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Communication

Synthesis of (Z)-3-Allyl-5-(4-nitrobenzylidene)-2-sulfanylidene-1,3-thiazolidin-4-one and Determination of Its Crystal Structure

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Abstract: To extend the existing library of arylidenerhodanines which display a potential biological activity, 3-*N*-allylrhodanine **1** was condensed under Knoevenagel conditions with *p*-nitrobenzaldehyde in acetic acid to afford the π -conjugated heterocyclic compound 3-allyl-5-(4-nitrobenzylidene)-2-sulfanylidene-1,3-thiazolidin-4-one **2**. Compound **2** was characterized by IR and NMR spectroscopy, and its UV-vis spectrum was compared with that of compound 3-allyl-5-(4-methoxybenzylidene)-2-sulfanylidene-1,3-thiazolidin-4-one **3**. The molecular structure is ascertained by a single-crystal X-ray diffraction study performed at 100 K.

Keywords: allylrhodanine; thione; crystal structure; UV-vis spectra; Knoevenagel condensation; Hirshfeld analysis



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1. Introduction

The five-membered heterocyclic compound rhodanine, also called 2-thioxo-4-thiazolidinone (see Figure 1) and its derivatives [1] not only play a role in organic chemistry as building blocks for further transformations but have also found application in various therapeutic areas [2,3] due to their broad spectrum of biological and pharmacological activities. These include antidiabetic activity [4], protein kinase inhibitors [5,6], topoisomerase II inhibition potency [7,8], anticancer activity against MCF-7 breast cancer [9,10] and potential cholinesterase inhibitors [11,12]. After approval of the *N*-substituted rhodanine Epalrestat [13] by the Food and Drug Administration (FDA) as an inhibitor drug for the treatment of diabetic neuropathy [14], several arylidene *N*-substituted rhodanine derivatives have also been identified as potential inhibitors of essential therapeutic targets such as PTP1B [15], α -amylase [16] and α -glucosidase [17] for the clinical management of Type 2 diabetes mellitus (T2DM) (Figure 1). Very recently, we successfully synthesized a series of novel dispirooxindoles-based rhodanine derivatives as potent inhibitors against α -amylase enzyme with in vivo hypoglycemic activity [18].

Arylidene-functionalized rhodanines were also recently screened to evaluate their anticancer activity against several cancer cell lines [19,20] or their propensity as antibacterial, antifungal or antioxidants agents [21–23]. In this context, we have reacted a series of 4-arylidene-5-thioxo-thiazolidin-2-ones with the secondary cyclic amine tetrahydroisoquinoline (THIQ) to convert them to (Z)-5-ylidene-2-aminothiazol-4(5*H*)-ones [18]. Some selected compounds incorporating the rhodanine motive and displaying a pharmacological activity are presented in Figure 1.

