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Preparation of Novel Complexes Bearing Diphosphine (dppm) Derived from Thiosemicarbazone Palladacycles †

Sara Bermúdez-Fernández *, Raquel Diz-Gil, Paula Munín-Cruz, Marcos Rúa-Sueiro, Juan M. Ortigueira and José M. Vila

Department of Inorganic Chemistry, University of Santiago de Compostela, Spain

* Correspondence: sarabegona.bermudez@rai.usc.es

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Abstract: The synthesis of palladium cyclometallated compounds with thiosemicarbazone ligands is described, as well as their reactivity with bidentate phosphine ligands. The synthesis of the ligands was carried out by a condensation reaction between a ketone and a thiosemicarbazide. Subsequently, metalation proceeds and the resulting product is reacted with bis(diphenylphosphino)methane (dppm) under the appropriate conditions to yield the compound with monocoordinated diphosphine.

Keywords: thiosemicarbazone; palladium; organometallic

1. Introduction

Thiosemicarbazones are compounds with the structure shown in Figure 1. They present different modes of coordination and give complexes with a wide spectrum of biological properties, such as antitumor, antifungal or antimicrobial [1].

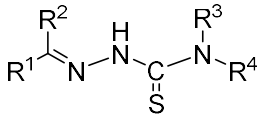


Figure 1. Structure of thiosemicarbazone.

Their applications are one of the main reasons to study this kind of ligands. Among the different organometallic compounds with thiosemicarbazones, palladium(II) and platinum(II) compounds are of special interest because of their square-planar structure [2–4].

Herein, the synthesis of several cyclometallated compounds derived from thiosemicarbazone ligands is presented. The mechanism of metallation was described by Trofimenko [5].

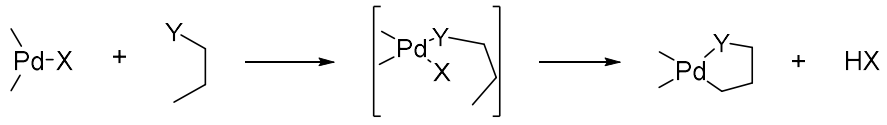


Figure 2. Cyclometallation reaction.

2. Materials and Methods

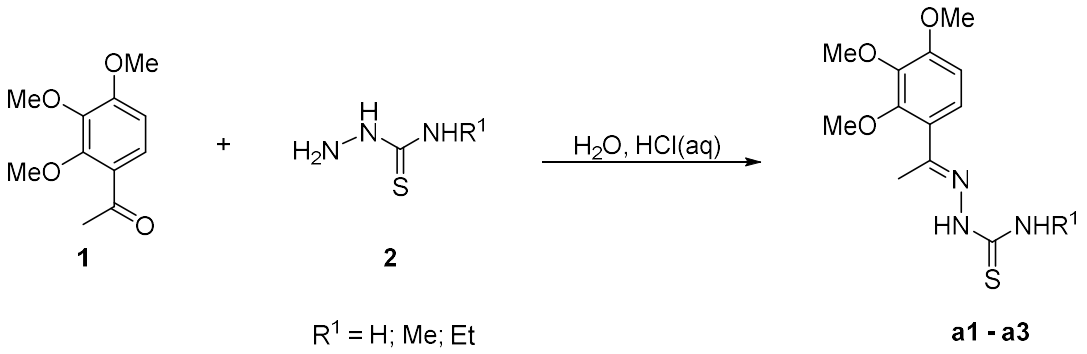
2.1. Materials and General Methods

All chemical reagents and solvents were commercial products that were used as received. Elemental analysis of C, H, N, and S were performed in a THERMO FINNIGAN FLASH 1112 analyzer model. IR analyses were recorded in a JASCO FT/IR-4600 spectrophotometer working in the ATR mode. ^{1}H-NMR and ^{31}P-{^{1}H}-NMR were recorded in a Varian Inova 400.

