

Designing a Phosphino-Thiosemicarbazone Ligand Capable to Stabilize Coinage Metal Ions [†]

Isabel Velo-Helena ¹, Sandra Fernández-Fariña ¹, Lara Rouco ², Miguel Martínez-Calvo ^{1,*} and Rosa Pedrido ^{1,*}

¹ Departamento de Química Inorgánica, Facultad de Química, Campus Vida, Universidade de Santiago de Compostela, Santiago de Compostela 15782, Spain; mariaisabel.velo.helena@usc.es (I.V.-H.); e-mail@e-mail.com (S.F.-F.)

² affiliations; e-mail@e-mail.com

* Correspondence: miguel.martinez.calvo@usc.es (M.M.-C.); rosa.pedrido@usc.es (R.P.)

[†] Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry; Available online: <https://ecsoc-26.sciforum.net>.

Abstract: Thiosemicarbazones are interesting organic skeletons due to their great coordinative versatility, their interesting biological and pharmacological properties, as well as their structural diversity. However, the isolation of their monovalent coinage metal complexes, such as Cu(I), Ag(I) or Au(I), is a partially studied field, since co-ligands with soft donor atoms such as phosphines, are required. In this context, our research group has been studying a new family of ligands capable of stabilising coinage complexes without the need for auxiliary co-ligands. To this end, it was decided to incorporate a phosphorus atom into the structure of a thiosemicarbazone kernel. This work presents the design, synthesis and structural characterisation of a new phosphino-thiosemicarbazone ligand.

Keywords: ligand; thiosemicarbazone; phosphine; coinage metal ions

Citation: Velo-Helena, I.; Fernández-Fariña, S.; Rouco, L.; Martínez-Calvo, M.; Pedrido, R. Designing a Phosphino-Thiosemicarbazone Ligand Capable to Stabilize Coinage Metal Ions. *Chem. Proc.* **2022**, *4*, x. <https://doi.org/10.3390/xxxxx>

Academic Editor(s): Julio A. Seijas

Published: 15 November 2022

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1. Introduction

Among the wide variety of organic skeletons reported to date, thiosemicarbazone ligands must be highlighted due to their interesting biological and pharmacological properties, as well as their structural diversity [1]. Nevertheless, in order to obtain their monovalent metal complexes, such as Cu(I) [2], Ag(I) or Au(I) [3], auxiliary co-ligands incorporating soft donor atoms were needed.

At this point, in the last few years we have designed and prepared a new family of thiosemicarbazone ligands featuring a phosphine unit [4]. The phosphino-thiosemicarbazone ligands were capable of stabilising M(I) complexes without the need for auxiliary co-ligands. For further study, we report herein the design, synthesis and structural characterisation of a new phosphino-thiosemicarbazone ligand functionalized with a nitro-phenyl ring. (Figure 1).

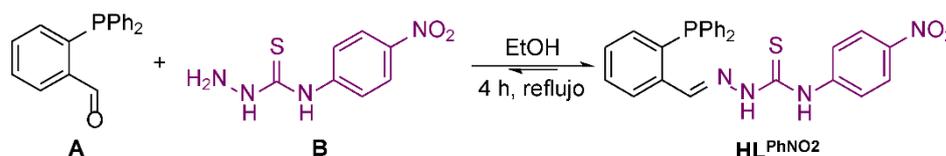


Figure 1. Synthesis of the phosphino-thiosemicarbazone ligand HL^{PhNO_2} .

2. Experimental Section

The new phosphino-thiosemicarbazone ligand $\text{HL}^{\text{PhNO}_2}$ has been carried out by means of imine condensation reaction (Figure 1). First, 2-diphenylphosphinobenzaldehyde (A) (0.50 g, 1.7 mmol) and 4-(4-Nitrophenyl)thiosemicarbazide (B) (0.72 g, 3.4 mmol) were mixed and dissolved in absolute ethanol. Then a catalytic amount of p-toluensulfonic acid was added to promote imine bonds formation. The reaction mixture was refluxed for 4 h using a Dean–Stark trap to remove the released water. The final white crystalline precipitate was isolated by concentration, filtration and washed with diethylether, giving rise to required $\text{HL}^{\text{PhNO}_2}$.

