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Cyclometallated Thiosemicarbazones Containing Fluorine Atoms: A Solubility Improvement †

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Abstract: A novel set of thiosemicarbazone palladacycles is discussed. The addition of a fluorine atom to the thiosemicarbazone ligand increases not only the solubility of the ligand itself, but also that of the ensuing cyclometallated complexes. Ligands are synthesized in acidic ethanolic solution, and then reacted with potassium tetrachloropalladate(II), to give the corresponding cyclopalladated compounds bearing a tetranuclear structure. Characterization will be carried by IR, ^{1}H NMR and ^{19}F NMR spectroscopies.

Keywords: thiosemicarbazone; palladium; cyclometallation; fluor; solubility

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1. Introduction

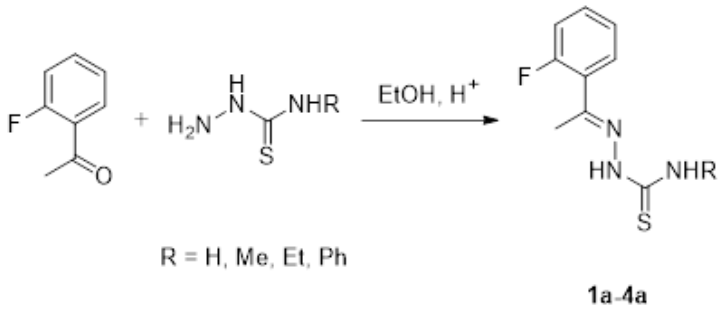
Cyclometallated compounds are of great relevance in biology [1,2] because they contain metal centers, such as palladium [3], platinum [4] or ruthenium [5], that have proved to be efficient anticancer agents. Furthermore, thiosemicarbazone ligands also possess certain biological activity [6,7], making these cyclometallated compounds an excellent choice for biological tests. The main problem of this compounds is their low solubility, being poorly soluble in water and common organic solvents, except DMSO, a solvent commonly used in these assays. Synthesis of more soluble complexes [8,9] is the main target in medicinal and biological chemistry.

In this research work, the synthesis and characterization of new cyclometallated compounds containing fluorine atoms in their structure, which leads to increased solubility, is discussed. Synthesis of thiosemicarbazone ligands is done in acidic ethanolic solution, unlike the usual synthesis in water [10–13] because of the increasing solubility, which makes these ligands water-soluble. Then, the ligands are reacted with a palladium salt in ethanol/water, to form the corresponding cyclometallated compounds with the thiosemicarbazone as a tridentate [*C*, *N*, *S*] ligands.

2. Experimental

2.1. Synthesis of Thiosemicarbazone Ligands

400 mg of 2-fluoroacetophenone and the corresponding amount of thiosemicarbazide (see Table 1) were added in 15 cm^3 of ethanol, following the reaction shown in Scheme 1. 0.5 cm^3 of concentrated hydrochloric acid were added, and the mixture was stirred at room temperature for 24 h. After that, the solvent was removed under reduced pressure and the residue was dried under vacuum.



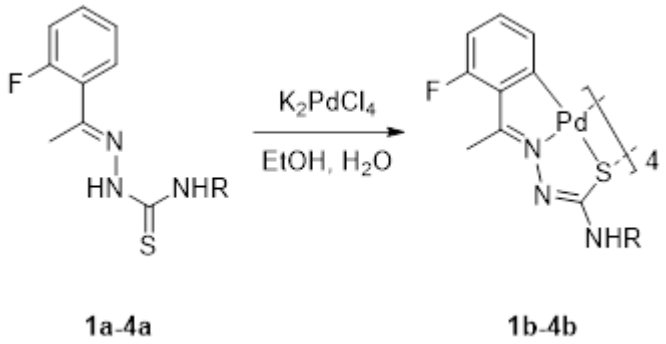
Scheme 1. Synthesis of thiosemicarbazone ligands.

Table 1. Quantities of reagents and efficiency for thiosemicarbazones synthesis.

Compound	R	Thiosemicarbazide/mg	Efficiency/%
1a	H	264	72
2a	Me	305	74
3a	Et	345	85
4a	Ph	484	69

2.2. Synthesis of Palladacycles

K_2PdCl_4 (see Table 2) was added in water (4 cm^3). After total solubilization, a solution of 100 mg of thiosemicarbazone in ethanol (8 cm^3) was added (shown in Scheme 2). The mixture was stirred at room temperature for 24 h. A suspension formed, that was centrifugated and the solid was dried under vacuum.



Scheme 2. Synthesis of cyclometallated compounds.

Table 2. Quantities of reagents and efficiency for complexes synthesis.

Compound	R	K_2PdCl_4/mg	Efficiency/%
1b	H	155	56
2b	Me	145	67
3b	Et	136	62
4b	Ph	114	51

3. Results and Discussion

Characterization was carried out by IR spectroscopy, ^1H and ^{19}F NMR spectroscopy.

