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Communication

Synthesis of (5Z)-3-Allyl-5-{[5-(4-methoxyphenyl)thiophen-2-yl]methylidene}-2-sulfanylidene-1,3-thiazolidin-4-one in L-Proline-Based Deep Eutectic Solvent

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Abstract: 3-*N*-allylrhodanine was condensed with 5-(4-methoxyphenyl)-thiophene-2-carbaldehyde in an L-proline-based deep eutectic solvent (DES) to obtain the π-conjugated heterocyclic rhodanine compound (5Z)-3-allyl-5-{[5-(4-methoxyphenyl)thiophen-2-yl]methylidene}-2-sulfanylidene-1,3-thiazolidin-4-one (**2**). Compound **2** was characterized by NMR spectroscopy, and its UV-vis spectrum was compared with that of the related derivative 3-allyl-5-(4-methoxybenzylidene)-2-sulfanylidene-1,3-thiazolidin-4-one (**1**). Preliminary results revealed that compound **2** is emissive at room temperature in solution.

Keywords: allylrhodanine; Knoevenagel condensation; deep eutectic solvent; UV-vis spectra; fluorescence

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1. Introduction

Rhodanines, thiazolidinediones, thiazolidinones and barbituric derivatives are very interesting heterocyclic compounds, and have been studied for a long time, as they present a number of pharmacological activities [1,2]. A review that recently analyzed the anticancer features of the rhodanines described over the last decade in the literature discusses the structure–activity relationship of those rhodanine derivatives [3]. Especially, the authors focused on substituents introduced in positions 3 and 5, trying to push forward further development of rational drug design. For example, analysis of the literature results suggests that the presence of a heteroaryl moiety in position 5 may allow better anticancer activity [3]. Rhodanine derivatives also display many other biological activities, such as inhibiting human carbonic anhydrase [4], α-amylase and α-glucosidase inhibitors [5], and as antihyperglycemic [6] or antimicrobial agents [7]. We previously described 2-(heteroarylimino)-1,3-thiazolidin-4-ones having an antiproliferative effect against human colon and breast cancer-derived cells [8] or being CDC25A inhibitors [9]. More recently, we worked on the functionalization of rhodanines via Knoevenagel reaction in an L-proline-based DES instead of employing a conventional Knoevenagel condensation protocol using organic solvents as the reaction medium. Some of the synthesized 5-arylidenerhodanines showed interesting antioxidant properties [10]. We then extended this zero-VOC strategy for Knoevenagel reaction to thiazolidine-2,4-dione and barbituric acid [11].

We present here the synthesis of the hitherto unknown 5-arylidenerhodanine **2** obtained from 5-(4-methoxyphenyl)-thiophene-2-carbaldehyde. This compound presents similarities with rhodanine-3-acetic acid derivative **A**, which was studied as a fluorescent probe for neurofibrillary tangles in Alzheimer's disease brains [12] (Figure 1). It is also related to donor–acceptor compounds, such as **B**, described in 2020 in the search for new thiophene-based dyes for organic metal-free dye-sensitized solar cells [13].