$\text{HL}^{\text{PhNO}_2}$: Yield 1.498 g, (91%). Elemental analysis, Calc. for $\text{C}_{26}\text{H}_{21}\text{N}_4\text{O}_2\text{PS}$: C, 64.5; H, 4.4; N, 11.6; S, 6.6. Found: C, 64.3; H, 4.4; N, 11.4; S, 6.3 %. MS ESI^+ (m/z): 483.1 [HL-H] $^-$. IR (KBr, cm^{-1}): ν IR (KBr, cm^{-1}): $\nu(\text{N-H})$ 3302 (d), $\nu(\text{C=N} + \text{C-N})$ 1539 (mf), 1514 (f), 1435 (m), $\nu(\text{NO}_2)$ 1333 (mf) $\nu(\text{C=S})$ 1111 (m), 748 (m). RMN ^1H (300 MHz, DMSO-d_6): δ/ppm , 12.30 (s, 1H, -NH), 10.33 (s, 1H, -NH), 8.87 (d, $J=4.9$ Hz, 1H), 8.48–6.82 (m, 18H, Ar-H). RMN ^{13}C (126 MHz, DMSO-d_6): δ/ppm , 175.24 (C=S), 145.22 (C=N), 143.47–123.76 (C-Ar). RMN ^{31}P (202 MHz, DMSO-d_6): δ/ppm , -12.76.

3. Results and Discussion

$\text{HL}^{\text{PhNO}_2}$ was characterized by the usual techniques for organic compounds. Analytical data are consistent with the ligand stoichiometry. IR spectrum shows the bands corresponding to the NH group at 3302 cm^{-1} , to the imine bond at 1539 , 1514 and 1435 cm^{-1} (Figure 2) and to the C=S thioamide group at 1111 and 748 cm^{-1} . MS ESI^+ exhibits a peak at $483.1(m/z)$ consistent with the monodeprotonated ligand molecule. Suitable crystals for X-ray diffraction were also obtained. The crystal structure corresponds with the oxidised $\text{HL}^{\text{PhNO}_2}$ ligand, that is shown in Figure 3. Main crystallographic data are summarised in Table 1 whereas bond lengths and angles are listed in Table 2. All bond distances and angles are in the order of those found in the literature for thiosemicarbazone and phosphine ligands and do not merit further discussion [4].

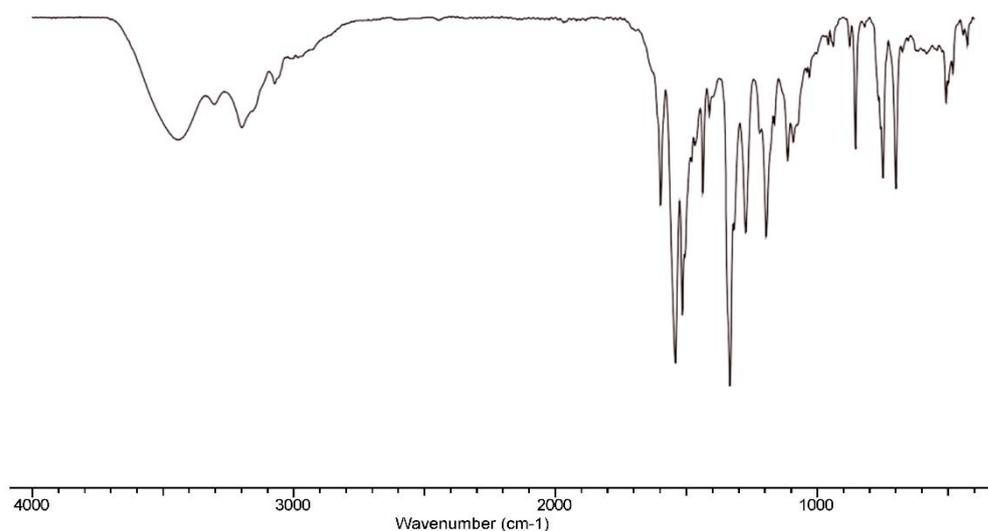


Figure 2. IR spectrum (cm^{-1}) of the phosphino-thiosemicarbazone ligand $\text{HL}^{\text{PhNO}_2}$.