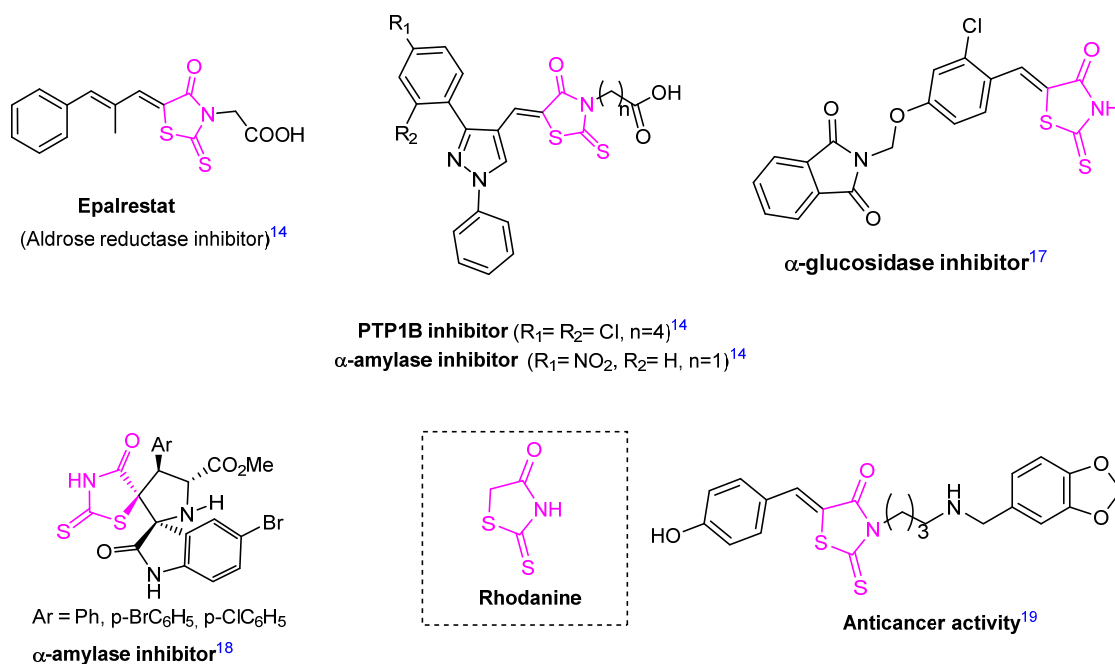
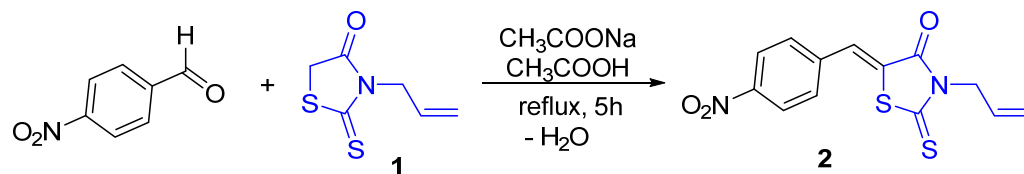


Figure 1. Examples of some rhodanines displaying a biological activity.

Furthermore, rhodanine derivatives attracted the attention of coordination chemists, since the soft C=S thione function (according Pearson's HSAB principle) [24] readily coordinates to a wide range of transition metal complexes producing complexes with Cu(I), Pd(II), Pt(II) etc. [25–28]. The research presented here is (i) a continuation of our investigations into the coordination chemistry of thione-type ligand on diverse metal centers [29–33] and (ii) the design of novel rhodanine-based scaffolds for probing their biological activities [18].

2. Results and Discussion

The hitherto unknown arylidene rhodanine derivate 3-allyl-5-(4-nitrobenzylidene)-2-sulfanylidene-1,3-thiazolidin-4-one **2** was obtained by addition of *p*-nitrobenzaldehyde to a solution of commercially available *N*-allylrhodanine **1** in acetic acid via a classical Knoevenagel condensation route [34] (Scheme 1). Note that the synthesis of an isomer of **2** bearing the NO₂ group at the meta-position has been described by Ajlaoui et al. by the reaction of *N*-allylrhodanine **1** with (3-nitrobenzylidene)-4-methyl-5-oxopyrazolidin-2-ium ylide [35] and its NH analogue 5-(3-nitrobenzylidene)-2-sulfanylidene-1,3-thiazolidin-4-one has been isolated by Hesse using an L-proline-based deep eutectic solvent [22].



Scheme 1. Knoevenagel synthesis of *N*-allylrhodanine **2**.

The structure of **2** was established using spectroscopic characterization and elemental analysis. On the infrared spectrum, an intense band at 1700 cm⁻¹ is associated with the carbonyl group and the thiocarbonyl vibration is observed at 1217 cm⁻¹. The NO stretching bands of the nitro group are located at 1509 and 1327 cm⁻¹ and the $\nu(\text{C}=\text{C})$ appear near 1590 cm⁻¹ (see Figure S1). The ¹H-NMR recorded in *d*₆-DMSO (Figure 2) reveals the aryl signals as doublets at δ 7.91 and 8.36 ppm. The chemical shift in the vinyl proton at δ 7.93 indicates that the exocyclic double bond has a *Z*-configuration, as already observed for other 5-arylidene rhodanines described in the literature [6]. Its signal appears at a lower