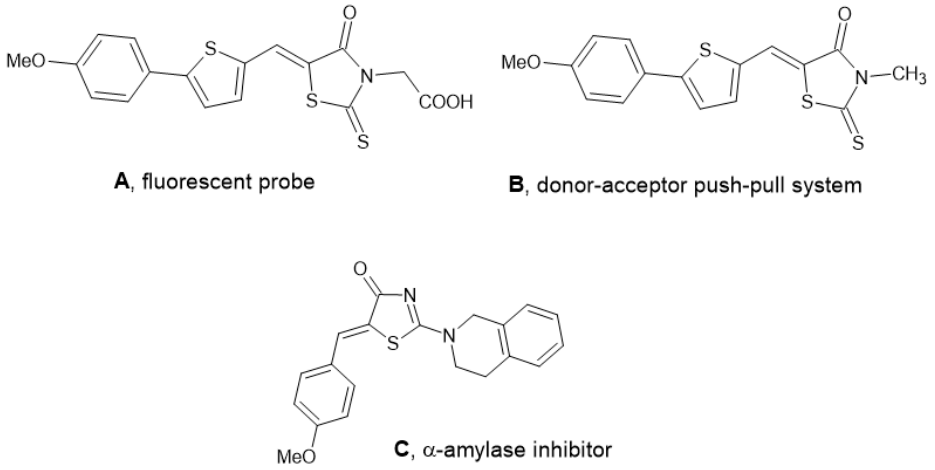


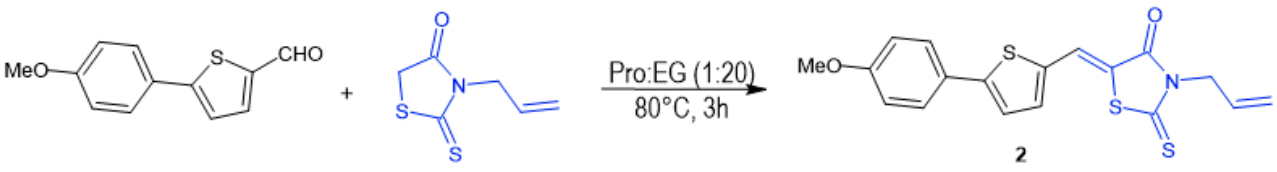
Figure 1. Examples of rhodanines displaying biological or photophysical activities.

So, compound **2** may be interesting for biological activities or for photoelectronic applications, but can also be studied by coordination chemists, as the C=S thione function present in rhodanine may coordinate with transition metal and form Cu(I) or Ag(I) complexes [14]. A nucleophilic addition of 1,2,3,4-tetrahydroisoquinoline (THIQ) may also take place on the thione function giving 2-aminothiazol-4(5*H*)-one similar to derivative **C**, described as an α-amylase inhibitor (Figure 1) [15].

2. Results and Discussion

Recently, we showed that L-proline-based DESs were very powerful when performing Knoevenagel condensations in short reaction times with high yields and without any purification [10,11]. However, the DES Pro:Gly (1:2) we previously used is quite viscous at ambient temperature [16], and, therefore, is sometimes not very easy to handle. Particularly, in some cases with certain substrates, agitation became very difficult over time when precipitation occurred in the reaction media. So, we turned our attention to other L-proline-based DESs that are less viscous.

5-(4-Methoxyphenyl)-thiophene-2-carbaldehyde was synthesized according to the reported procedure [17] and engaged in Knoevenagel condensation with *N*-allylrhodanine in Pro:EG (1:20). After 3 h at 80 °C, the reaction workup only involved the addition of water for separating the targeted product from the aqueous phase containing the DES. Derivative **2** was obtained in pure form at a 96% yield, and no further purification was needed (Scheme 1).



Scheme 1. Synthesis of targeted rhodanine **2**.

The ^{1}H-NMR spectrum (Figure 2) was in agreement with the reported spectra of compounds **A** and **B** [12,13]. Especially, the vinylic proton appeared at δ 8.07 ppm, which indicates a *Z*-configuration for the exocyclic double bond, as usually observed in 5-arylidene rhodanines [18,19]. Camero et al. have shown that a *Z*/*E* photoisomerization is possible on 2-(1,1-dicyanomethylene)rhodanines functionalized with oligothiophenes [20]. In this case, the vinylic proton appearing at δ 8.0–8.15 ppm in the *Z*-form was offset to δ 7.30–7.45 ppm in the *E*-form [20].

