

Synthesis of N-P-Fluorothiosemicarbazone and of bis(N-P-Fluorophenylthiourea). Crystal Structure and Conformational Analysis of N, N'-bis(4-Fluorophenyl)hydrazine-1,2-Bis(carbothioamide)

[Sirine Salhi](#) , [Dorra Dorra Kanzari-Mnallah](#) , [Isabelle Jourdain](#) , [Michael Knorr](#) ^{*} , [Carsten Strohmann](#) , [Jan-Lukas Kirchhoff](#) , [Hédi Mrabet](#) , Azaiez Ben Akacha

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Communication

Synthesis of *N*-*p*-fluorothiosemicarbazone and of bis(*N*-*p*-fluorophenylthiourea). Crystal structure and conformational analysis of *N,N'*-bis(4-fluorophenyl)hydrazine-1,2-bis(carbothioamide)

Sirine Salhi ^{1,2}, Dorra Kanzari-Mnallah ^{1,*}, Isabelle Jourdain ^{2,*}, Michael Knorr ^{2,*}, Carsten Strohmnn ³, Jan-Lukas Kirchhoff ³, Hédi Mrabet ¹ and Azaiez Ben Akacha ¹

¹ University of Tunis El Manar, Laboratory of Selective Organic and Heterocyclic Synthesis-Biological Activity Evaluation (LR17ES01), 2092-Tunis-Tunisia; sirine.salhi@etudiant-fst.utm.tn, azaiez.benakacha@fst.utm.tn

² Université de Franche-Comté, Institut UTINAM UMR 6213 CNRS, 16, Route de Gray, 25030 Besançon, France; isabelle.jourdain@univ-fcomte.fr

³ Technische Universität Dortmund, Anorganische Chemie, Otto-Hahn Straße 6, 44227 Dortmund, Germany; carsten.strohmnn@tu-dortmund.de, jan-lukas.kirchhoff@tu-dortmund.de

* Correspondence: michael.knorr@univ-fcomte.fr; dorrakanzari@gmail.com; Tel. + [33] 3 81 66 62 70

Abstract: Reaction of the phosphonated hydrazone (2-hydrazineylidenepropyl) diphenylphosphine oxide **1** with *p*-fluorophenyl-isothiocyanate yields as major product the thiosemicarbazone $\text{Ph}_2\text{P}(=\text{O})\text{CH}_2\{\text{C}=\text{N}-\text{NH}(\text{C}=\text{S})-\text{N}(\text{H})\text{C}_6\text{H}_4\text{F}\}\text{CH}_3$ (2-(1-(diphenylphosphoryl)propan-2-ylidene)-*N*-(4-fluorophenyl)hydrazine-1-carbothioamide) **2** along with bis(*N*-*p*-fluorophenylthiourea) **3** as minor product. This latter compound **3** was isolated as main product by direct treatment of *p*- $\text{FC}_6\text{H}_4\text{N}=\text{C}=\text{S}$ with hydrazine in a 2:1 ratio. Both **2** and **3** were characterized by NMR. Furthermore, the molecular structure of **3** was elucidated by an X-ray diffraction study, revealing both intra- and intermolecular secondary interactions. A conformational DFT study, at the B3LYP/6-311 G++ (d, p) level of theory, confirms a good match between the calculated structure and the experimental one.

Keywords: thiourea; thiosemicarbazone; crystal structure; conformational analysis; supramolecular network

1. Introduction

In some previous papers, we have described the synthesis and conformational analysis of a series of phosphonated hydrazones $\text{Ph}_2\text{P}(=\text{O})\text{CH}_2\text{C}(=\text{N}-\text{NH}_2)\text{CH}_3$ and $[\text{R}^1\text{R}^2\text{C}(\text{CH}_2\text{O})_2\text{P}(=\text{O})\text{CH}_2-\text{C}(=\text{N}-\text{N}(\text{H})\text{R}^5)\text{C}(\text{H})\text{R}^3\text{R}^4]$ bearing a six-membered 1,3,2-dioxaphosphorinane heterocycle, which were obtained by treatment of their respective allene precursors with hydrazines [1-4]. The reactivity of these compounds has been subsequently investigated, for example with ethylorthoformate leading to 4-phosphopyrazoles [5].

Since these hydrazones contain a potentially reactive $\text{N}=\text{N}(\text{H})\text{R}$ group, these compounds also appeared as suitable starting materials for nucleophilic addition reaction vis-à-vis reactive unsaturated substrates such as isothiocyanates $\text{R}-\text{N}=\text{C}=\text{S}$ to afford β -phosphonated thiosemicarbazones. We were intrigued to explore this route, since thiocarbamates feature both promising biological activities (see selected examples in Figure 1) and found also since the seventies a widespread use as ligands in coordination chemistry [6-9].