field than that of the *E*-isomer due to the stronger deshielding effect of the carbonyl group compared to the sulfur atom [36]. Four multiplets between 4.90–5.90 ppm are assigned to the allyl group. A pseudo doublet of triplet is present at δ 4.67 for the NCH₂, resulting from ³*J* and ⁴*J* allylic couplings of 5.2 and 1.4 Hz, respectively. The terminal vinyl gives rise to two broad doublets of doublets at δ 5.17 and 5.21 ppm with *trans* and *cis* coupling across the double bond of 17.7 (H1H2) and 10.9 (H'1H2) Hz. The two doublets at δ 5.15 and 5.22 are broad with a small coupling of 1.2 Hz. These apparent quartets result from a ⁴*J* allylic coupling with H3 and a geminal ²*J* coupling between H1H'1s with similar values. (Figure 1). The proton decoupled ¹³C NMR spectrum (Figure 3) reveals the presence of two signals at δ 193.2 and 166.9 ppm attributed to the thiocarbonyl and carbonyl groups of the rhodanine moiety. A resonance at δ 46.7 corresponds to NCH₂, and olefinic carbon appears at 118.4 (C1) and 130.6 (C2, C7).

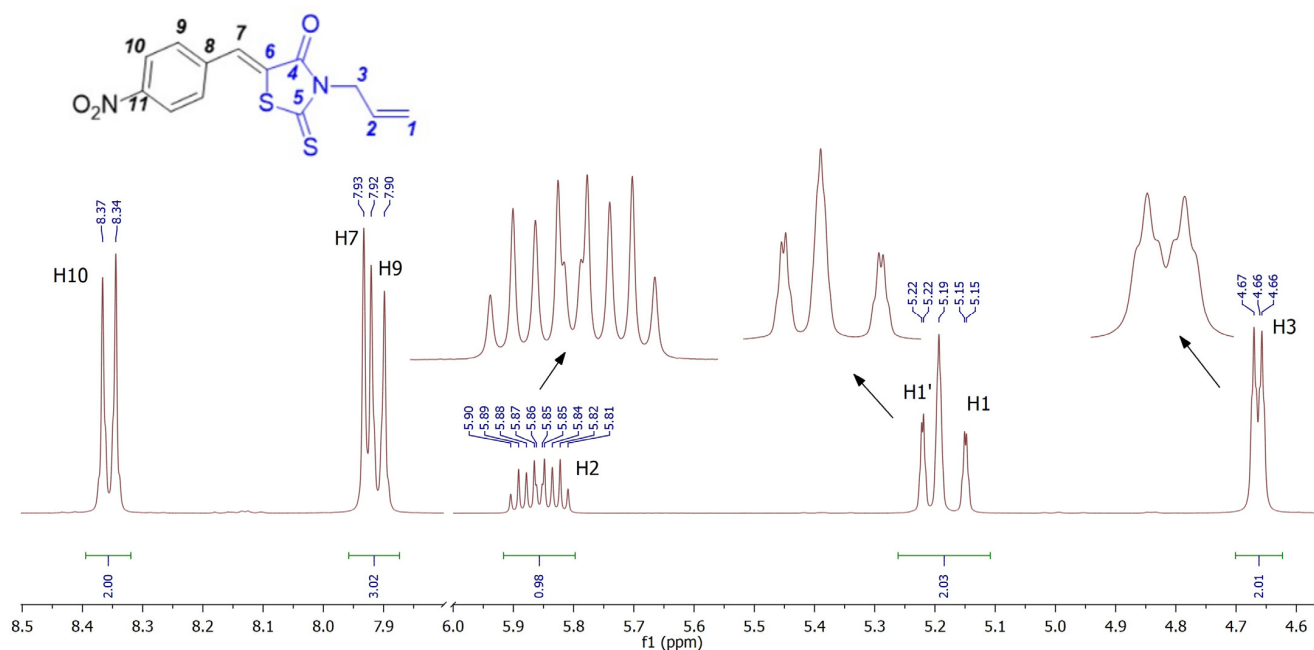


Figure 2. ¹H NMR spectra (400 MHz, DMSO-d₆) of compound **2** at 298 K.

