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Synthesis and catalytic study in the Suzuki-Miyaura reaction of a family of palladium compounds †

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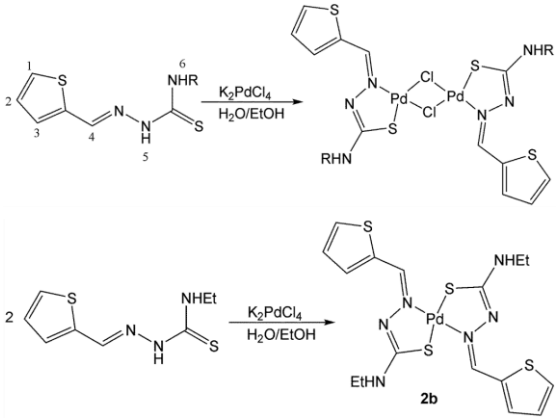
Abstract: Thiosemicarbazone ligands are known for their versatility towards metal coordination, forming very stable compounds with metals such as palladium. In addition, palladium derivatives are used more often than not as catalyst in C–C cross coupling reactions like the Suzuki–Miyaura reaction, however the commercially available catalyst are not of much air or thermal stability. That is the reason why in this communication we present the synthesis, characterisation and catalytic study of a family of palladium – thiosemicarbazone compounds as an improvement to the thermal and air stability of commercial catalyst.

Keywords: Palladium, catalysis, Suzuki-Miyaura

1. Introduction

Carbon−Carbon cross−coupling reactions are of great relevance in organic synthesis [1] and also, in industrial and in pharmaceutical processes. Palladium based compounds appear to be outstanding catalysts in the C−C cross−coupling reactions [2], and although there are commercially available catalysts such as $[Pd(PPh_3)_4]$ or $[Pd(OAc)_2]$, they fail to comply with air and thermal stability, so by tuning the ligands this problem can be overcome. Thiosemicarbazones are a family of ligands formed by the reaction between a carbonyl group and a tiosemicarbazide. They present different coordination modes from mono to tetradentate due to the presence of a variety of donor atoms in their structure, and in solution they present thiol–thione equilibrium [3]; although their most common coordinative fashion is as bidentate ligands forming a five membered ring, which is also the most stable [4]. Furthermore, thiosemicarbazone ligands themselves are known for showing cytotoxic activity. For this reason the combination of both functions makes palladium – thiosemicarbazone compounds an interesting new tool in chemistry.

Given our vast experience in the synthesis and characterisation of cyclopalladated compounds [5] and their use as catalysts in the Suzuki–Miyaura reaction [6, 7], we reasoned that by using the thiosemicarbazone as bidentate instead of tridentate, the greater accessibility of palladium would give a better catalytic activity. For this reason the synthesis of ligands **1–3** (scheme1) was carried out. A thiophene substituent and substitution of the iminic methyl for hydrogen made formation of the cyclopalladated ring more difficult. What follows is the methodology and the results obtained.



Scheme 1: Synthesis of the palladium derivatives.

2. Discussion

The compounds synthetized have been fully characterised using the standard spectroscopy techniques ^{1}H NMR, IR and X-ray diffraction in the case of compound **2b**. In all cases the displacement of the ^{1}H NMR signals to higher field proves that the thiosemicarbazone ligands (compounds **1-3**) are attached to the metal giving compounds **1a-3a** (see scheme 1).

The presence of the H3 resonance in the metalated compounds shows that the ligands act as bidentate [N, S]. In addition, absence of the signal for the hidrazinic proton indicates a thiolic coordination. This is corroborated in the case of the IR spectra due to the disappearance of the υ(C=S) stretch placed *ca* 805-860 cm^{-1} [8]. Finally, the synthesis of compound **2b** provided crystals suitable for X-ray diffraction. The structure confirms without any doubt the thiol fashion of the thiosemicarbazone and the bidentate coordination in the solid state. This structure also shows the *trans*-disposition of both thiosemicarbazone ligands around the metal and the monomeric nature of the compound **2b** as shown in figure 1.

