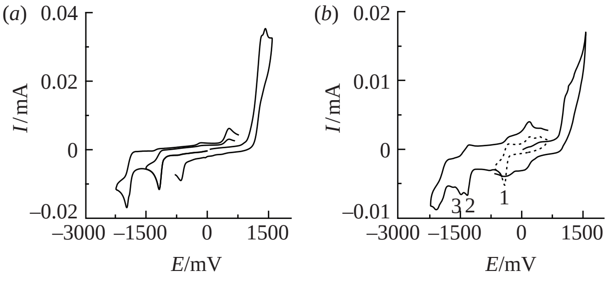


Figure 3 Cyclic voltammograms for (*a*) ligand **4b** and (*b*) its complex **5b**, glassy carbon electrode, DMF (5×10^{-4} M), Bu_4NClO_4.

[†] *Crystallographic data for complex* **5e**. $C_{33}H_{24}Br_2CuN_6O_2S_2 \cdot CH_2Cl_2$, ($M_r = 895$), tetragonal, space group $P4/n$, $a = 31.6531(6)$ and $c = 7.7612(7)$ Å, $V = 7776.1(7)$ nm^3, $Z = 8$, $d_{calc} = 1.528$ g cm^{-3}, $F(000) = 3544.00$, the final $R = 1.151$, $wR = 0.1783$ and $S = 1.151$ for 4034 observed reflections with $I > 2\sigma(I)$. The measurements were performed on a STOE STADI VARI PILATUS-100 K with graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods, and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with SHELXTL using full-matrix least-squares procedures based on F^2 values.[27] Hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on the parent atoms. For more details, see Online Supplementary Materials.

CCDC 1835050 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.

Note that the reduction peaks for coordinated ligand fragment in copper-containing complexes are doubled [see Figure 3(*b*) and Table 1]. This can be explained by the fact that two organic fragments in copper(I)-containing intermediates are conjugated *via* copper atoms, and therefore, they are reduced stepwise at different potentials.

In summary, we have prepared and characterized new copper(II) complexes with anionic thiohydantoin type ligand. The synthesis is experimentally simple and allows one to avoid the undesirable hydrolysis of thiohydantoin fragment and reduction of copper ions in the course of complex formation. The complexes obtained are prospective for the studying of biological activity.

This work was supported by the Russian Foundation for Basic Research (grant no. 16-03-00921) and carried out using equipment acquired at the expense of the M. V. Lomonosov Moscow State University development program.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.09.025.

References

1 A. Ahmedova, P. Marinova, G. Tyuliev and M. Mitewa, *Inorg. Chem. Commun.*, 2008, **11**, 545.

2 S. S. Kandil, G. B. El-Hefnawy and E. A. Baker, *Thermochim. Acta*, 2004, **414**, 105.

3 M. M. Chowdhry, D. M. Mingos, A. J. White and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 2001, **20**, 3495.

4 M. M. Chowdhry, A. D. Burrows, D. M. P. Mingos, A. J. White and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1995, 1521.

5 E. K. Beloglazkina, A. G. Majouga, A. A. Moiseeva, M. G. Tsepkov and N. V. Zyk, *Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 351 (*Izv. Akad. Nauk, Ser. Khim.*, 2007, 339).

6 M. Arca, F. Demartin, F. A. Devillanova, A. Garau, F. Isaia, V. Lippolis and G. Verani, *Inorg. Chem.*, 1998, **37**, 4164.

7 J. S. Casas, E. E. Castellano, A. Macias, N. Playa, A. Sánchez, J. Sordo, J. M. Varela and J. Zukerman-Schpector, *Inorg. Chim. Acta*, 1995, **238**, 129.

8 K. I. Tischenko, E. K. Beloglazkina, M. A. Proskurnin, A .G. Majouga, M. E. Muratova, D. A. Skvortsov and N. V. Zyk, *Russ. Chem. Bull., Int. Ed.*, 2016, **65**, 1254 (*Izv. Akad. Nauk, Ser. Khim.*, 2016, 1254).

9 A. G. Majouga, E. K. Beloglazkina, A. V. Yudina, A. V. Mironov and N. V. Zyk, *Inorg. Chem. Commun.*, 2015, **51**, 114.