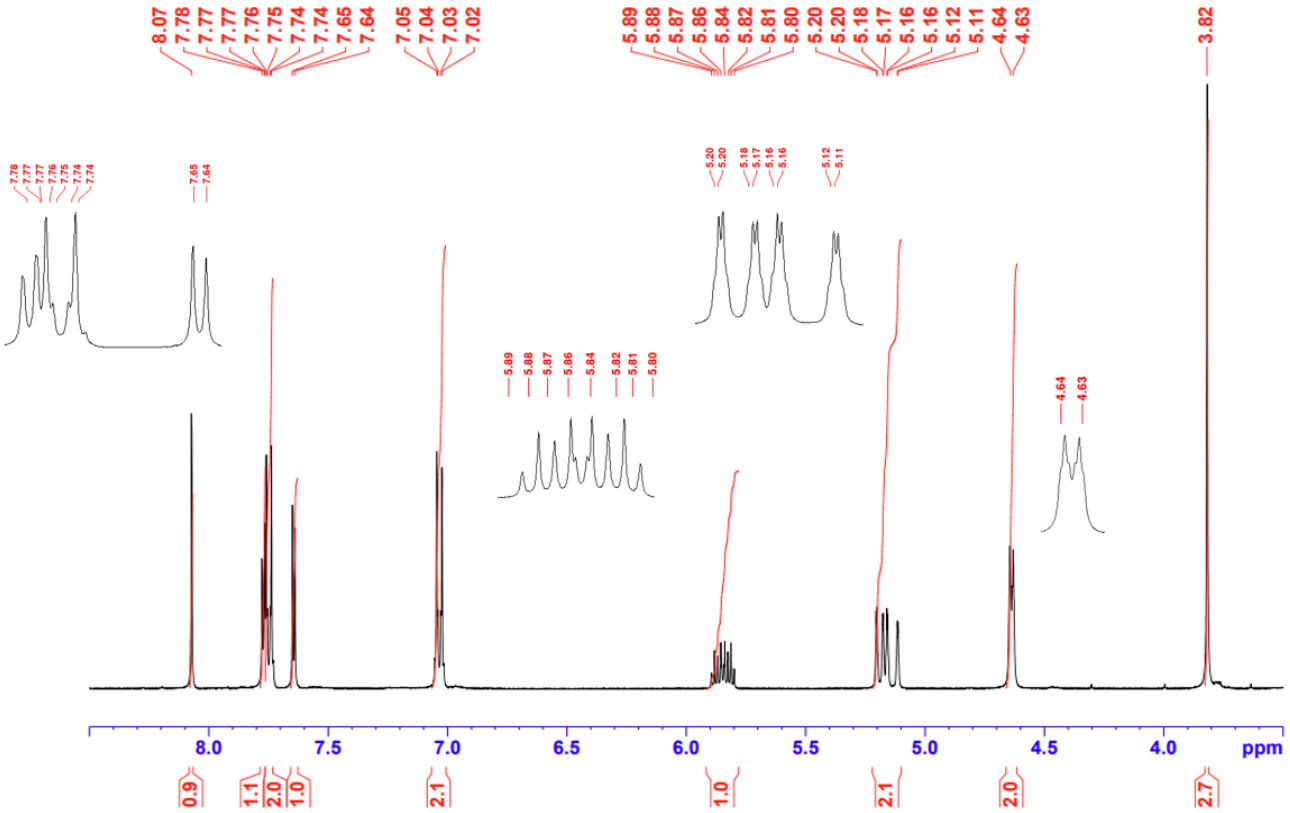


Figure 2. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of derivative **2**.

The thiophene ring gave rise to two doublets at δ 7.64 and 7.77 ppm with a ^{3}J coupling of 3.8 Hz, whereas the aromatic protons appeared at δ 7.03 and 7.75 ppm with a ^{3}J coupling of 8.3 Hz. Signals of the protons in the allyl group were observed between 4.63 and 5.89 ppm and were consistent with reported data on *N*-allylrhodanines [21,22]. A pseudo doublet of triplets appeared at δ 4.63 ppm for the NCH_2, two doublets of doublets could be seen at δ 5.19 and 5.13 ppm for the terminal vinylic protons (with *Jtrans* = 17.0 Hz, *Jcis* = 10.1 Hz and *Jgem* = 1.4 Hz), and the signal at δ 5.84 ppm corresponded to the internal vinylic proton.

The $^{13}C\{^{1}H\}$ NMR also showed characteristic signals of the N-allyl group (CH_2 at δ 46.2 ppm and $=CH_2$ at δ 118.5 ppm) and rhodanine moiety (C=S at δ 191.8 and C=O at δ 166.3 ppm). The structure of compound **2** was also confirmed by HRMS analysis (see Figures S3 and S4 in Supplementary Materials).

Finally, the UV-vis spectrum of highly π-conjugated **2** bearing a thiophene linker was compared to that of 3-allyl-5-(4-methoxybenzylidene)-2-thioxothiazolidin-4-one **1** (Figure 3). This literature-known compound [22,23] had already been synthesized in our former study [21]. Firstly, the introduction of a thiophene moiety between the *N*-allylrhodanin and anisole fragments induced an increase in the molar extinction coefficients of all bands (Table 1). Secondly, there was a bathochrome effect of about 23 nm for the first band and, which is remarkable, of 59 nm for the second band. This bathochromic shift was due to the extension of the conjugation that may result in a decrease in the energy difference between the HOMO and LUMO orbitals.