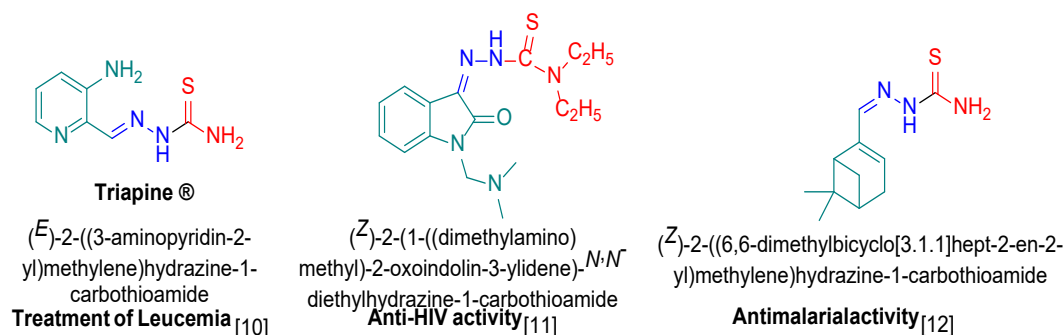
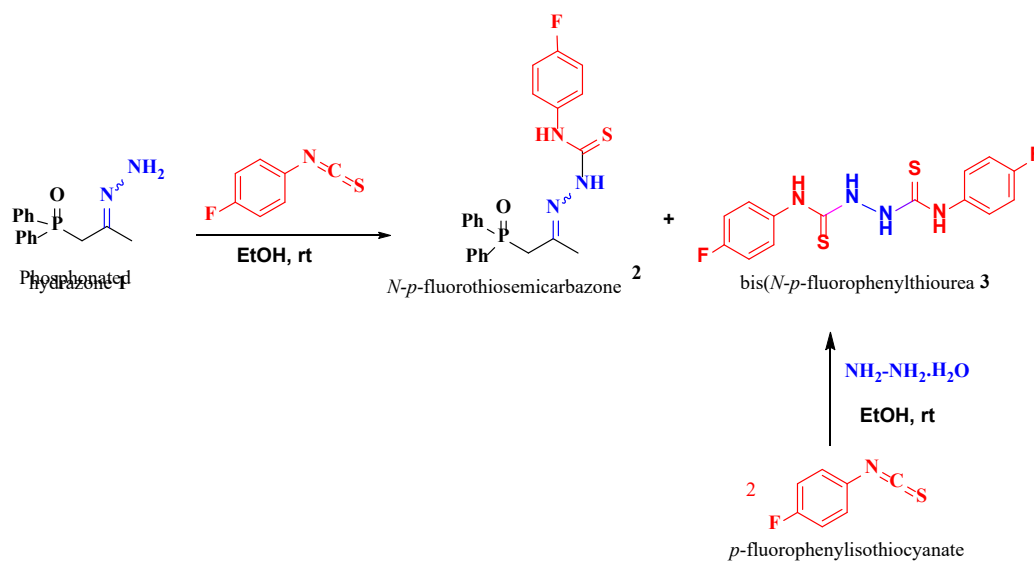


Figure 1. Examples of thiosemicarbazones structures featuring a biological activity.

We describe here our preliminary finding concerning the reactivity of (2-hydrazineylidenepropyl) diphenylphosphine oxide with *p*-fluorophenyl-isothiocyanate yielding the targeted thiosemicarbazone $\text{Ph}_2\text{P}(=\text{O})\text{CH}_2\{\text{C}=\text{N}-\text{NH}(\text{C}=\text{S})-\text{N}(\text{H})\text{C}_6\text{H}_4\text{F}\}\text{CH}_3$ **2**. During the work-up, we noticed also the formation of second species in minor amounts, the hitherto unknown compound bis(*N-p*-fluorophenylthiourea) **3**. The topic of this communication is focused on (i) the optimized preparation, (ii) spectroscopic and detailed crystallographic characterization of this nitrogen- and sulfur-rich compound, whose molecular structure was also (iii) subjected to a theoretical conformational analysis by means of a DFT-study.

2. Results and Discussion

The synthesis of *N-p*-fluorothiosemicarbazone **2** is achieved through a condensation reaction of *p*-fluorophenylisothiocyanate with phosphonated hydrazone **1**. The ^1H and ^{13}C $\{^1\text{H}\}$ NMR spectra of this compound didn't show any impurities, even the ^{19}F NMR spectrum contained only the signals of product **2** (Figure S1). However, after crystallization from hot ethanol, a partial decomposition due to cleavage of the $\text{Ph}_2\text{P}(=\text{O})$ moiety is observed, resulting in the formation of a secondary product, bis(*N-p*-fluorophenylthiourea) **3**. Whereas compound **2** displays resonances at about δ 29 ppm in its ^{31}P $\{^1\text{H}\}$ NMR spectrum, that of **3** is silent for this nucleus. To fully characterize this new compound, it was synthesized independently via a nucleophilic addition reaction of *p*-fluorophenylisothiocyanate with hydrazine monohydrate (Scheme 1).



Scheme 1. Synthesis of *N-p*-fluorothiosemicarbazone **2** and bis(*N-p*-fluorophenylthiourea) **3**.

The structure of compound **3** was confirmed by NMR, IR spectroscopy, and X-ray crystallography. In the IR spectrum of **3**, the strong bands at 3222 and 3074 cm^{-1} are assigned to N-H stretching. The C-N stretching frequency is observed at 1409 cm^{-1} . The thione C=S stretching band

appears at 1180 cm^{-1} (Figure S2). This is in good agreement with the characteristic absorption bands observed in the theoretical IR spectrum (Figure S3) and in accordance with the literature [13,14]. The ^1H -NMR spectrum recorded in $\text{DMSO-}d_6$ (Figure 2) reveals the aryl signals in the range δ 7.15 to 7.53 ppm. The broad signal at δ 9.91 ppm can be assigned to the proton of the NH group attached to the phenyl ring, and consequently, the second resonance at δ 9.71 ppm is attributed to the NH group adjacent to the C=S group. The proton-decoupled ^{13}C NMR spectrum (Figure 3) reveals a signal at δ 182.48 ppm, characteristic for a thiocarbonyl group. The doublet appearing at 159.86 ppm is assigned to the carbon C2 due to a strong $^1J_{\text{FC}}$ coupling of 241 Hz. The remaining peaks observed between 115 and 136 ppm correspond to aromatic carbons, as attributed in Figure 2. Both the ^1H and ^{13}C NMR spectra reveal the presence of other signals, we suppose that they are due to a second conformational isomer in low equilibrium concentration.