The UV-vis spectrum of highly π -conjugated **2** bearing a strongly electron-withdrawing NO₂-group exerting a -M effect is shown in Figure 4. For comparison, we have also recorded the benzylidene derivative **3** bearing a MeO-group (+M effect) at the *para*-position of the aryl cycle [34]. This literature-known compound has been synthesized using the same experimental procedure described for **2** in 84% yield. The superposition of their UV-vis spectra reveals a bathochromic shift in the absorption bands for **2** compared to **3**, indicating that the NO₂-group causes a diminution in the energetic gap between the frontier orbitals HOMO-LUMO with respect to the methoxy group. The UV-vis spectra recorded in solvents of different polarity are shown in the Supplementary Materials as Figure S2. We tentatively attribute the adsorption bands presented in Table 1 as *n*- π^* and π - π^* transitions but exclude a push-pull effect despite the strong acceptor propensity of the *p*-nitro group.

Table 1. Absorption data of compounds **2** and **3** in CH₂Cl₂ at 298 K.

Comp.	Absorption: λ_{abs} nm ($\epsilon \times 10^{-3} \text{M}^{-1} \text{cm}^{-1}$)
2	239 (5.5), 281 (6.7), 303 sh (4.8), 381 (17.9), 399 sh (16.0)
3	242 (2.8), 262 (3.2), 294 (6.1), 313 sh (3.6), 399 (18.1)

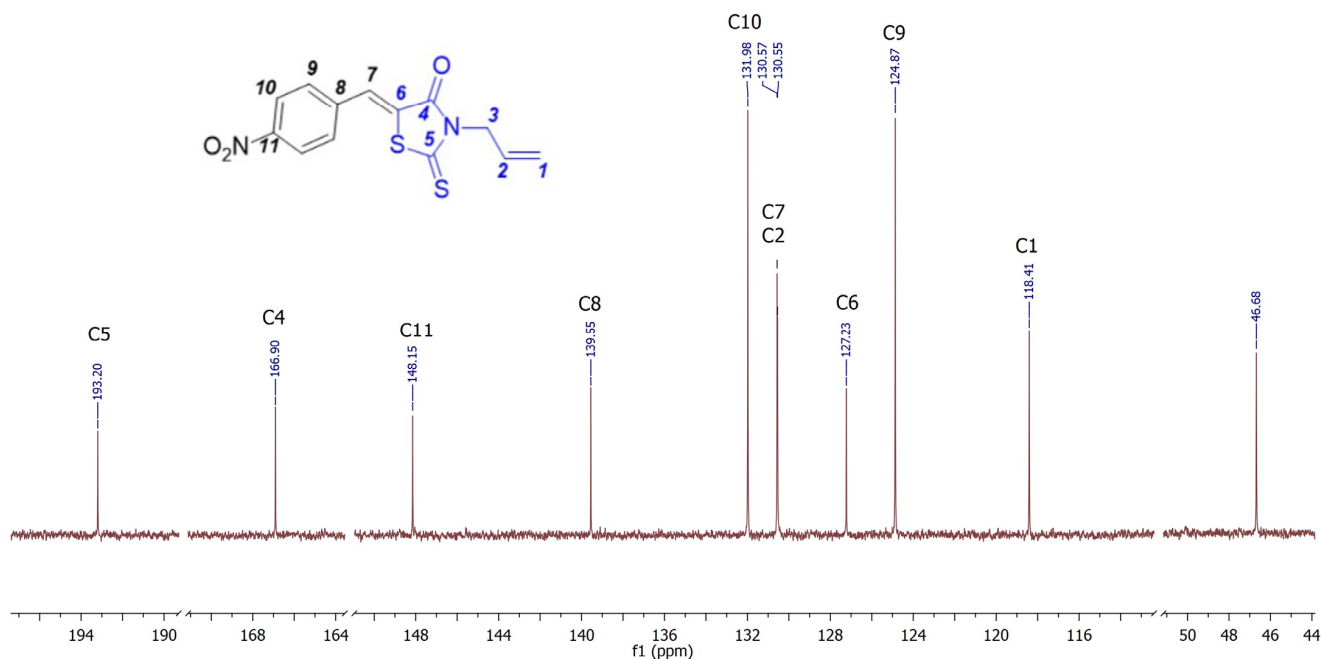


Figure 3. ^{13}C NMR spectra (100 MHz, DMSO-d_6) of compound **2** at 298 K. The DMSO-d_6 signal has been cut off.