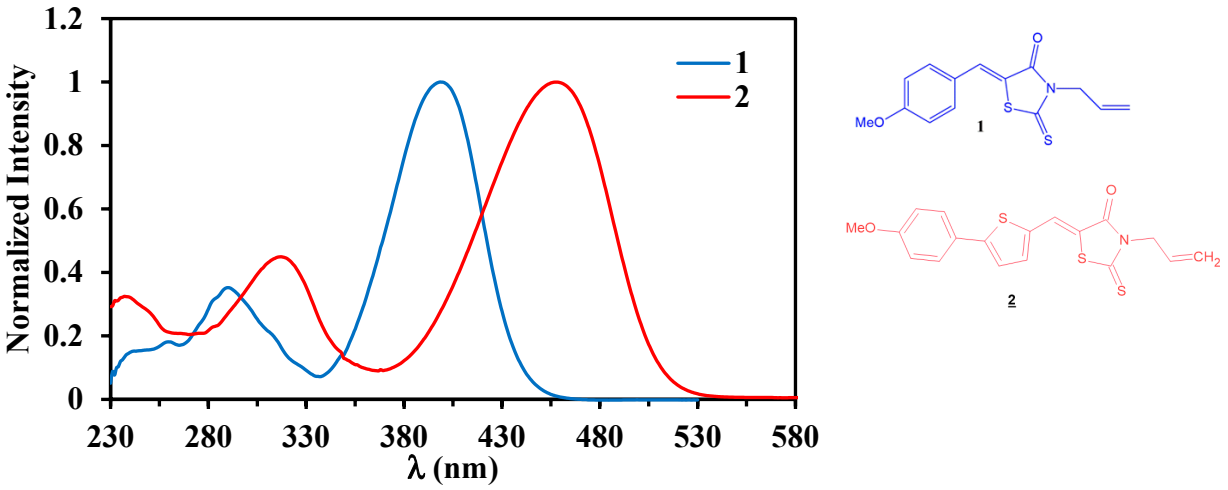


Figure 3. Superposition of normalized absorption spectra recorded for **1** and **2** in CH_2Cl_2 at rt.

Table 1. Absorption data of compounds **1** and **2** in CH_2Cl_2 at rt.

Compound	Absorption: λ_{abs} nm ($\varepsilon \times 10^{-3}$ $M^{-1}cm^{-1}$)
1	242 (2.8), 262 (3.2), 294 (6.1), 313 sh (3.6), 399 (18.1)
2	236 (6.3), 317 (8.8), 458 (19.5)

During this study, we were also interested in the luminescence properties of compound **2** in solution. After excitation at 450 nm, an intense emission band was observed (Figure 4) with a maximum at 535 nm. The fluorescence quantum yield $Ø_F$ of **2** equaled 31%, and was determined using pyrene ($Ø_F$ = 27%) in CH_2Cl_2 as a luminescence quantum yield standard [24]. This fluorescence band can be assigned to the lowest energy singlet state $S_1 \rightarrow S_0$ transition. To understand more in depth the contribution of the orbitals involved in the observed emission, detailed photophysical studies and theoretical calculations regarding this compound and other molecules of this family are underway.

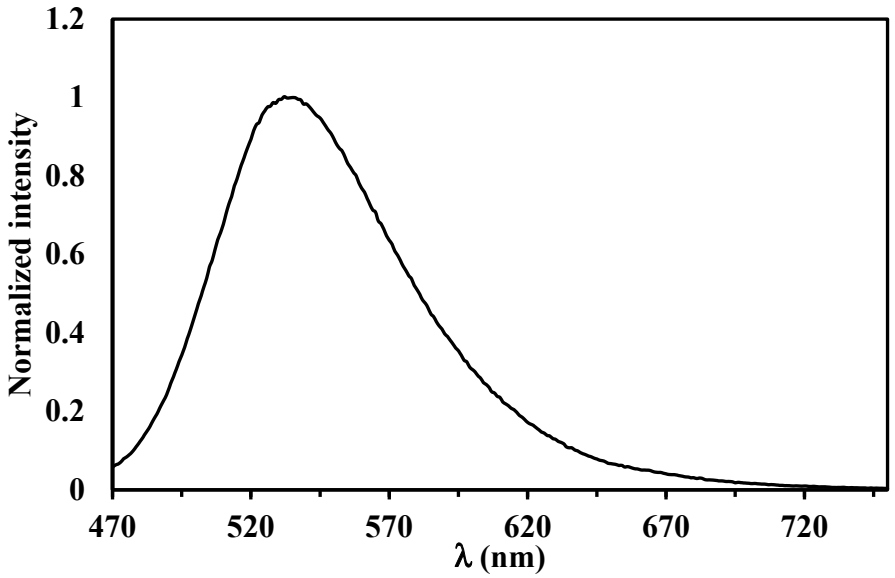


Figure 4. Normalized emission of **2** recorded in CH_2Cl_2 at room temperature.