3.1. IR Spectroscopy

In Table 3 the IR stretches are shown for thiosemicarbazone ligands and cyclometallated compounds, and the differences between them show the ligand coordination to the palladium center.

Table 3. IR stretch data.

Compound	R	ν (C=N)	Δν (C=N)	ν (N-H)	ν (C=S)
1a	H	1557	-	3254/3212/3146	825
2a	Me	1563	-	3285/3217	829
3a	Et	1566	-	3265/3206	833
4a	Ph	1552	-	3277/3240	831
1b	H	1525	32	3268/3161	-
2b	Me	1528	35	3226	-
3b	Et	1521	45	3201	-
4b	Ph	1520	32	3216	-

3.2. ^{1}H NMR Spectroscopy

The ^{1}H NMR spectra of thiosemicarbazones (see Figure 1) is in agreement with the formation of the ligands.

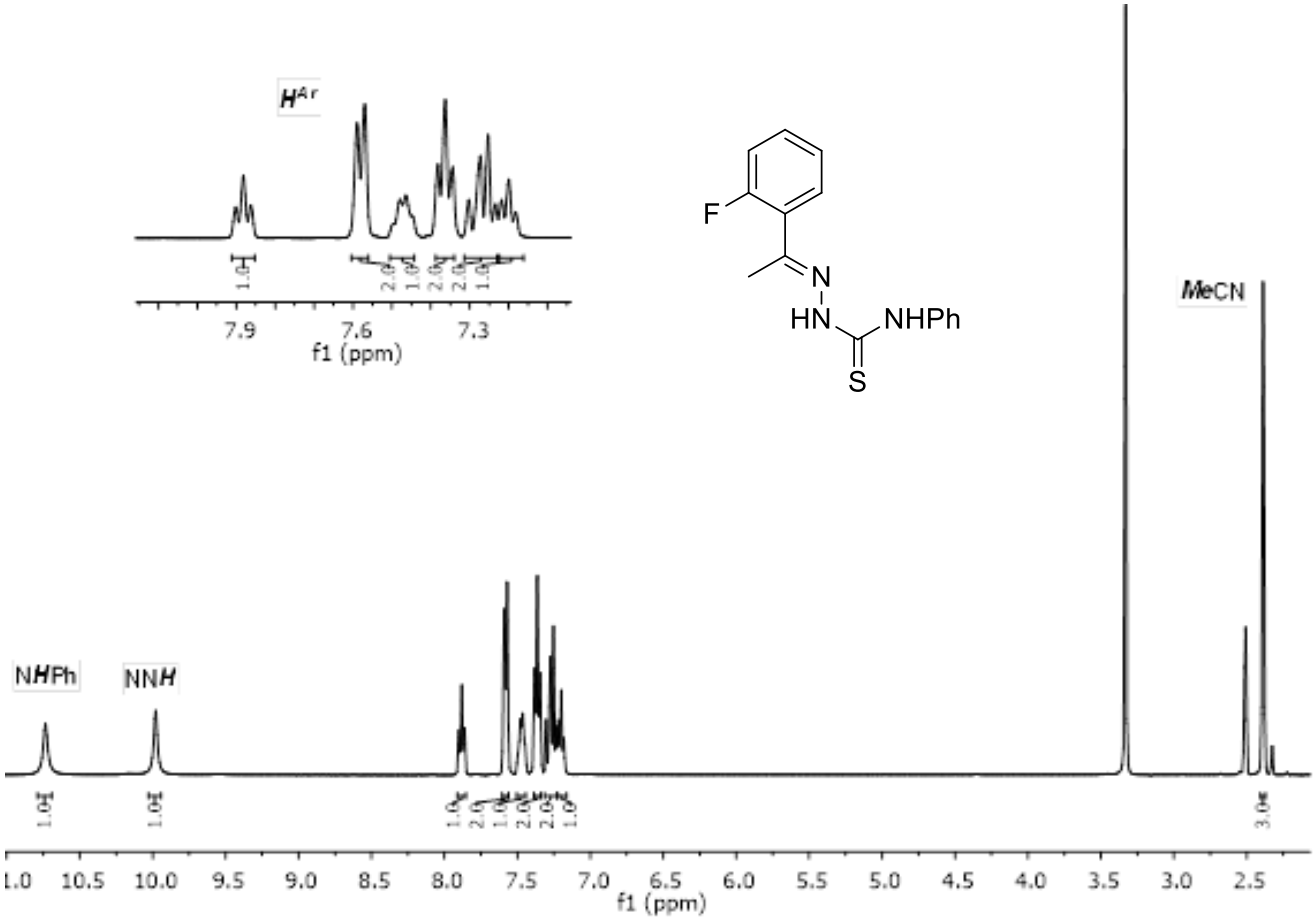


Figure 1. ^{1}H NMR spectrum of compound 4a in DMSO-d_6.