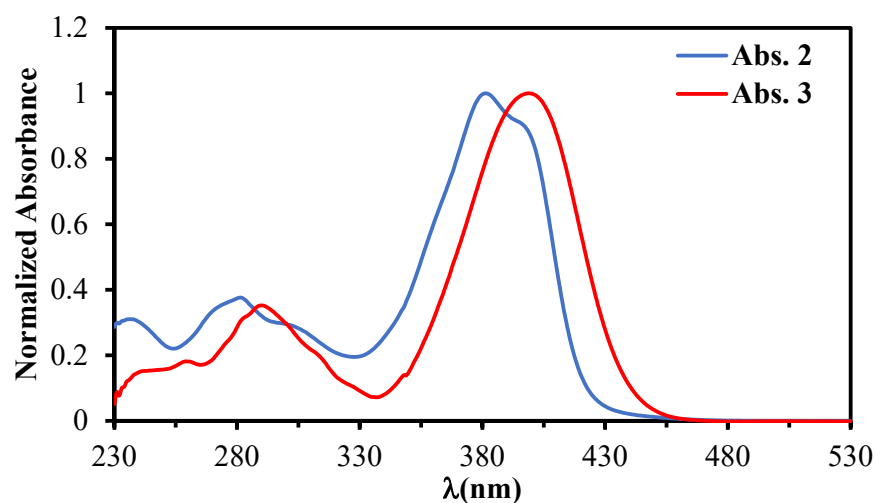


Figure 4. Superposition of the normalized absorption spectra recorded of **2** and **3** in CH_2Cl_2 at 298 K.

To complete the characterization of this compound, we examined **2** crystallizing in the monoclinic space group $P2_1/c$ by an X-ray diffraction study performed at 100 K. As shown in Figure 5, the two cycles linked through the $\text{C6}=\text{C7}$ double bond are almost coplanar including the nitro group (torsion angle: $5.81(5)^\circ$); the allyl substituent points out of this plane in a perpendicular manner (torsion angle C4N1C1C2 93.6°). The C8 atom of the six-membered benzylidene cycle and the S1 atom are *cis*-arranged with respect to the $\text{C6}=\text{C7}$ double bond. Overall, the structure resembles those of other benzylidenerhodanines found in the Cambridge Structural Database (CSD) such as 3-allyl-5-(3-methoxybenzylidene)-2-sulfanylidene-1,3-thiazolidin-4-one (refcod GACVOY) [37], 3-allyl-5-(4-fluorobenzylidene)-2-sulfanylidene-1,3-thiazolidin-4-one (refcod ISAMIA) [38], 3-allyl-5-(4-chlorobenzylidene)-2-sulfanylidene-1,3-thiazolidin-4-one (refcod JADVUI) [39] and 5-benzylidene-3-(prop-2-en-1-yl)-2-sulfanylidene-1,3-thiazolidin-4-one (refcod QIBKOE) [35]. Other crystallographically characterized *N*-allyl rhodanines containing five-membered heterocycles within their framework are 2-thio-3-allyl-5-(2-(3'-methylthiazolidinyldene))-thiazolidine-2,4-dione (ref-

cod SALAZO) [40] and (*E*)-3-Allyl-5-(2-thienylmethylene)-2-thioxo-1,3-thiazolidin-4-one (refcod MUGFUR) [41]. Particularly noteworthy is the occurrence of an intramolecular C-H...S contact between the H9 atom attached at C9 of the aromatic cycle and S1 forming a *pseudo*-six-membered cycle with $d(\text{C-H} \cdots \text{S})$ 2.51 Å, with the angle C-H...S being 133.4°. This kind of contact is also observed in the structures JADVUI ($d(\text{C-H} \cdots \text{S})$ 2.55 Å, angle 133°) and GACVOY ($d(\text{C-H} \cdots \text{S})$ 2.55 Å, angle 133°) [37].