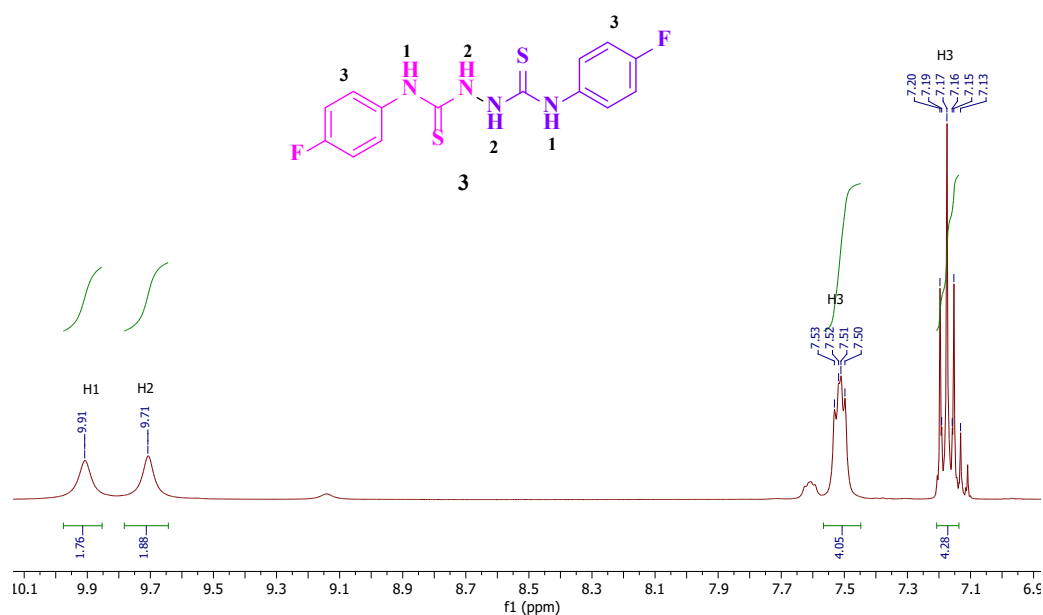


Figure 2. ^1H NMR spectrum (400 MHz, $\text{DMSO-}d_6$) of compound **3** at 298 K. The remaining weak resonances indicate the presence of a second conformer of **3** at low equilibrium concentration.

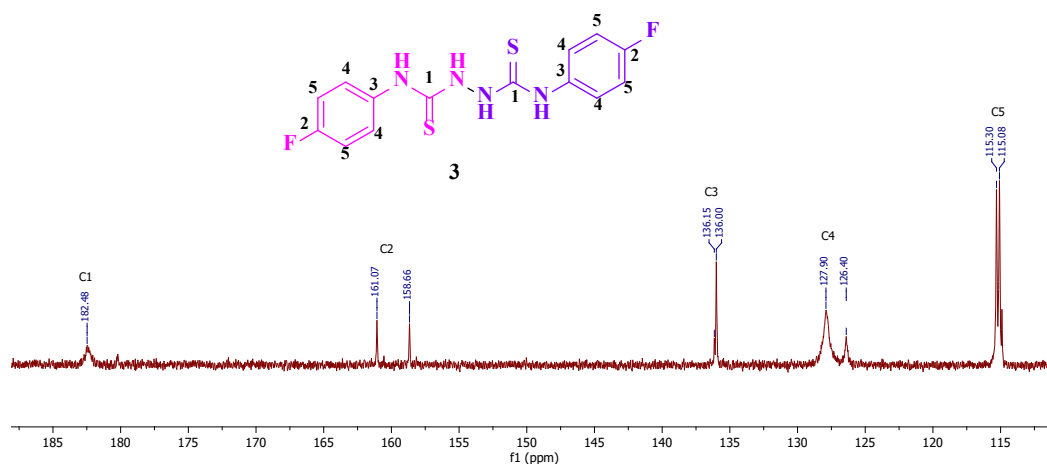


Figure 3. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (100 MHz, $\text{DMSO-}d_6$) of compound **3** at 298 K. The $\text{DMSO-}d_6$ signal has been cut off.