^{1}H NMR spectra of cyclometallated compounds (see Figure 2) were not done in DMSO-d_6, usual solvent for these complexes. Their high solubility allows to run the spectra in $CDCl_3$.

The disappearance of the hydrazinic proton resonance and the *ortho* aromatic proton resonance in the cyclometallated compounds spectra is consequent on cyclometallation. A doublet for the MeCN group is due to the coupling with the fluorine atom.

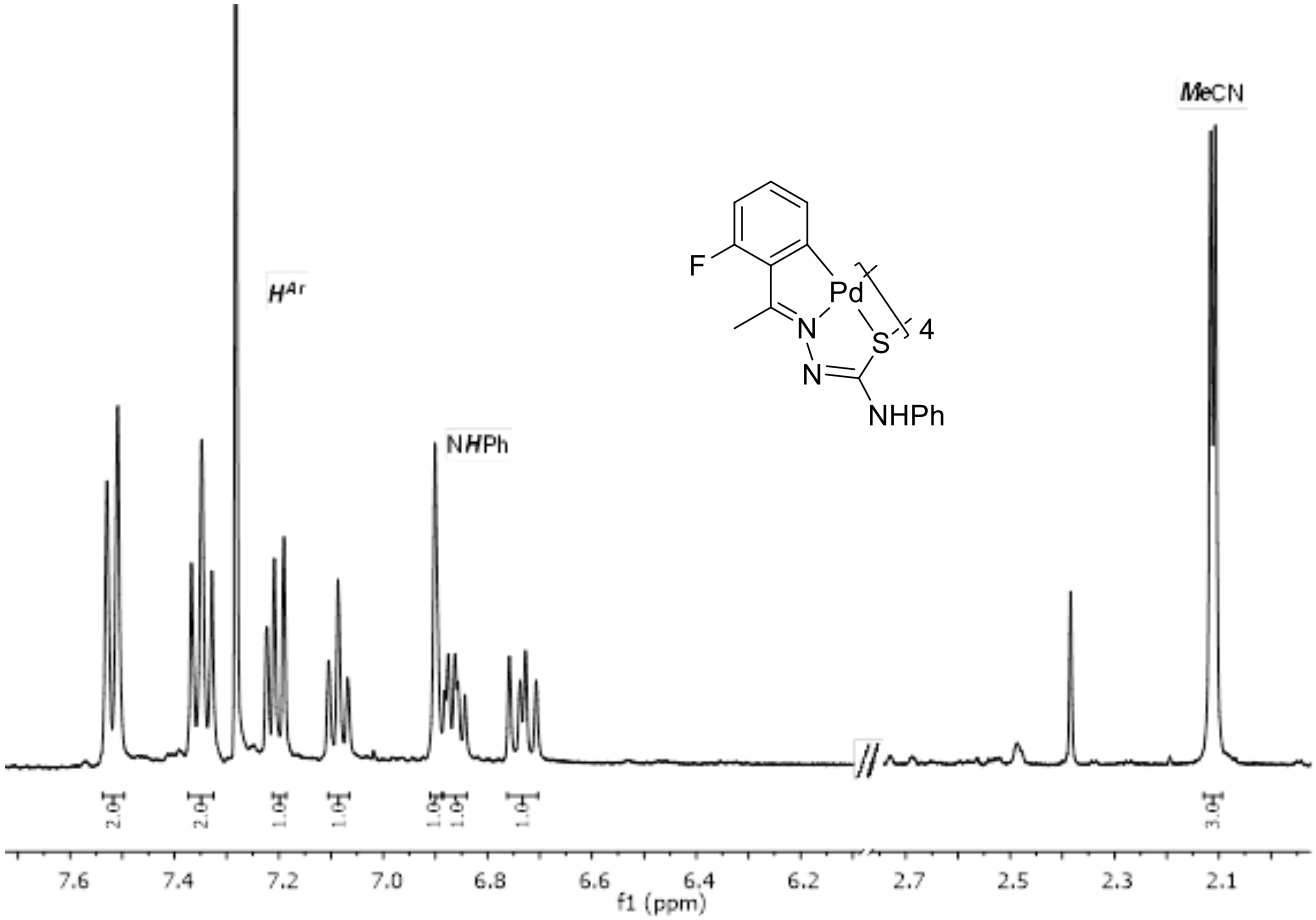


Figure 2. ^{1}H NMR spectrum of compound 4b in $CDCl_3$.

3.3. ^{19}F NMR Spectroscopy

One signal appears in the ^{19}F NMR spectra (see Figure 3). The downfield shift of the resonance confirms cyclometallation.