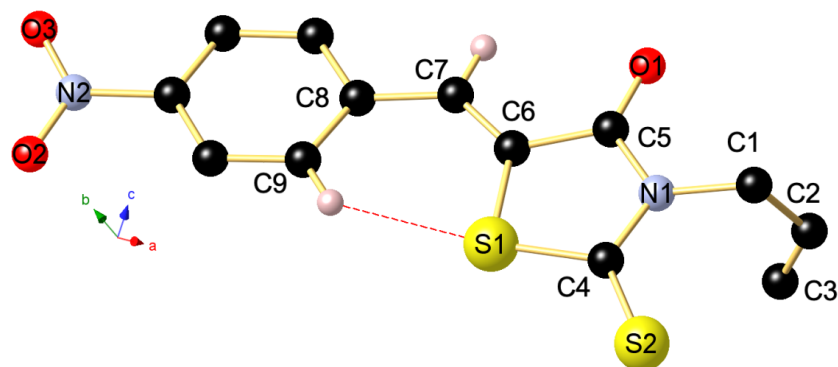


Figure 5. Molecular structure of **2**. Selected bond lengths (Å) and angles (deg) of **2**. Apart from H7 and H9, all other H atoms are omitted for clarity. S1–C6 1.7536(16), S1–C4 1.7614(16), S2–C4 1.6227(16), N1–C4 1.375(2), N1–C1 1.472(2), C1–C2 1.375(2), C2–C3 1.314(3), N1–C5 1.388(2), C5–O12 1.217(2), C5–C6 1.487(2), C6–C7 1.346(2), C7–C8 1.458(2); C3–C2–C1 127.19(16), C2–C1–N1 113.87(14), C1–N1–C4 122.77(14), N1–C4–S2 127.50(13), N1–C4–S1 110.22(11), C4–S1–C6 92.80(8), S1–C6–C5 109.14(11), S1–C6–C7 130.41(12), C6–C5–N1 110.90(13), C6–C7–C8 130.11(14), O2–N2–O3 123.61(14).

In the packing (Figure 6), several secondary weak intermolecular interactions are present such as C-H contacts with the NO₂ group of neighbored molecules ($d(\text{C13-H13} \cdots \text{O2}^1)$ 2.505(11) Å, angle 153.4°, symmetry code ¹ $1 + x, y, 1 + z$) and ($d(\text{C3-H3B} \cdots \text{O3}^2)$ 2.70(2) Å, angle 162.0°, symmetry code ² $1 - x, 1 - y, -z$). Furthermore, a shorter C-H...O contact occurs with the carbonyl C=O ($d(\text{C10-H10} \cdots \text{O1}^1)$ 2.4260(13) Å, angle 130.7°). An intermolecular C-H...S contact occurs between a CH group of the allyl substituent and the thione function ($d(\text{C2-H2} \cdots \text{S2}^3)$ 2.9259(5) Å, angle 144.0°, symmetry code ³ $1 + x, 1/2 - y, -1/2 + z$). As observed for the *p*-chloro derivative [39], the cohesion of the crystal structure also is ensured by an π - π stacking interaction between individual molecules forming inversion dimers. The centroid-to-centroid separation between two stacked benzylidene rings amounts to 3.7986(12) Å (see Figure S3).

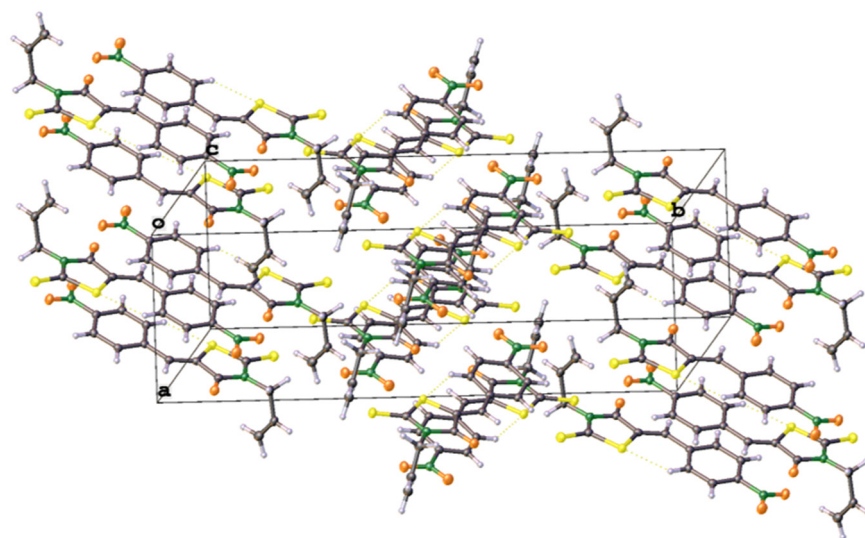


Figure 6. OLEX-generated view of the unit cell of **2** indicating the π - π stacking interaction between individual molecules [42].