In conclusion, we synthesized and fully characterized the new derivative **2**, which may be interesting for biological study or for further functionalization. Finally, studying luminescence properties of **2** revealed its fluorescence in solution at room temperature.

3. Materials and Methods

All reactions were routinely checked by TLC analysis on an Alugram SIL G/UV254 (Macherey-Nagel) with spots visualized by UV light. The melting point was determined in open capillaries on a Stuart SMP30 apparatus (Bibby Scientific Ltd, Staffordshire, United-Kingdom) and was uncorrected. The ^{1}H and ^{13}C-NMR spectra were measured on an AC Bruker 400 MHz spectrometer (Bruker, Wissembourg, France) in DMSO-d_6; chemical shifts are reported in parts per million (ppm). All coupling constants (*J*) are given in Hz. UV-vis spectra were obtained on a VARIAN-Cary 300 array spectrophotometer (Varian, Melbourne, Australia). The IR spectrum was obtained on a ThermoScientific Nicolet IS5 apparatus (ThermoScientific, Madison, WI, USA).

5-(4-Methoxyphenyl)-thiophene-2-carbaldehyde was prepared according to the published method [17].

Formation of DES L-Proline:Ethylene Glycol (1:20)

In a round-bottomed flask, the hydrogen bond donor and hydrogen bond acceptor were mixed in the appropriate molar ratio and stirred at 60 °C until a clear solution formed. The DES was then used without further purification.

General procedure for the Knoevenagel condensation

A total of 2 g of DES was introduced in a 10 mL round-bottom flask. Next, aldehyde (1 mmole) and N-allylrhodanine (1 mmole) were sequentially added to the DES, and the reaction mixture was stirred at 80 °C for 3 h. Water was added at room temperature and the precipitate was collected by filtration and washed with 15 mL of water. No further purification was needed.

(5*Z*)-3-Allyl-5-{[5-(4-methoxyphenyl)thiophen-2-yl]methylidene}-2-sulfanylidene-1,3-thiazolidin-4-one 2. Red solid (348 mg yield = 96%). M.p.: 149 °C. ^{1}H NMR (DMSO-d_6): δ 3.81 (s, 3H, OCH_3), 4.64 (td, *J* = 5.6 and 1.4 Hz, 2H, NCH_2), 5.13 (dd, *J* = 17.0 and 1.4 Hz, 1H, $=CH_2$), 5.19 (dd, *J* = 10.1 and 1.4 Hz, 1H, $=CH_2$), 5.84 (ddt, *J* = 10.1, 17.0 and 5.6 Hz, 1H, =CH), 7.03 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.64 (d, *J* = 3.8 Hz, 1H, H-thiophene), 7.75 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.77 (d, *J* = 3.8 Hz, 1H, H-thiophene), 8.07 (s, 1H, =CH). ^{13}C NMR (DMSO-d_6): δ 46.2, 55.4, 114.8, 117.8, 118.5, 124.7, 125.2, 126.4, 127.5, 130.3, 135.5, 138.0, 152.3, 160.3, 166.3, 191.8. HRMS LDI (-) FT-ICR: m/z [M]- calcd for $[C_{18}H_{15}NO_2S_3]^{\bullet-}$: 373.027041; found: 373.027077. IR-ATR: 1698 ν(C=O), 1205 ν(C=S) cm^{-1}.

Supplementary Materials: The following supporting information are available online: Figure S1. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of derivative **2**; Figure S2. ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of derivative **2**; Figure S3. LDI (-) FT-ICR mass spectrum achieved for sample **2** with $[C_{18}H_{15}NO_2S_3]^{\bullet-}$ ion at m/z 373.027077. Figure S4. Experimental (red) and theoretical (black) isotopic distributions for $[C_{18}H_{15}NO_2S_3]^{\bullet-}$ ion achieved by LDI (-) FT-ICR MS. Figure S5. IR spectrum of derivative **2**.

Author Contributions: S.H. prepared the compound; A.K. obtained UV-vis and emission spectra; S.H., I.J., A.K. and M.K. designed this study, analyzed data and wrote this paper. All authors have read and agreed to the published version of the manuscript.

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