2.2. Synthesis and Characterization

2.1.1. Synthesis of Thiosemicarbazone Ligands

The thiosemicarbazones were prepared by condensation reactions between a ketone and a thiosemicarbazide and obtained as described in the literature [6] (Scheme 1). The ligands **a1-a3** were satisfactorily characterized by elemental analysis, IR, and ^{1}H-NMR.



Scheme 1. Synthesis of thiosemicarbazone ligand.

To a solution of thiosemicarbazide (**2**) (4,218 mmol) in water (40 cm^{3}) $HCl_{(aq)}$ was added until complete solution. Then, the corresponding amount of ketone (**1**) (4,218 mmol) was incorporated. The mixture was stirred for 4 h at room temperature. The white solid formed was collected by filtration and dried under vacuum.

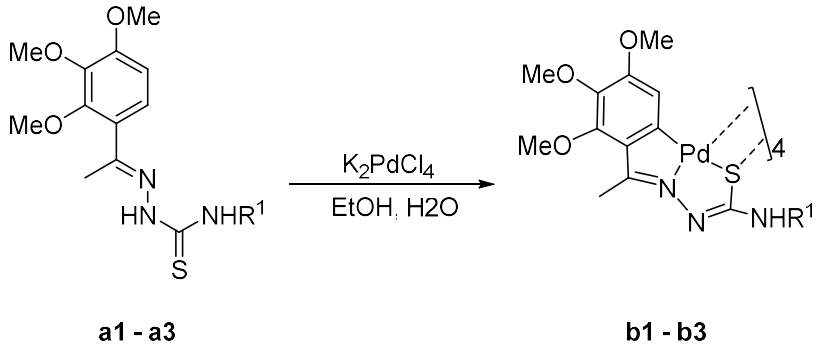
a1: Yield: 95%. Elemental Anal. Calc. $C_{12}H_{17}N_3O_3S$ (283,35): C 50.9, N 14.8, H 6.1, S 11.3%. Found: C 49.5, N 13.8, H 6.0, S 14.6%. IR (ATR, $\tilde{\nu}$/cm^{-1}): 826 (C=S), 1594 (C=N), 3359, 3258, 3172 (N-H). ^{1}H-NMR (DMSO-d_6, δ/ppm): 10,13 (s, 1H, NNH), 8,18 (s, 1H, NH_2), 7,61 (s, 1H, NH_2), 7,20 (d, ^{3}J = 8,7 Hz, 1H, H^{6}), 6,79 (d, ^{3}J = 8,8 Hz 1H, H^{5}), 3,81 (s, 3H, OMe), 3,78 (s, 3H, OMe), 3,74 (s, 3H, OMe), 2,27 (s, 3H, MeCN).

a2: Yield: 98%. Elemental Anal. Calc. $C_{13}H_{19}N_3O_3S$ (297,37): C 52.5, N 14.1, H 6.4, S 10.8%. Found: C 52.6, N 13.9, H 6.6, S 10.7%. IR (ATR, $\tilde{\nu}$/cm^{-1}): 811 (C=S), 1590 (C=N), 3331, 3196 (N-H). ^{1}H-NMR (DMSO-d_6, δ/ppm): 10,12 (s, 1H, NNH), 8,23 (m, 1H, NHMe), 7,18 (d, ^{3}J = 8,7 Hz, 1H, H^{6}), 6,80 (d, ^{3}J = 8,7 Hz, 1H, H^{5}), 3,81 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.75 (s, 3H, OMe), 2,98 (d, ^{3}J = 4,5 Hz, 3H, NHMe), 2,22 (s, 3H, MeCN).

a3: Yield: 97%. Elemental Anal. Calc. $C_{14}H_{21}N_3O_3S$ (311,40): C 54.0, N 13.5, H 6.8, S 10.3%. Found: C 54.2, N 13.5, H 6.9, S 10.6%. IR (ATR, $\tilde{\nu}$/cm^{-1}): 806 (C=S), 1592 (C=N), 3345, 3208, (N-H). ^{1}H-NMR (DMSO-d_6, δ/ppm): 10,05 (s, 1H, NNH), 8,25 (m, 1H, NHCH_2CH_3), 7,17 (d, ^{3}J = 8,7 Hz, 1H, H^{6}), 6,81 (d, ^{3}J = 8.7 Hz, 1H, H^{5}), 3,81 (s, 3H, OMe), 3,78 (s, 3H, OMe), 3,75 (s, 3H, OMe), 3,64–3,46 (m, 2H, NH$CH_2$$CH_3$), 2,22 (s, 3H, MeCN), 1,11 (t, ^{3}J = 7,0 Hz, 3H, NHCH$_2$$CH_3$).