These interactions have also been assessed by means of a Hirshfeld surface analysis using the *CrystalExplorer17* software (Figure 7) [43,44]. The Hirshfeld surface was mapped over d_{norm} in the range from -0.2156 to -1.1392 (arbitrary units). The corresponding fingerprints plots are presented in the Supplementary Materials (Figure S4).

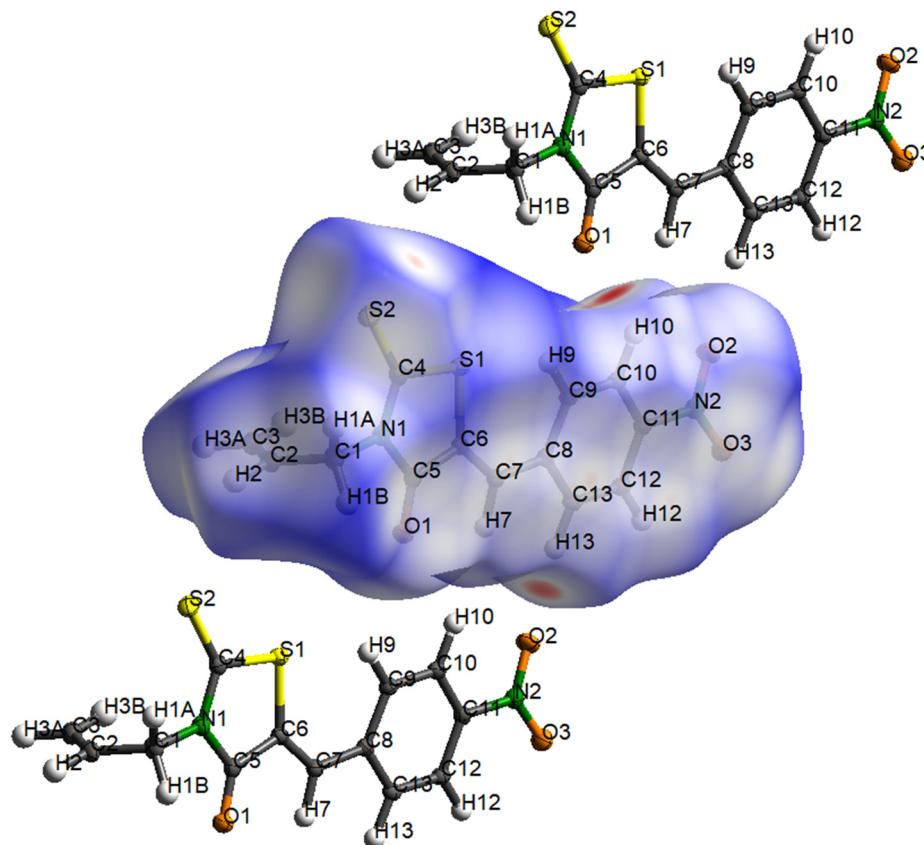


Figure 7. View of the Hirshfeld surface of compound **2** revealing some loose contacts in the crystal structure.

3. Materials and Methods

All reagents were purchased from commercial suppliers and used as received. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 400 (Bruker, Wissembourg, France) spectrometer at 400 and 100 MHz, respectively. The infrared spectrum was recorded on a Vertex 70 spectrometer (Bruker, Wissembourg, France) in ATR mode. UV–Visible spectra were obtained on a VARIAN–Cary 300 array spectrophotometer (Varian, Melbourne, Australia). Elemental analyses were performed on a Thermo Fisher Flashsmart CHNS elemental analyzer.