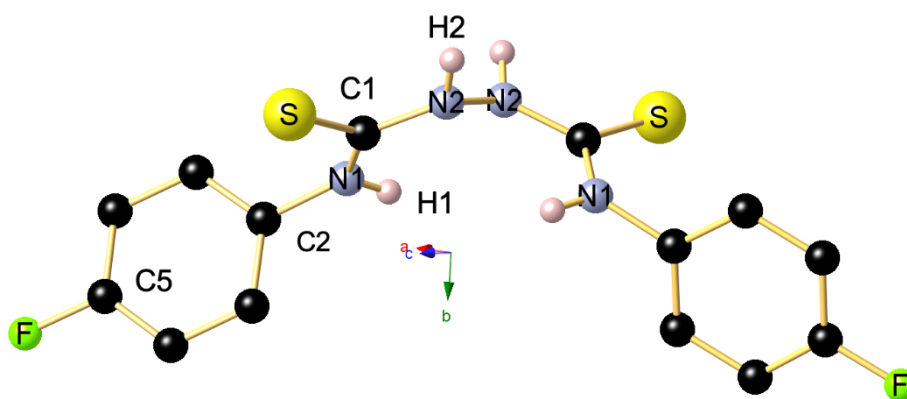


Figure 4. Molecular structure of **3** in the crystal. Selected bond lengths (Å) and angles (°): S1–C1 1.6970 (17), F1–C5 1.366 (2), N2–N2' 1.404 (3), N2–C1 1.367 (2), N1–C1 1.332 (2), N1–C2 1.440 (2); C1–N2–N2' 119.70 (16), C1–N1–C2 122.29 (14), N2–C1–S1 118.08 (12), N1–C1–N2 118.08 (15), C3–C2–N1 119.35 (16), C7–C2–N1 119.77 (16), F1–C5–C4 118.36 (19), F1–C5–C6 118.33 (19). Symmetry operation to generate equivalent atoms: $1+x, +y, 3/2-z$.

As shown in Figure 4, a crystallographic investigation of bis(*N*-*p*-fluorophenylthiourea) **3** performed at 100 K shows that the molecule is highly symmetric, the midpoint of the central N2–N2' bond being an inversion center. Both the C1–N1 and C1–N2 bonds of 1.332(2) and 1.367(2) Å are shorter than the C2–N1 bond (1.440 (2) Å), reflecting a partial double bond character. The torsion angle C1–N2–N2'–C1 amounts to -125.52° , so **3** adopts a *s-cis* or *cisoid* conformation similar to that reported in previous studies for related derivatives bearing a phenyl or cyclohexyl cycle (see also below for the conformational analysis) [15,16]. In fact, Akinchan *et al.* studied bis(*N*-phenylthiourea) and found a *s-cis* conformation of the two thiosemicarbazone moiety (Figure 5a). A *s-cis* conformation of the thiosemicarbazone moiety was also reported by Jaiswal *et al.* [16] for the structure of bis(*N*-cyclohexylthiourea) Figure 5b). However, a *transoid* conformation around the central N–N bond was crystallographically ascertained for *N,N'*-bis(benzamidothiocarbonyl)hydrazine (Figure 5c) and for *N,N'*-(hydrazine-1,2-diyl dicarbonothioyl)bis(2-chlorobenzamide) [17–19]. This *transoid* conformation observed for the latter benzoyl derivatives is probably forced by an intramolecular O...H bonding.

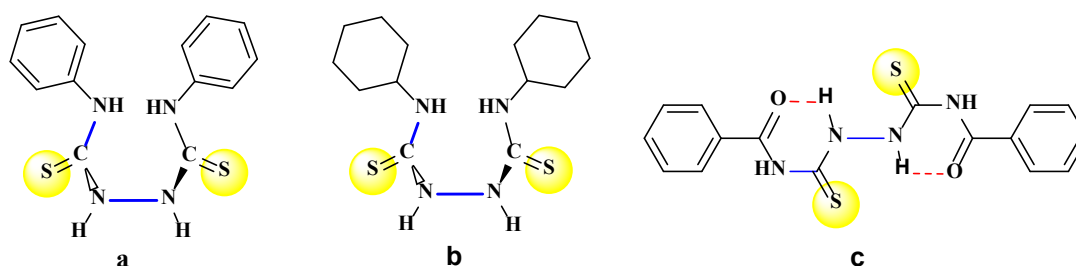


Figure 5. Other examples of crystallographically characterized bis(thioureas) adopting a *cisoid* (a, b) or a *transoid* conformation (c) with respect to the central N–N bond.

All hydrogen atoms from the NH groups are involved in intermolecular hydrogen bonds with sulfur atoms as shown in Figure 6.