2.1.2. Synthesis of Cyclometallated Compounds

Cyclometallated compounds (**b1-b3**) were prepared by reaction of potassium tetrachloropalladate and the corresponding thiosemicarbazone ligand (**a1-a3**) in ethanol/water. Metallation under these conditions gave the tetranuclear compounds. With the ligand as tridentate [*C, N, S*] (Scheme 2). The compounds **b1-b3** were fully characterized by elemental analysis, IR, and ^{1}H-NMR.



Scheme 2. Synthesis of cyclometallated compounds behavior thiosemicarbazone ligand.

A solution of potassium tetrachloropalladate (II) (0,7658 mmol, 0,250 g) in water (7 cm^3), was added in ethanol (40 cm^3), and a yellow suspension was formed. Then, the thiosemicarbazone ligand (**a1-a3**) (0,7659 mmol) was incorporated. The mixture was stirred for 24 h at room temperature. A yellow solid was formed, which was centrifuged and recrystallized from dichloromethane-hexane and dried under vacuum.

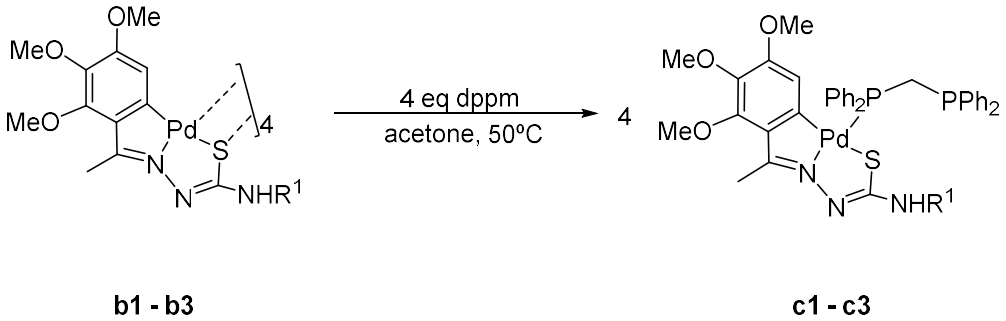
b1: Yield: 43%. Elemental Anal. Calc. $[C_{12}H_{15}N_3O_3PdS]_4$ (1551,00): C 37.2, N 10.8, H 3.9, S 8.3%. Found: C 36.3, N 10.0, H 3.9, S 10.3%. IR (ATR, $\tilde{\nu}/cm^{-1}$): 1579 (C=N), 3319, 3209 (N-H). ^{1}H-NMR (DMSO-d_6, δ/ppm): 6,78 (s, 1H, H^5), 6,41 (s, 2H, N$\underline{H}_2$), 3,80 (s, 3H, OMe), 3,62 (s, 3H, OMe), 3,58 (s, 3H, OMe), 1,92 (s, 3H, $\underline{Me}$CN).

b2: Yield: 48%. Elemental Anal. Calc. $[C_{13}H_{17}N_3O_3PdS]_4$ (1607,12): C 38.9, N 10.5, H 4.3, S 8.0%. Found: C 40.3, N 9.1, H 4.9, S 7.0%. IR (ATR, $\tilde{\nu}/cm^{-1}$): 1560 (C=N), 3246 (N-H). ^{1}H-NMR (DMSO-d_6, δ/ppm): 7,16 (s, 1H, H^5), 6,85 (m, 1H, $NHCH_3$), 3,92 (s, 3H, OMe), 3,82 (s, 3H, OMe), 3,75 (s, 3H, OMe), 2,00 (s, 3H, MeCN), 1,25 (t, ^3J = 6,9 Hz, 3H, $NHCH_3$).