The asymmetric unit of the $\text{HL}^{\text{PhNO}_2}$ ligand consists of a ligand molecule showing an E conformation with respect to the imine group. In addition, the phosphine skeleton and the thiosemicarbazone branch are oriented towards the same side giving rise to a *syn* conformer. (Figure 3).

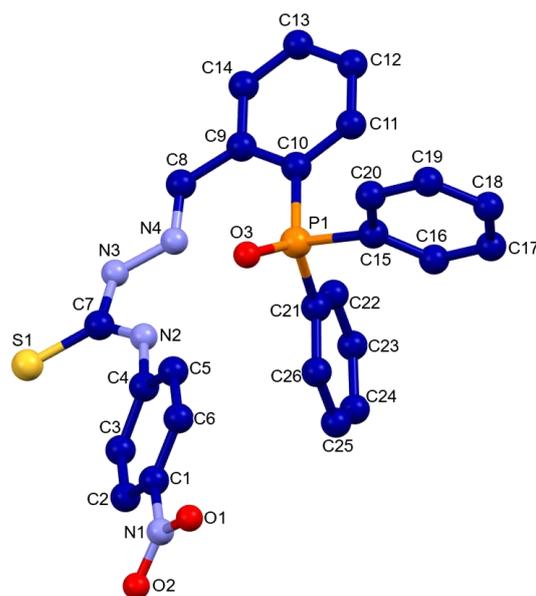


Figure 3. Crystal structure of the phosphino-thiosemicarbazone ligand $\text{HL}^{\text{PhNO}_2}$.

Table 1. Main crystallographic data for $\text{HL}^{\text{PhNO}_2}$.

Crystallographic Data	
Formula	C ₂₆ H ₂₁ N ₄ O ₂ ·3.0PS
Molecular weight	489.3
Crystal system	Monoclinic
Crystal size/mm	0.70 × 0.11 × 0.03
Volume/Å ³	2327.1(3)
Space group	P2 ₁ /n
Z	4
a/Å	13.7284(8)
b/Å	7.2366(5)
c/Å	23.5622(14)
α/°	90
β/°	96.214(3)
γ/°	90
d/g·cm ⁻³	1.383
μ/mm ⁻¹	0.191
F(000)	432
Interval θ/°	2.41–28.13
Measured reflexions	33,552
Independent reflexions [R _{int}]	5787 [0.0396]
Residues/e·Å ⁻³	0.58 and -0.29
R	0.0392
wR	0.0889

Table 2. Selected bond length (Å) and angles (°) for $\text{HL}^{\text{PhNO}_2}$.

Main Bond Distances (Å)			
C8-N4	1.271(2)	C10-P1	1.843(1)
N4-N3	1.376(2)	P1-C21	1.823(1)
N3-C7	1.356(2)	C8-C9	1.452(2)
C7-S1	1.683(2)	P1-C15	1.826(2)

N1-O1	1.227(2)	P1-O3	1.377(4)
C7-N2	1.346(2)	C1-N1	1.463(2)
N4-C8	1.271(2)	N1-O2	1.229(2)
Main Bond Angles (°)			
C8-N4-N3	117.7(1)	O2-N1-O1	123.6(2)
N4-N3-C7	119.2(1)	C10-P1-C15	101.27(7)
N3-C7-S1	118.7(1)	C21-P1-C10	103.88(7)
N2-C7-N3	114.0(1)	C21-P1-C15	102.48(7)
N2-C7-S1	127.3(1)		

The $\text{HL}^{\text{PhNO}_2}$ ligand has crystallised with the phosphorus atom oxidised. This fact causes intramolecular hydrogen bonds to be established (Figure 4) involving the hydrogen in the thioamide position [N2-H2N...O1 2.795 Å], which possibly condition the *syn* arrangement adopted by the phosphine skeleton and the thiosemicarbazone branch. In addition, intermolecular hydrogen bonds established by the thioamide sulphur and and the hydrazide hydrogen atoms allow the interaction between two neighbouring ligand molecules [N3-H3N...S1 3.461(2) Å].