10 E. K. Beloglazkina, A. G. Majouga, I. V. Yudin, N. A. Frolova, N. V. Zyk, V. D. Dolzhikova, A. A. Moiseeva, R. D. Rakhimov and K. P. Butin, *Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 1015 (*Izv. Akad. Nauk, Ser. Khim.*, 2006, 978).

11 O. O. Krasnovskaya, Y. V. Fedorov, V. M. Gerasimov, D. A. Skvortsov, A. A. Moiseeva, A.V. Mironov, E. K. Beloglazkina, N. V. Zyk and A. G. Majouga, *Arab. J. Chem.*, DOI: 10.1016/j.arabjc.2016.04.013.

12 A. G. Majouga, M. I. Zvereva, M. P. Rubtsova, D. A. Skvortsov, A. V. Mironov, D. M. Azhibek, O. O. Krasnovskaya, V. M. Gerasimov, A. V. Udina, N. I. Vorozhtsov, E. K. Beloglazkina, L. Agron, L. V. Mikhina, A. V. Tretyakova, N. V. Zyk, N. S. Zefirov, A. V. Kabanov and O. A. Dontsova, *J. Med. Chem.*, 2014, **57**, 6252.

13 K. Tishchenko, E. Beloglazkina, M. Proskurnin, V. Malinnikov, D. Guk, M. Muratova, O. Krasnovskaya, A. Udina, D. Skvortsov, R. R. Shafikov, Y. Ivanenkov, V. Aladinskiy, I. Sorokin, O. Gromov, A. Majouga and N. Zyk, *J. Inorg. Biochem.*, 2017, **175**, 190.

14 A. G. Majouga, E. K. Beloglazkina, A. A. Moiseeva, O. V. Shilova, E. A. Manzheliy, M. A. Lebedeva, E. S. Davies, A. N. Khlobystov and N. V. Zyk, *Dalton Trans.*, 2013, **42**, 6290.

15 E. K. Beloglazkina, O. Yu. Kuznetsova, A. G. Majouga, A. A. Moiseeva and N. V. Zyk, *Mendeleev Commun.*, 2014, **24**, 37.

16 E. K. Beloglazkina, A. G. Majouga, A. A. Moiseeva, N. V. Zyk and N. S. Zefirov, *Mendeleev Commun.*, 2009, **19**, 69.

17 E. S. Raper, *Coord. Chem. Rev.*, 1994, **129**, 91.

18 B. Krebs and G. Henkel, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 769.

19 E. K. Beloglazkina, A. G. Majouga, A. V. Mironov, A. V. Yudina, O. Y. Kuznetsova and N. V. Zyk, *Polyhedron*, 2014, **76**, 45.

20 E. K. Beloglazkina, A. G. Majouga, A. V. Mironov, A. V. Yudina, A. A. Moiseeva, M. A. Lebedeva, A. N. Khlobystov and N. V. Zyk, *Polyhedron*, 2013, **63**, 15.

21 E. K. Beloglazkina, N. I. Vorozhtsov, L. A. Sviridova, O. S. Grogorkevich, D. D. Korablina, A. A. Moiseeva, N. V. Zyk and A. G. Majouga, *Inorg. Chem. Commun.*, 2016, **71**, 86.

22 A. V. Mironov, E. V. Antipov, E. K. Beloglazkina, A. G. Majouga, O. O. Krasnovskaya, V. M. Gerasimov and N. V. Zyk, *Russ. Chem. Bull., Int. Ed.*, 2013, **62**, 672 (*Izv. Akad. Nauk, Ser. Khim.*, 2013, 671).

23 A. G. Majouga, E. K. Beloglazkina, S. Z. Vatsadze, N. A. Frolova and N. V. Zyk, *Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 2850 (*Izv. Akad. Nauk, Ser. Khim.*, 2004, 2734).

24 A. I. Khodair, *Carbohydr. Res.*, 2001, **331**, 445.

25 J. C. Jeffery, T. Riis-Johannessen, C. J. Anderson, C. J. Adams, A. Robinson, S. P. Argent, M. D. Ward and C. R. Rice, *Inorg. Chem.*, 2007, **46**, 2417.

26 A. Shah, E. Nosheen, S. Munir, A. Badshah, R. Qureshi, Z. U. Rehman, N. Muhammad and H. Hussain, *J. Photochem. Photobiol. B*, 2013, **120**, 90.

27 G. M. Sheldrick, *Acta Crystallogr.*, 2008, **A64**, 112.

Received: 6th April 2018; Com. 18/5531