b3: Yield: 50%. Elemental Anal. Calc. $[C_{14}H_{19}N_3O_3PdS]_4$ (1663,20): C 40.4, N 10.1, H 4.6, S 7.7%. Found: C 39.8, N 9.9, H 4.6, S 7.0%. IR (ATR, $\tilde{\nu}/cm^{-1}$): 1558 (C=N), 3291 (N-H). ^{1}H-NMR (DMSO-d_6, δ/ppm): 6,85 (s, 1H, H^5), 6,49 (m, 1H, $NHCH_2CH_3$), 4,26 (m, 2H, $NHCH_2CH_3$), 3,82 (s, 3H, OMe), 3,69 (s, 3H, OMe), 3,59 (s, 3H, OMe), 2,02 (s, 3H, MeCN), 1,10 (m, 3H, $NHCH_2CH_3$).

2.1.3. Study the Reactivity of Cyclometallated Compound with Diphosphine dppm

To study the reactivity of these compounds the diphosphine, dppm, was chosen. The reaction was performed according to the literature procedure [7] to give a mononuclear compound (Scheme 3). The compounds **c1-c3** were satisfactorily characterized by elemental analysis, ^{1}H-NMR and ^{31}P-{^{1}H}-NMR.



Scheme 3. Synthesis of mononuclear cyclometallated compound with dppm ligand.

The phosphine (dppm) (0.1041 mmol, 0.040 g) and the corresponding tetranuclear compound (0,0260 mmol) were added in a flask. Then, 3 vacuum—nitrogen cycles were done. After this, deoxygenated acetone was added (18 cm^3), and the mixture stirred at 50 °C for 4 h. The resulting solution was recrystallized from dichloromethane-hexane and dried under vacuum.

c1: Yield: 74%. Elemental Anal. Calc. $C_{37}H_{37}N_3O_3P_2PdS$ (772,15): C 57.8, N 5.4, H 4.8, S 4.2%. Found: C 56.4, N 5.3, H 4.6, S 3.3%. ^{1}H-NMR (acetone-d_6, δ/ppm): 7—8 (m, PPh_2), 5,71 (m, 3H, H^5, NH_2), 3,78 (s, 3H, OMe), 3,61 (s, 3H, OMe), 3,42 (m, 2H, PCH_2P), 2,96 (s, 3H, OMe), 2,44 (s, 3H, MeCN). NMR ^{31}P–{^{1}H} (acetona-d_6, δ/ppm): 27,38 (d, ^2J = 88,0 Hz, P^A); -23,81 (d, ^2J = 87,8 Hz, P^B).

c2: Yield: 73%. Elemental Anal. Calc. $C_{38}H_{39}N_3O_3P_2PdS$ (786,18): C 58.1, N 5.3, H 5.0, S 4.1%. Found: C 59.5, N 5.4, H 5.8, S 3.3%. ^{1}H-NMR (acetone-d_6, δ/ppm): 7—8 (m, PPh_2), 5,77 (s, 1H, $NHCH_3$), 5,59 (s, 1H, H^5), 3,79 (s, 3H, OMe), 3,59 (s, 3H, OMe), 2,97 (s, 3H, OMe), 3,45 (m, 2H, PCH_2P), 3,09 (s-ancho, 3H, $NHCH_3$), 2,48 (s, 3H, MeCN). NMR ^{31}P–{^{1}H} (acetona-d6, δ/ppm): 27,84 (d, ^2J = 91,2 Hz, P^A); -23,79 (d, ^2J = 78,0 Hz, P^B).