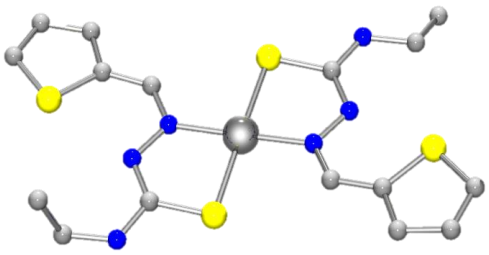


Figure 1: Molecular structure of compound **2b,** the hydrogen atoms have been omitted for clarity.

Once the compounds were fully characterized they were tested as catalysts for the Suzuki-Miyaura reaction, using as substrates either 4′-bromoacetophene (as activating substrate) or 4′-bromoanisole (as deactivating substrate) together with phenylboronic acid (as described in the Materials and Methods section). The results are collected in the Table 1. From them it can be seen that the best conditions in the Suzuki-Miyaura reaction were 80º C using the activating substrate and using less favourable conditions the best catalyst was compound **2a.** This result is opposed to the low catalytic activity of **2b,** so the presence of more labile bonds such as Pd-Cl favours the catalytic activity of the compound. According to the data, the secondmost important factor is changing the NHR group. The greatest difference is between the NH*Me* and NH*Et* species (**1a** and **2a** respectively). Changing one carbon in the chain the catalytic activity considerably. The major differences in the catalytic activity are in the entrance related to 40º C were **2a** is still a good catalyst, however **1a** and **3a** cannot reach 50% conversion.

Table 1: Results for the catalytic studies.

Catalyst	T °C	XAr	time/h	Max. Conv. %
1a	80	4′-bromoacetophenone	24	37
	40	4′-bromoacetophenone	24	27
	r. t.	4′-bromoacetophenone	24	11
	80	4′-bromoanisole	24	6
2a	80	4′-bromoacetophenone	24	93
	40	4′-bromoacetophenone	24	79
	r. t.	4′-bromoacetophenone	24	27
	80	4′-bromoanisole	24	12
2b	80	4′-bromoacetophenone	24	14
	40	4′-bromoacetophenone	24	10
	r. t.	4′-bromoacetophenone	24	0
	80	4′-bromoanisole	24	0
3a	80	4′-bromoacetophenone	24	92
	40	4′-bromoacetophenone	24	17
	r. t.	4′-bromoacetophenone	24	6
	80	4′-bromoanisole	24	2

3. Materials and Methods

3.1 General Procedures. Solvents were purified by standard methods. All compounds were purchased from Sigma-Aldrich. Elemental analyses were performed with a LECO analyzer, Model CHNS-932. IR espectra were recorded as Nujol mulls or polythene discs on Perking-Elmer 1330, Mattson Model Cygnus-100, and Bruker Model IFS-66V spectrophotometers. ^{1}H NMR spectra in solution were recorded in $CDCl_3$ or DMSO-d_6 at room temperature on Bruker DPX 250 spectrometer operating at 250.13MHz using 5 mm o.d. tubes; chemical shifts, in ppm, are reported downfield relative to TMS using the solvent signal (DMSO-d_6, δ^1H = 2.46ppm) as reference. Coupling constants are reported in Hz. All chemical shifts are reported downfield from standards.

3.2 Synthesis of the Ligands: 2-Thiophenecarboxaldehyde was added to a solution of 4-R-thiosemicarbazone (R=Me, Et or Ph for compounds **1**, **2** and **3** respectively) in acidified water. The mixtures were stirred for 4h and the resulting pale yellow precipitates were filtrated, washed with water and dried.

3.2.1 *Compound **1:*** yield 91%, ^{1}H RMN (*DMSO-d_6*) δ ppm 7.64 (d, ^3J(H1H2) = 5.03 Hz, 1H, H1), 7.10 (dd, ^3J(H2H1) = 5.01, ^3J(H2H3) 2.65 Hz, 1H, H2), 7.41 (d, ^3J(H3H2) = 2.65 Hz, 1H, H3), 8.22 (s, 1H, H4), 11.47 (s, 1H, H5) 8.15 (t,^3J(H6H7) = 4.53 Hz, 1H, H6), 2.98 (d,^3J(H7H6)= 4.60 Hz, 3H, H7). IR cm^{-1} 3173 (ṽ NH), 1593 (ṽ C=N), 822 (ṽ C=S). Anal. Found: C, 42.4; H, 4.6; N, 21.0; S, 32.1 %, $C_7H_9N_3S_2$ requires C, 42.2; H, 4.6; N, 21.0; S, 32.1 %.