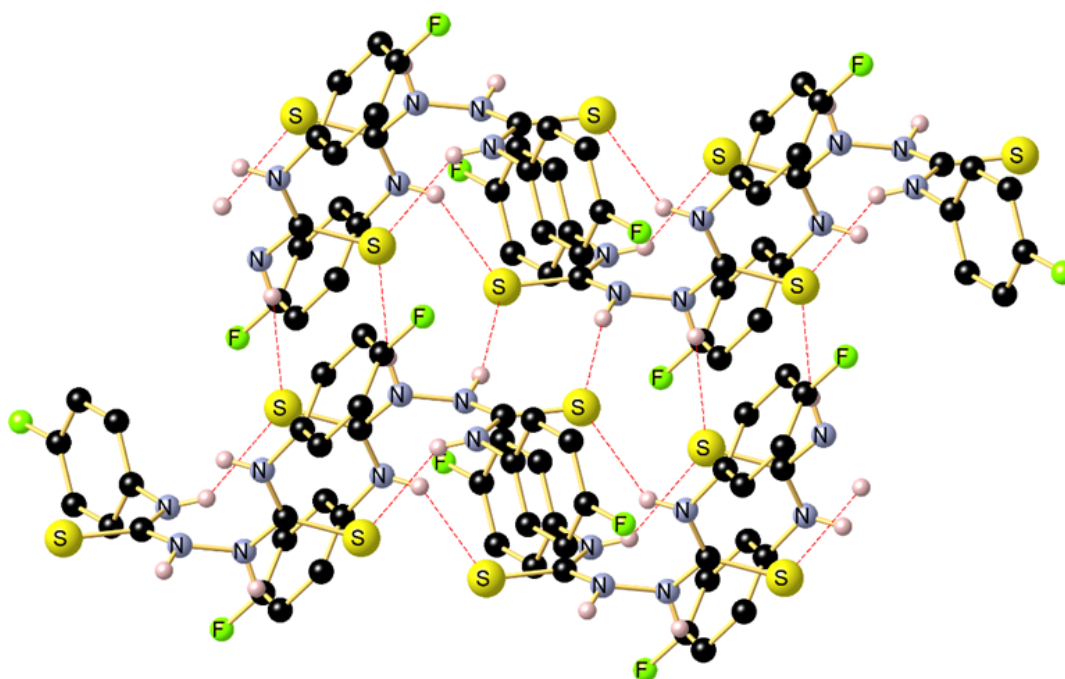


Figure 6. Supramolecular secondary interactions occurring in the crystal structure of **3**.

Additionally, the inter- and supramolecular interactions of compound **3** were further analyzed using a Hirshfeld analysis. *CrystalExplorer21* was employed to calculate a three-dimensional Hirshfeld surface [20]. The surface is depicted in Figure 7. Particularly significant are the very strong N2–H2...S1 interactions in the solid state, which are prominently observable. The bond length of 3.2749(16) Å (N2–S1) and the highly linear bond angle of 164.4(19) ° further confirm the presence of a strong hydrogen bond within the crystal. As the entire molecule is symmetrically related to the asymmetric unit, this type of interaction occurs twice with two different molecules in the solid state, leading to the formation of four strong contacts. Moreover, additional interactions can be identified on the Hirshfeld surface. The somewhat weaker N1–H1...S1 interaction, despite having a shorter overall bond length of 3.2675(15) Å (N1–S1), exhibits a smaller angle of 141.9(18) °. As a result, the H2–S1 contact is shorter [2.42(2) Å] compared to the longer H1–S1 contact [2.56(2) Å]. Nevertheless, multiple contacts are present here as well, which contribute to the extended supramolecular network. Finally, a weaker C6–H6...F1 interaction is observed, with a bond length of 3.291(2) Å (C6–F1) and an angle of 135.8(18) °. This indicates that, due to the lower degree of linearity, this interaction is relatively weak. The analysis of the fingerprint plots, whose illustrations can be found in the Supporting Information (Figure S4), also suggests that the S–H contacts are particularly pronounced and reflect the most significant supramolecular interactions.