c3: Yield: 82%. Elemental Anal. Calc. $C_{39}H_{41}N_3O_3P_2PdS$ (800,20): C 58.5, N 5.3, H 5.2, S 4.0%. Found: C 60.6, N 4.7, H 5.0, S 3.5%. ^{1}H-NMR (acetone-d_6, δ/ppm): 7—8 (m, PPh_2), 5,70 (s, 1H, $NHCH_2CH_3$), 5,58 (s, 1H, H^5), 3,83 (s, 3H, OMe), 3,62 (s, 3H, OMe), 3,49 (m, 2H, PCH_2P), 3,15 (m, 2H, $NHCH_2CH_3$) 3,02 (s, 3H, OMe), 2,52 (s, 3H, MeCN), 1,17 (m, 3H, $NHCH_2CH_3$). NMR ^{31}P–{^{1}H} (acetona-d_6, δ/ppm): 27,38 (d, ^2J = 92,9 Hz, P^A), -23,81 (d, ^2J = 92,3 Hz, P^B).

3. Results and Discussion

*3.1. Thiosemicarbazone Ligands (***a1-a3***)*

The conformational isomer *E* was mainly obtained in the compounds **a1-a3**; this may be due to intramolecular hydrogen bridging interactions between the iminic group and the thioamidic group [8].

The ^{1}H-NMR spectrum for **a1** shows the NNH proton resonance as a singlet ca. 10 ppm. The NHR' resonance was a broad signal ca. 8 ppm. For **a2** and **a3,** singlets (1H) were observed and also two singlets for **a1**. The H^5/H^6 signals (AB spin system) were correctly assigned ca. 7 ppm. Three singlets were assigned to the MeO resonances ca. 3.5 ppm. The MeCN group showed a singlet ca. 2.3 ppm. The remaining methyl and ethyl groups signals were assigned accordingly.

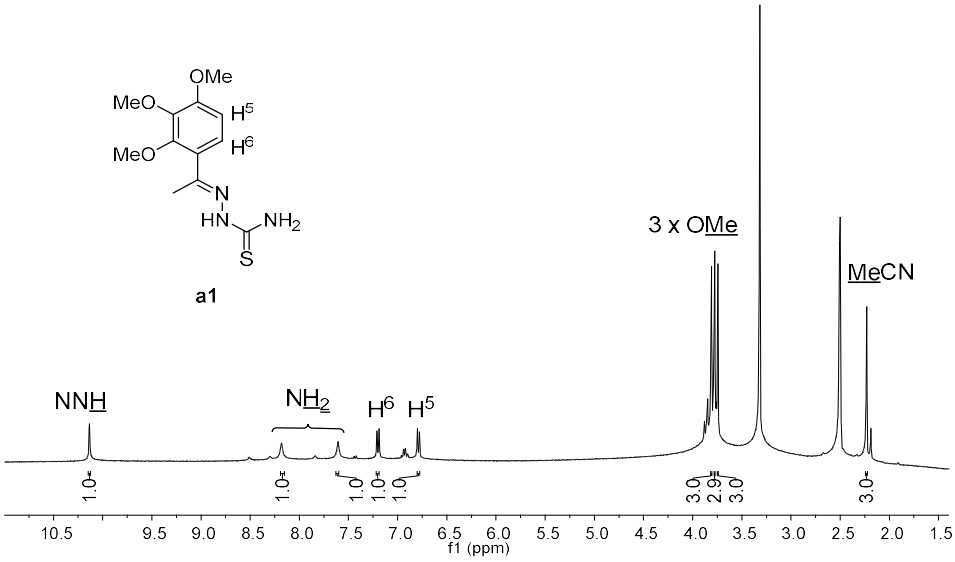


Figure 3. ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) of the compound (**a1**).

*3.2. Discussion for Cyclometallated Compounds (***b1-b3***)*

The most significant changes on going from the ligand spectra to those of the complexes **b1, b2** and **b3**, was the absence of the AB spin system resonances. Only a singlet assigned to H^5 was observed. The remaining resonances showed slight variations from the parent spectra for **a1-a3**.