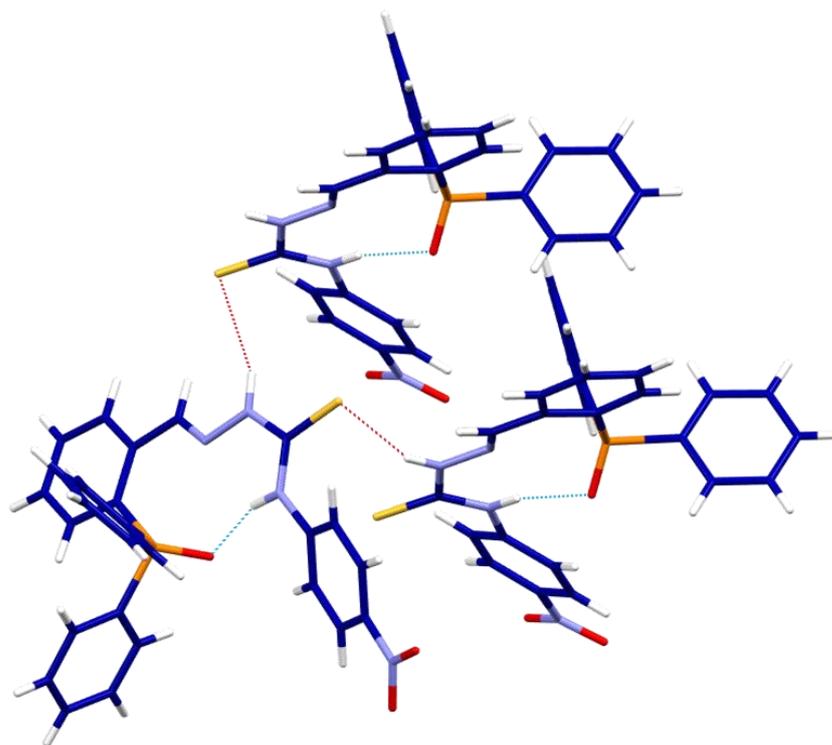


Figure 4. Intra- (light blue) and intermolecular (red) hydrogen bonds $\text{HL}^{\text{PhNO}_2}$.

The $\text{HL}^{\text{PhNO}_2}$ structure in the solid state is worthy of analysis for comparative purposes between the free ligand or when it is bound to different metal ions. By observing its arrangement, it should be noted that the O/S donor atoms are oriented in opposite directions. For this reason, a previous conformational rotation would be necessary to achieve both atoms coordination to the same metal ion.

4. Conclusions

The new phosphine-thiosemicarbazone ligand $\text{HL}^{\text{PhNO}_2}$ has been isolated in high purity and yield. Its crystal structure shows an opposite orientation of oxygen and sulphur

donor atoms, which would imply a conformational rotation prior to coordination to the same metal ion.