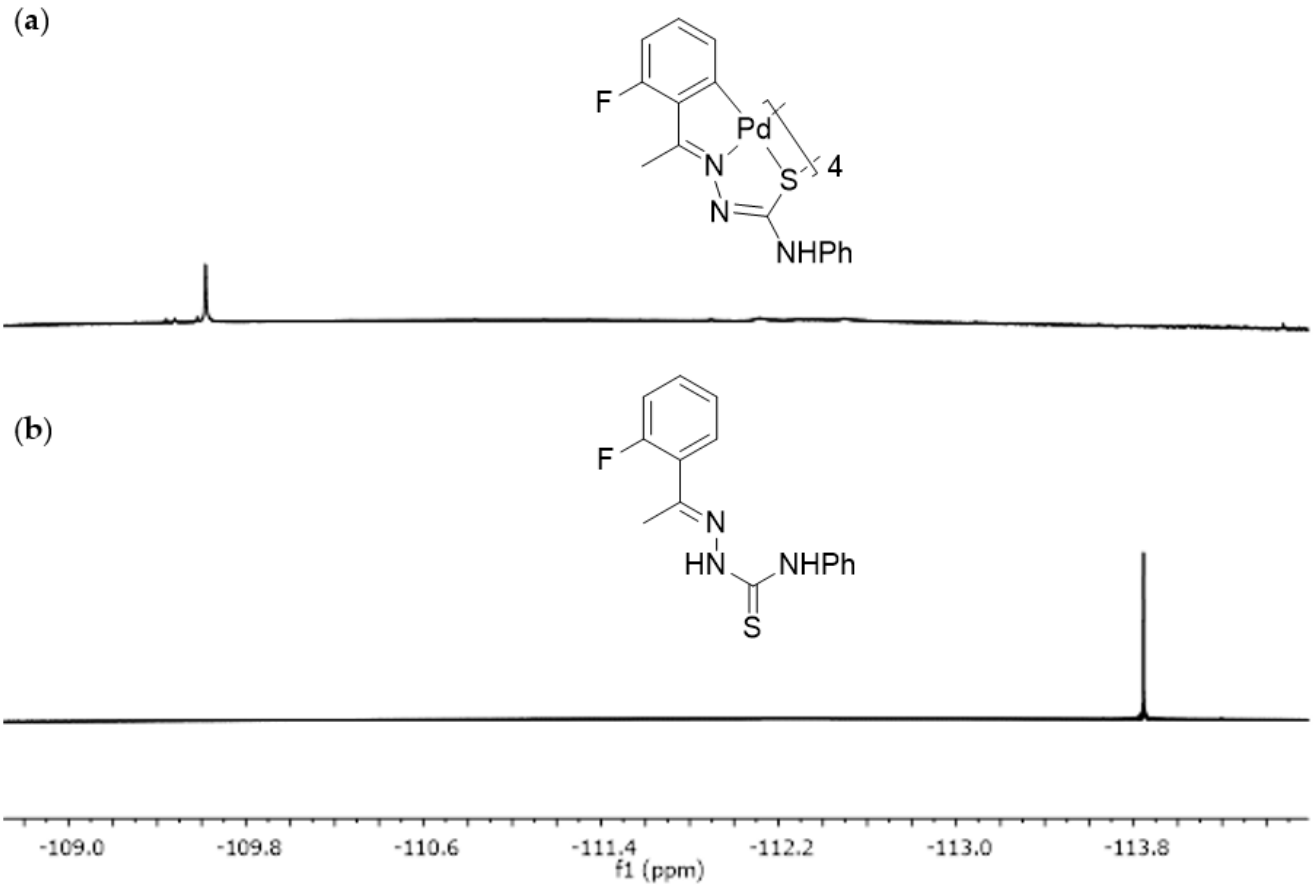


Figure 3. ^{19}F NMR stacked spectra in $CDCl_3$ of: (**a**) compound 4b and (**b**) compound 4a.

4. Conclusions

- ✓ Synthesis of fluorinated thiosemicarbazone ligands and cyclometallated tetranuclear compounds was accomplished.
- ✓ An increase in solubility was observed for thiosemicarbazone ligands, changing the solvent medium from water to ethanol.
- ✓ Also, an increase in the solubility of the cyclometallated compounds was observed, as shown by the ^1H NMR spectra in $CDCl_3$.
- ✓ IR data confirm cyclometallation of the ligands in the thiolic form, and the C-H activation in the fluor-containing phenyl ring.
- ✓ ^1H NMR spectra confirm the expected results. The disappearance of the hydrazinic proton (NNH) and the multiplicity change in the aromatic protons agrees with complex formation, with the thiosemicarbazone acting as a tridentate [*C, N, S*] ligand.
- ✓ ^{19}F NMR spectra show the downfield shift of the fluorine resonance. This is caused by the ligand's cyclometallation.

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

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