3.2.2 *Compound **2:*** yield 93% ^{1}H NMR *(DMSO-d_6)* δ ppm 7.64 (d, ^3J (H1H2)= 5.13 Hz, 1H, H1), 7.14-7.07 (m, 1H, H2), 7.42 (d,^3J (H3H2)= 2.96 Hz, 1H, H3), 8.22 (s, 1H, H4), 11.41 (s, 1H, H5), 8.17 (t, ^3J(H6H7) = 5.78 Hz, 1H, H6), 3.61-3.50 (m, 2H, H7), 1.11 (t, ^3J(H8H7) = 7.08 Hz, 3H, H8). IR cm^{-1} 3210-3326 (ṽ NH), 1595 (ṽ C=N), 810 (ṽ C=S). Anal. Found: C, 45.2; H, 5.2; N, 19.6; S, 30.0 %, $C_8H_{11}N_3S_2$ requires C, 45.0; H, 5.2; N, 19.7; S, 30.1 %.

3.2.3 *Compound **3***: yield 88% ^{1}H RMN (*DMSO-d_6*) δ ppm 7.69 (d, ^3J(H1H2) = 4.97 Hz, 1H, H1), 7.13 (dd, ^3J (H2H1) = 4.99, ^3J(H2H3) = 3.69 Hz, 1H, H2), 7.54 (m, 3H, 2x*H*o, H3), 9.80 (s, 1H, H4), 11.82 (s,

1H, H5), 8.33 (s, 1H, H6), 7.34 (m, 2H, H*m*), 7.19 (m, 1H, H*p*). IR cm^{-1} 3304 (ṽ NH), 1549 (ṽ C=N), 856 (ṽ C=S). Anal. Found: C, 54.6; H, 4.7; N, 16.0; S, 24.0 %, $C_{12}H_{11}N_3S_2$ requires C, 55.1; H, 4.2; N, 16.1; S, 24.5 %.

3.3 Synthesis of the palladium derivatives: an amount of K_2PdCl_4 was dissolved in 3 mL of water, to this 20 mL of EtOH (96% v.v) were added to form a suspension and then the corresponding amount of ligand. In the case of compounds **1a**, **2a** and **3a** the stoichiometry ligand: Palladium is 1:1, while in the case of compound **2b** the stoichiometry is 2:1. The mixtures were stirred for 24h and the yellow precipitates were filtered of, washed with EtOH (96% v.v) and dried.

*3.3.1 Compound **1a**:* yield 83% ^{1}H RMN (*DMSO-d*$_6$) δ ppm 7.66 (d ^3J(H1H2) = 5.06 Hz, 1H, H1), 7.13-7.05 (m, 1H, H2), 7.30 (d, ^3J(H3H2) = 3.49 Hz, 1H, H3), 8.53 (s, 1H, H4), 7.82-7.74 (m, 1H, H5), 2.77 (d, ^3J(H6H5) = 4.66 Hz, 3H, H6). IR cm^{-1} 3378 (ṽ NH), 1561 (ṽ C=N), 302 and 326 (ṽ Pd-Cl). Anal. Found: C, 24.6; H, 2.4; N, 12.5; S, 18.9 %, $C_{14}H_{16}N_6S_4Pd_2Cl_2$ requires C, 24.7; H, 2.4; N, 12.4; S, 18.8 %.

*3.3.2 Compound **2a**:* yield 88%, ^{1}H RMN (*DMSO-d*$_6$) δ ppm 7.99 (d, ^3J(H1H2) = 4.98 Hz, 1H, H1), 7.21 (m, 1H, H2), 7.75 (d, ^3J (H3H2) = 3.77 Hz, 1H, H3),8.51 (s, 1H, H4), 7.83 (t, ^3J(H5H6)= 5.16 Hz, 1H, H5), 1.16 (t, ^3J(H7H6) = 7.15 Hz, 3H, H7). IR cm^{-1} 3299 (ṽ NH), 1558 (ṽ C=N), 300 and 317 (ṽ Pd-Cl).). Anal. Found: C, 27.1; H, 2.8; N, 11.9; S, 18.1 %, $C_{16}H_{20}N_6S_4Pd_2Cl_2$ requires C, 27.1; H, 2.9; N, 11.8; S, 18.1 %.