References

- (a) Liberta, A.E.; West, D.X. Antifungal and antitumor activity of heterocyclic thiosemicarbazones and their metal complexes: Current status. *BioMetals* **1992**, *5*, 121–126. <https://doi.org/10.1007/bf01062223>; (b) Hu, W.X.; Zhou, W.; Xia, C.N.; Wen, X. Synthesis and anticancer activity of thiosemicarbazones. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2213–2218, <https://doi.org/10.1016/j.bmcl.2006.01.048>; (c) Bal, T.R.; Anand, B.; Yogeewari, P.; Sriram, D. Synthesis and evaluation of anti-HIV activity of isatin β -thiosemicarbazone derivatives. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4451–4455, <https://doi.org/10.1016/j.bmcl.2005.07.046>; (d) Bajaj, K.; Buchanan, R.M.; Grapperhaus, C.A. Antifungal activity of thiosemicarbazones, bis(thiosemicarbazones), and their metal complexes. *J. Inorg. Biochem.* **2021**, *225*, 111620, <https://doi.org/10.1016/j.jinorgbio.2021.111620>; (e) Gonçalves, A.C.R.; Carneiro, Z.A.; Oliveira, C.G.; Danuello, A.; Guerra, W.; Oliveira, R.J.; Ferreira, F.B.; Veloso-Silva, L.L.W.; Batista, F.A.H.; Borges, J.C.; de Albuquerque, S.; Deflon, V.M.; Maia, P.I.S. Pt(II), Pd(II) and Au(III) complexes with a thiosemicarbazone derived from diacetylmonooxime: Structural analysis, trypanocidal activity, cytotoxicity and first insight into the antiparasitic mechanism of action. *Eur. J. Med. Chem.* **2017**, *141*, 615–631. <https://doi.org/10.1016/j.ejmech.2017.10.013>.
- Lobana, T.S.; Rekha; Butcher, R.J.; Castiñeiras, A.; Bermejo, E.; Bharatam, P.V. Bonding Trends of Thiosemicarbazones in Mononuclear and Dinuclear Copper(I) Complexes: Syntheses, Structures, and Theoretical Aspects. *Inorg. Chem.* **2006**, *45*, 1535–1542. <https://doi.org/10.1021/ic051018j>.
- (a) Casas, J.S.; Castellano, E.E.; Couce, M.; Ellena, D.J.; Sánchez, A.; Sordo, J.C.; Taboada, J. A gold(I) complex with a vitamin K3 derivative: Characterization and antitumoral activity. *Inorg. Biochem.* **2006**, *100*, 1858–1860. <https://doi.org/10.1016/j.jinorgbio.2006.07.006>; (b) Lobana, T.S.; Khanna, S.; Butcher, R.J. Synthesis of a fluorescent gold(I) complex with a thiosemicarbazone, [Au₂(3-NO₂-Hbtsc)₄]Cl₂ · 2CH₃CN. *Inorg. Chem. Commun.* **2008**, *11*, 1433–1435. <https://doi.org/10.1016/j.inoche.2008.09.023>; (c) Molter, A.; Rust, J.; Lehmann, C.W.; Deepa, G.; Chiba, P.; Mohr, F. Synthesis, structures and anti-malaria activity of some gold(I) phosphine complexes containing seleno- and thiosemicarbazonato ligands. *Dalton Trans.* **2011**, *40*, 9810–9820. <https://doi.org/10.1039/c1dt10885a>.
- (a) Castiñeiras, A.; Pedrido, R.; Pérez-Alonso, G. A Convenient Mode to Stabilize MI Metal Ions by Using Thiosemicarbazones. *Eur. J. Inorg. Chem.* **2008**, *32*, 5106–5111. <https://doi.org/10.1002/ejic.200800708>; (b) Castiñeiras, A.; Pedrido, R. Novel Fluorescent Cationic Silver Thiosemicarbazone Clusters Containing Different Eight-Membered Ag₄S₄ Metallacycles. *Inorg. Chem.* **2009**, *48*, 4847–4855, <https://doi.org/10.1021/ic900062y>; (c) Castiñeiras, A.; Pedrido, R. A thiosemicarbazone ligand functionalized by a phosphine group: Reactivity toward coinage metal ions. *Dalton Trans.* **2010**, *39*, 3572–3584, <https://doi.org/10.1039/b918962a>; (d) Castiñeiras, A.; Pedrido, R.; Auroliphlicity in gold(I) thiosemicarbazone clusters. *Dalton Trans.* **2012**, *41*, 1363–1372, <https://doi.org/10.1039/c1dt11680k>. (e) González-Barcia, L.M.; Romero, M.J.; González Noya, A.M.; Bermejo, M.R.; Maneiro, M.; Zaragoza, G.; Pedrido, R. The Golden Method Electrochemical Synthesis Is an Efficient Route to Gold Complexes. *Inorg. Chem.* **2016**, *55*, 7823–7825, <https://doi.org/10.1021/acs.inorg-chem.6b01362>.