A mixture of 3-allylrhodanine (1.73 g, 10 mmol), anhydrous sodium acetate (0.82 g, 10 mmol) and 4-nitrobenzaldehyde (1.90 g, 12.5 mmol) was refluxed in 10 mL of glacial acetic acid for 5 h. After cooling, yellow crystals were collected by filtration and washed with H_2O (2×5 mL), EtOH (2×5 mL) and Et $_2\text{O}$ (5 mL). Yield: 95%. Anal. Calc. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3\text{S}_2$ (M.W = $306.37 \text{ g}\cdot\text{mol}^{-1}$): C, 50.97; H, 3.29; N, 9.14; S, 20.93%. Found: C, 50.99; H, 3.38; N, 9.28; S, 20.87%. IR-ATR: $1700 \nu(\text{C}=\text{O})$, $1217 \nu(\text{C}=\text{S}) \text{ cm}^{-1}$. ^1H NMR (DMSO- d_6) at 298 K: δ 4.66 (td, $^3J = 5.2$, $^4J = 1.4$, 2H_3 , NCH_2), 5.17 (dd, $^3J = 17.7$, $J = 1.2$, H1 , $=\text{CH}_2$), 5.21 (dd, $^3J = 10.9$, $J = 1.2$, $\text{H1}'$, $=\text{CH}_2$), 5.85 (tdd, $^3J = 17.7$, $^3J = 10.9$, $^4J = 5.2$, H2 , $=\text{CH}$), 7.91 (d, $^3J = 8.82$, 2H9 , Ar-H), 7.93 (s, H7 , $=\text{CH}$), 8.35 (d, $^3J = 8.82$, 2H10 , Ar-H) ppm. ^{13}C NMR (DMSO- d_6) at 298 K: δ 46.7 (C3), 118.4 (C1), 124.9 (C9), 127.2 (C6), 130.5 and 130.6 (C7, C2), 132.0 (C10), 139.6 (C8), 148.2 (C11), 166.9 (C5), 193.2 (C4) ppm.

Since the grown single crystals of **2** used for the determination of the crystal structure were quite small, $\text{CuK}\alpha$ radiation was employed instead of $\text{MoK}\alpha$ radiation. A suitable crys-

tal was mounted on an Bruker APEX-II CCD diffractometer Crystal data for $C_{13}H_{10}N_2O_3S_2$: $M = 306.35 \text{ g}\cdot\text{mol}^{-1}$, plate-shaped dark yellow crystals, crystal size $0.90 \times 0.55 \times 0.14 \text{ mm}^3$, monoclinic, space group $P2_1/c$ $a = 7.8215(4) \text{ \AA}$, $b = 26.4778(17) \text{ \AA}$, $c = 7.1851(4) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 116.5790(10)^\circ$, $\gamma = 90^\circ$, $V = 1130.75(13) \text{ \AA}^3$, $Z = 4$, $D_{\text{calc}} = 1.529 \text{ g/cm}^3$, $T = 100 \text{ K}$, $R_1 = 0.0360$, $Rw_2 = 0.0966$ (all data) for 2726 reflections with $I > 2\sigma(I)$ and 2832 independent reflections, $GOF = 1.060$ Largest diff. peak/hole/ $e \text{ \AA}^{-3}$ 0.406/−0.313. The structure was solved using intrinsic phasing and refined using full-matrix least-squares against F^2 (SHELXT, SHELXL 2015) [45,46]. The data were collected using graphite-monochromated $\text{CuK}\alpha$ radiation $\lambda = 1.54178 \text{ \AA}$ and have been deposited at the Cambridge Crystallographic Data Centre as CCDC 2327984. (Supplementary Materials). The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk/getstructures>.

4. Conclusions

We have shown that arylidenerhodanine **2** is easily accessible in high yields and crystallographically evidenced that this π -conjugated heterocycle features both intra- and intermolecular secondary interactions. We are currently exploring the propensity of this compound to act as an S-donor ligand in coordination chemistry.

Supplementary Materials: CIF file, Check-CIF report, UV-Vis and IR spectra and Hirshfeld fingerprint plots. Figures S1–S4.

Author Contributions: B.M. prepared the compound; C.S. and T.S. collected the X-ray data and solved the structure; I.J., S.B. and M.K. designed the study and analyzed the data and wrote the paper. All authors have read and agreed to the published version of the manuscript.

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

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

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