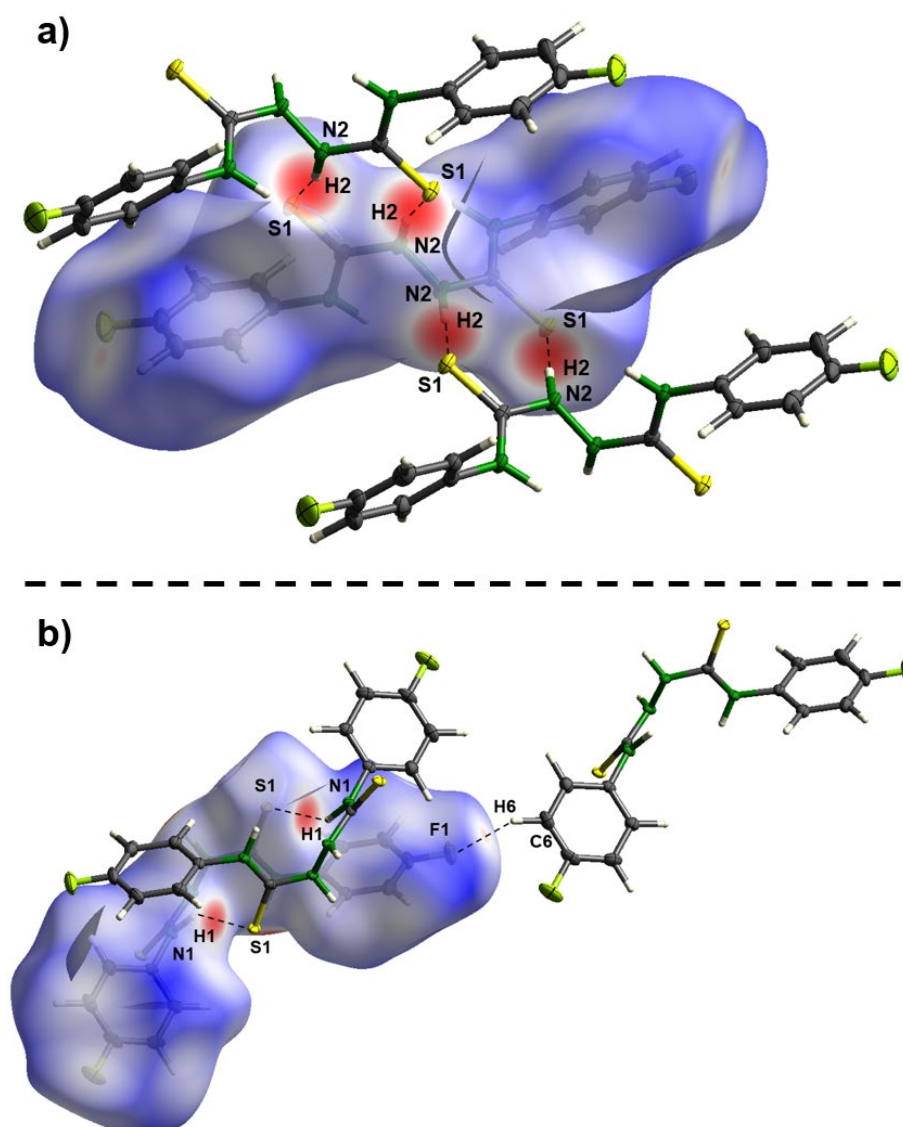


Figure 7. Hirshfeld surface of compound **3** (−0.4235 to 1.5420 arbitrary units): a) Visualization of the very strong N2–H2⋯S1 interactions with two other molecules in the solid state; b) Representation of the strong N1–H1⋯S1 interactions with another molecule in the solid state, as well as weak C6–H6⋯F1 interactions in the solid state of compound **3**.

To optimize the electronic structure of bis (*N*-*p*-fluorophenylthiourea) **3**, a theoretical study DFT calculation using the B3LYP/ 6-311++ G (d, p) basis set was performed both in the gas and solvent (ethanol) phases. The optimized molecular geometry of **3** adopting an *s-cis* or *cisoid* conformation of the thiosemicarbazone moiety is reported in Figure 8.

A comparison of selected geometrical parameters of the DFT-optimized structures in gas-phase as well as in ethanol with the experimental structure obtained by SCXRD was investigated. The essential bond lengths and angles values are shown in Table 1, the torsion angles are given in Table S3. It can be observed that calculated parameters are very close to the experimental ones. Indeed, the calculated C5–N4–N21–C22 torsion angle equal to -127.52° in the gas phase (-119.95° in EtOH) corresponds well to the experimental value of -125.65° , indicating a skew conformation of the molecule (Table S3). A similar conformation was crystallographically found for the bis(*N*-phenylthiourea) (Figure 5a) with a

C5–N4–N21–C22 torsion angle of $-121.8(3)^\circ$ [15].

Also, the calculated S1–C5 bond of 1.666 Å in the gaseous phase (1.684 Å in ethanol) is similar to the experimental value of 1.697(17) Å, revealing a double bond character (Table 1). These values match again with those reported in the literature [15, 16]. For example, Akinchan *et al.* [15]

experimentally found the bond length of S1-C5 in the bis(*N*-phenylthiourea) (Figure 5a) equal to 1.681(3) Å. Jaiswal *et al.* reported experimental and calculated values (using DFT, B3LYP, 6-311 ++ G (d, p), in gaseous phase) of 1.695(3) and 1.696 Å for the S1-C5 bond in bis(*N*-cyclohexylthiourea) (Figure 5b) [16].

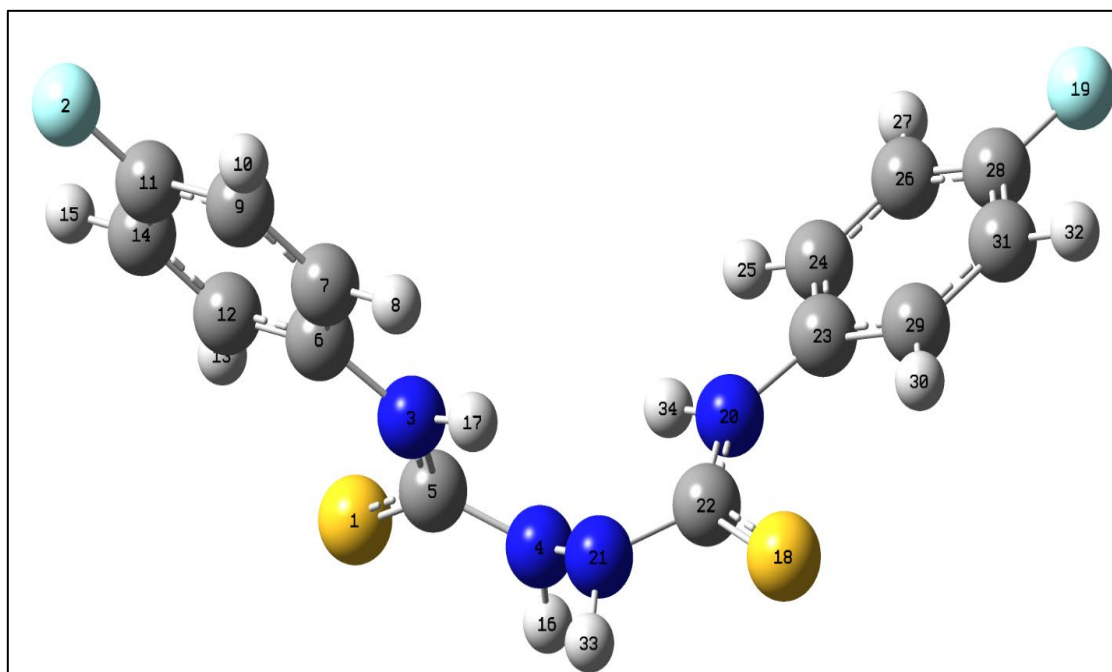


Figure 8. Optimized structure of 3 using DFT/ B3LYP/6-311++ G (d,p).