*3.3.3 Compound **2b**:* yield 70% ^{1}H RMN (*DMSO-d*$_6$) δ ppm 7.93 (d, ^3J(H1H2) = 5.12 Hz, 1H, H1), 7.20-7.15 (m, 1H, H2), 7.63 (d, ^3J(H3H2) = 3.37 Hz, 1H, H3), 7.68 (s, 1H, H4), 8.07-8.02 (m, 1H, H5), 1.17 (dt, ^3J (H6H5), = 7.12, ^3J (H6H7)= 3.23 Hz, 2H, H6). IR cm^{-1} 3382 (ṽ NH), 1517 (ṽ C=N).). Anal. Found: C, 35.8; H, 4.3; N, 15.4; S, 23.7 %, $C_{16}H_{20}N_6S_4Pd_2$ requires C, 36.2; H, 3.8; N, 15.4; S, 24.2 %.

*3.3.4 Compound **3a**:* yield 96% ^{1}H RMN (*DMSO-d*$_6$) δ ppm 8.00 (d, ^3J = 4.9Hz, 1H, H1), 7.78 (d, ^3J = 4.9 Hz, 1H, H3) 9.84 (s, 1h, H4), 8.13 (s, 1H, H5), 7.68-7.03 (m 6H, H2, H*o*, H*m*, H*p*). IR cm^{-1} 3370 (ṽ NH), 1510 (ṽ C=N), 311 and 338 (ṽ Pd-Cl). Anal. Found: C, 35.4; H, 2.8; N, 10.0; S, 15.3 %, $C_{24}H_{20}N_6S_4Pd_2Cl_2$ requires C, 35.8.1; H, 2.5; N, 10.5; S, 15.9 %.

Table 2: crystallographic data for compound **2b**

Empirical formula	**$C_{32}H_{40}N_{12}Pd_2S_8$**
Molecular weight	1006.07
Temperature	293(2) K
Wavelength	0,71073 Å
Crystal system	Triclínico
Space group	P-1
Unit cell dimensions	a = 10.779(5) Å, α = 89.769(5)° b = 15.898(5) Å, β = 82.885(5)° c = 16.653(5)Å, γ = 87.574(5)°
Volume	2829.2(18) Å3
Z	2
Calculated density	1.366 mg/m3
Absorption coefficient	1.045mm-1
F(000)	1170
Crystal size	0,04 x 0,06 x 0,08 mm3
θ range for data collection	1,23 – 26,48°
Index ranges	-13 ≤ h ≤ 13, -19 ≤ k ≤ 19, -19≤ l ≤ 20
Reflections collected/independent	38992 / 11630 [R(int) = 0,1129]
Data/restraints/parameters	11630 / 0 / 633
Goodness-of-fit on F^2	0,997
Final R indices [I>2σ(I)]	R1 = 0,0641, wR2 = 0,1331
R índices (all data)	R1 = 0,1387, wR2 = 0,1660

3.4 Catalysis: the catalysis proves were carried out in a Radley Carousel 12 Plus Reaction Station with 6mL of a mixture of solvents THF:water 1:2, using as substrates 4-bromoanisole, 4-bromoacetophenone and phenylboronic acid and K_3PO_4 as base.

4. Conclusions

This communication shows that thiosemicarbazones act as bidentate ligands and their coordination towards the metal is in the thiol form as shown by ^{1}H NMR, IR and X-ray diffraction. The metalated compounds were tested for the Suzuki-Miyaura reaction as catalyst. The results were that these compounds were not such good catalyst as the cyclopalladated derivatives. However, compound **2a** shows good conversion in the most favourable conditions. In addition, these experiments prove that the changes in the NHR part of the ligand considerably affect the catalytic activity of the metalated compound.

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Conflicts of Interest: The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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