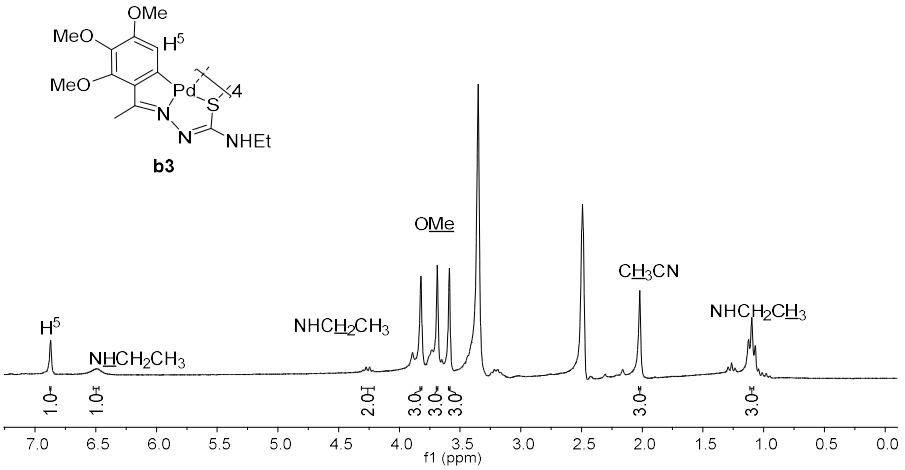


Figure 4. ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) of the compound (**b3**).

*3.3. Discussion for Cyclometallated Compounds with Diphosphine Ligands (***c1-c3***)*

The ^{1}H-NMR spectra for **c1**-**c3** show the resonances for the protons from the starting material and they were correctly assigned. Shielding by the phosphine phenyl ring shifts the H^5 and NHR' signals to highfield ca. 5.8 ppm. This shielding also affects the C4-MeO group, its signed appears ca. 2.5 ppm. The ($PPh_2CH_2PPh_2$) resonance was a multiplet in agreement with a complex AA'XX' pattern.

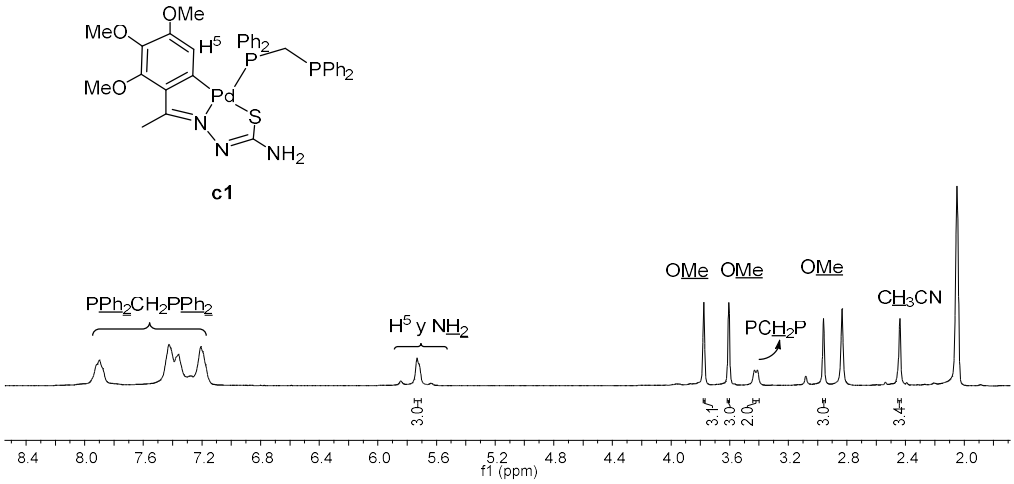


Figure 5. ^{1}H-NMR spectrum (400 MHz, acetone-d_6) of the compound (**c1**).

4. Conclusions

The thiosemicarbazone ligands have been synthesized following the procedure described in the literature and were obtained as the *E* isomer.

The cyclopalladated compounds have been synthesized and they were obtained as tetranuclear species.

Reaction with the diphosphine dppm gave the mononuclear compound in all cases.

Conflicts of Interest: The authors declare no conflict of interest.

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