Table 1. Selected bond lengths (Å) and angles (°) for 3 from X-ray diffraction and DFT optimization.

Bond lengths (Å)	Exp SCXRD	Calc. in gas phase	Calc. in EtOH	Angles (°)	Exp. SCXRD	Calc. in gas phase	Calc. in EtOH
S1-C5	1.697 (17)	1.666	1.684	C5-N4-N21	119.70 (16)	120.35	120.84
F2-C11	1.366 (2)	1.354	1.361	C5-N3-C6	122.29 (14)	132.86	127.48
N4-N21	1.404 (3)	1.396	1.392	N4-C5-S1	118.08 (12)	117.25	118.46
N4-C5	1.367 (2)	1.415	1.388	N3-C5-S1	123.81 (13)	130.02	126.85
N3-C5	1.332 (2)	1.349	1.343	C7-C6-N3	119.35 (16)	115.79	118.59
N3-C6	1.440 (2)	1.416	1.426	N3-C5-N4	118.08 (15)	112.69	114.68
C6-C7	1.394 (2)	1.402	1.395	F2-C11-C9	118.36 (19)	118.94	118.71

*The atom numbering is shown in the optimized structure of 3.

3. Materials and Methods

All reagents were obtained from commercial suppliers and used without further purification. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were acquired using a Bruker AC 400 spectrometer (Bruker, Wissembourg, France) operating at 400 MHz and 100 MHz, respectively. The infrared spectrum was recorded in ATR mode using a Vertex 70 spectrometer (Bruker, Wissembourg, France).

Synthesis of compound 2: *p*-fluorophenyl-isothiocyanate (0.01 mol, 1.53g) was added dropwise to a solution of β -phosphonate hydrazone 1 (0.01 mol, 2.72 g) and absolute ethanol (25 mL). The reaction mixture is stirred at room temperature until the formation of white precipitate. Yield = 2.3 g, 65%, $\text{C}_{22}\text{H}_{21}\text{FN}_3\text{OPS}$ (M.W. = 425.46 g. mol $^{-1}$) white solid, mp ($^{\circ}\text{C} \pm 2$): 198. *Z*-isomer: $^{31}\text{P}\{^1\text{H}\}$ NMR ($\text{DMSO}-d_6$) at 298 K: 28.94. ^{19}F NMR ($\text{DMSO}-d_6$) at 298 K: -117.41. ^1H NMR ($\text{DMSO}-d_6$) at 298 K: 1.81 (d, $^4J_{\text{HP}}$ 2.2 Hz, 3H, CH_3), 4.01 (d, $^2J_{\text{HP}}$ 15.55 Hz, 2H, $\text{CH}_2\text{-P}$), 7.14-7.94 (m, H_{arom}), 9.84 (s, 1H, N-NH), 11.16 (s, 1H, NH-*p*-F-Ph). $^{13}\text{C}\{^1\text{H}\}$ NMR ($\text{DMSO}-d_6$) at 298 K: 25.82 (d, $^3J_{\text{CP}}$ 2.51 Hz, CH_3), 126.85-136.00 (m, C_{arom}), 146.54 (d, $^2J_{\text{CP}}$ 9.08 Hz, C=N), 159.91 (d, $^1J_{\text{CF}}$ 241.8 Hz, C-F), 177.59 (s, C=S). *E*-isomer: $^{31}\text{P}\{^1\text{H}\}$ NMR

(DMSO- d_6) at 298 K: s, 26.97. ^{19}F NMR (DMSO- d_6) at 298 K: -117.33. ^1H NMR (DMSO- d_6) at 298 K: 2.01 (d, $^4J_{\text{HP}}$ 1.35 Hz 3H, CH_3), 3.73 (d, $^2J_{\text{HP}}$ 13.4 Hz, 2H, $\text{CH}_2\text{-P}$), 7.14-7.94 (m, H_{arom}), 9.63 (s, 1H, N-NH), 10.72 (s, 1H, NH- p -F-Ph). $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6) at 298 K: 19.01 (d, $^3J_{\text{CP}}$ 2.51 Hz, CH_3), 34.61 (d, $^1J_{\text{CP}}$ = 61.69 Hz, $\text{CH}_2\text{-P}$), 126.85-136.00 (m, C_{arom}), 147.89 (d, $^2J_{\text{CP}}$ 8.9 Hz, C=N), 159.83 (d, $^1J_{\text{CF}}$ 241.9 Hz, C-F), 176.89 (s, C=S).

Synthesis of compound 3: p -fluorophenyl isothiocyanate (0.01 mol, 1.53 g) was dissolved in 25 mL of ethanol. To this solution, hydrazine monohydrate (0.005 mol, 0.25 g) was added dropwise. The resulting mixture was then stirred at room temperature for 2 hours. The precipitate was filtered and washed with ice-cold ethanol and crystallized from hot ethanol. Yield: (1.35 g, 80%). $\text{C}_{14}\text{H}_{12}\text{F}_2\text{N}_4\text{S}_2$ (M.W. = 338.39 g.mol $^{-1}$) white solid, mp >225 °C, IR-ATR: 3074 $\nu(\text{NH})$, 1180 $\nu(\text{C}=\text{S})$ cm^{-1} . ^{19}F NMR (DMSO- d_6) at 298 K: -117.48. ^1H NMR (DMSO- d_6) at 298 K: δ 7.15-7.53 (m, H_{arom}), 9.71 (s, $\text{HN-C}=\text{S}$), 9.91 (s, HN-Ar) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6) at 298 K: δ 115.19 (C5), 127.15 (C4), 136.00 (C3), 159.86 (d, $^1J_{\text{CF}}$ 242.1 Hz, C2), 182.48 (C1) ppm.

The crystallographic data collection was performed on a Bruker D8 Venture four-circle diffractometer from Bruker AXS GmbH (Karlsruhe, Germany). CPAD detectors used were Photon II from Bruker AXS GmbH; X-ray sources: Microfocus source $\text{I}\mu\text{S}$; and microfocus source $\text{I}\mu\text{S}$ Mo and Cu, respectively, from Incoatec GmbH with mirror optics HELIOS and a single-hole collimator from Bruker AXS GmbH. Programs used for data collection were APEX4 Suite [21] (v2021.10-0) and integrated programs SAINT (V8.40A; integration) as well as SADABS (2018/7; absorption correction) from Bruker AXS GmbH [21]. The SHELX programs were used for further processing [22]. The solution of the crystal structures was done with the help of the program SHELXT [23], the structure refinement with SHELXL [24]. The processing and finalization of the crystal structure data was done with program OLEX2 v1.5 [25]. All non-hydrogen atoms were refined anisotropically. For the hydrogen atoms, the standard values of the SHELXL program were used with $U_{\text{iso}}(\text{H}) = -1.2 U_{\text{eq}}(\text{C})$ for CH_2 and CH and with $U_{\text{iso}}(\text{H}) = -1.5 U_{\text{eq}}(\text{C})$ for CH_3 . All H atoms were refined freely using independent values for each $U_{\text{iso}}(\text{H})$.

Crystal data for $\text{C}_{14}\text{H}_{12}\text{F}_2\text{N}_4\text{S}_2$, $M = 338.39 \text{ g}\cdot\text{mol}^{-1}$, white crystals, crystal size $0.231 \times 0.147 \times 0.032 \text{ mm}^3$, monoclinic, space group C2/c $a = 26.6377(17) \text{ \AA}$, $b = 6.4831(4) \text{ \AA}$, $c = 9.2178(6) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 96.244(3)^\circ$, $\gamma = 90^\circ$, $V = 1582.42(17) \text{ \AA}^3$, $Z = 4$, $D_{\text{calc}} = 1.420 \text{ g/cm}^3$, $T = 100 \text{ K}$, $R_1 = 0.0600$, $R_w = 0.0785$ (all data) for 12604 reflections with $I > 2\sigma(I)$ and 2051 independent reflections, GOF = 1.058 Largest diff. peak/hole / $\text{e \AA}^{-3}$ 0.27/-0.27.

Data were collected using graphite monochromated $\text{MoK}\alpha$ radiation $\lambda = 0.71073 \text{ \AA}$ and have been deposited at the Cambridge Crystallographic Data Centre as CCDC 2382121. (Supplementary Materials). The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk/getstructures>.

Theoretical calculations

All computations were performed with the Gaussian 09 program [26, 27]. The conformation was optimized using DFT geometry optimizations using hybrid B3LYP [28] functional and the 6-311++ G (d, p) basis set. To be sure that all optimized structure lay at a local point on the potential energy surface, harmonic vibrational frequencies of all structures were performed. None of the predicted spectra has any imaginary frequencies.

4. Conclusions

We have demonstrated that the N - p -fluorothiosemicarbazone $\text{Ph}_2\text{P}(=\text{O})\text{CH}_2\{\text{C}=\text{N-NH}(\text{C}=\text{S})\text{-N}(\text{H})\text{C}_6\text{H}_4\text{F}\}\text{CH}_3$ **2** is readily accessible as main product by treatment of hydrazone $\text{Ph}_2\text{P}(=\text{O})\text{CH}_2\text{C}(=\text{N-NH}_2)\text{CH}_3$ **1** with p -fluorophenyl-isothiocyanate. As side-product, also formation of minor amounts of bis(N - p -fluorophenylthiourea) **3** was evidenced, which alternatively has been synthesized in a targeted manner by direct addition of hydrazine hydrate to p -fluorophenylisothiocyanate. For this latter compound, whose crystal structure reveals both intra- and intermolecular secondary interactions, also a conformational analysis has been performed by means of DFT computing. We are currently investigating whether treatment of **1** with other aryl- and

alkylisothiocyanates constitutes a general synthetic access to thiosemicarbazone and are analyzing more in detail conformational aspects. We are furthermore probing their potential as functionalized *S,N* chelate ligands in coordination chemistry.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, CIF file, Check-CIF report, Hirshfeld fingerprint plots, IR.

Author Contributions: S.S. prepared the compound and D.K.-M performed the conformational analysis; C.S. and J.-L.K collected the X-ray data and solved the structure; I.J and M.K designed the study and analyzed the data and wrote the paper. A.B.-A., I.J., D.K.-M., H.M and M.K contributed with the conceptualization.

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Data Availability Statement: The X-ray data are at CCDC as stated in the paper.

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

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