



Formation, Spectral and Theoretical Studies of 1-(4,4-Dimethyl-2,6-Dithioxo-1,3,5-Triazinan-1-yl)-3-(Diethylaminocarbonyl)Thiourea

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Abstract

The reaction of diethylcarbamic chloride (one mole equivalent), ammonium thiocyanate (two mole equivalents) and thiosemicarbazide (one mole equivalent) in an acetone medium resulted in the formation of the unexpected 4,4-dimethyl-2,6-dithioxo-1,3,5-triazinan-1-yl)-3-(diethylaminocarbonyl)-thiourea in 83% yield. The chemical structure of the title compound was confirmed by IR, NMR and elemental analysis. Further, a suggested mechanism has been proposed to illustrate the route for the formation of the title compound. In addition, theoretical evaluations of the stable geometries of compound 3 were carried out using semi-empirical molecular quantum calculations with the PM3 method.

Keywords: Thiosemicarbazone, Cyclization reaction, Spectroscopic analysis, Computational calculations.

Introduction

Compounds containing 1,3,5-triazine moieties exhibit several interesting applications.¹⁻⁸ Therefore, a range of simple and efficient procedures for the synthesis of 1,3,5-triazines have been reported.⁹⁻¹¹ For instance, the reaction of a mixture of primary alcohols, aldehydes and iodine in an aqueous ammonia under microwave conditions gave the corresponding nitriles *in situ*.¹² Such intermediates undergo cycloaddition with sodium azide and dicyandiamide to give 1,3,5-triazines in high yields.¹² The reaction of nitriles with triflic acid or triflic anhydride at low temperatures gave nitrilium salts as intermediates, which reacted with nitriles at higher temperatures to give substituted 1,3,5-triazines in moderate to good yields.¹³

1,3,5-Triazines can also be produced in high yields from the reaction of carboxylic acids and zinc dimethyl imidodicarbonimidate in dichloromethane containing pyridine with

molecular sieves as an activated surface.¹⁴ Copper(II) acetate can be used as an effective catalyst to produce 1,3,5-triazine in good to excellent yields through the oxidative coupling of alcohols and amidine hydrochlorides, in air.¹⁵ Various substituted 1,2,4-triazines were also synthesized in moderate to good yields from the condensation of aldehydes, 1,2-diketones, and hydrazine hydrate in ethanol containing sodium *tert*-butoxide as a base under conventional heating or microwave irradiation.¹⁶

Moreover, 1,3,5-triazines were synthesized in moderate to good yields from carbamides and amidinothiureas, produced *in situ* from isothiocyanates and *N,N*-diethylamidines.¹⁷ On the other hand, compounds containing thiourea moieties are very useful materials.¹⁸⁻²⁰

Thioureas can be produced efficiently from amines, isocyanides, thiocyanates, and cyanamides.^{21–26} Due to their antimicrobial and antifungal properties.²⁷ The formation of compounds that contain both 1, 3, 5-triazine and thiourea moieties are of great interest. Herein, we report the reaction between diethylcarbamoyl isothiocyanate and thiosemicarbazide in acetone at reflux that yielded the unexpected product, 1-(4,4-dimethyl-2,6-dithioxo-1,3,5-triazinan-1-yl)-3-(diethylaminocarbonyl)thiourea.

The formation of this compound is based on the involvement, of one mole of acetone in the cyclization process. The entity of the synthesized product was confirmed using various spectroscopic and analytical tools. Further, semi empirical molecular orbital calculations were used to determine the nature of the interaction between different reactive sites.^{28, 29}

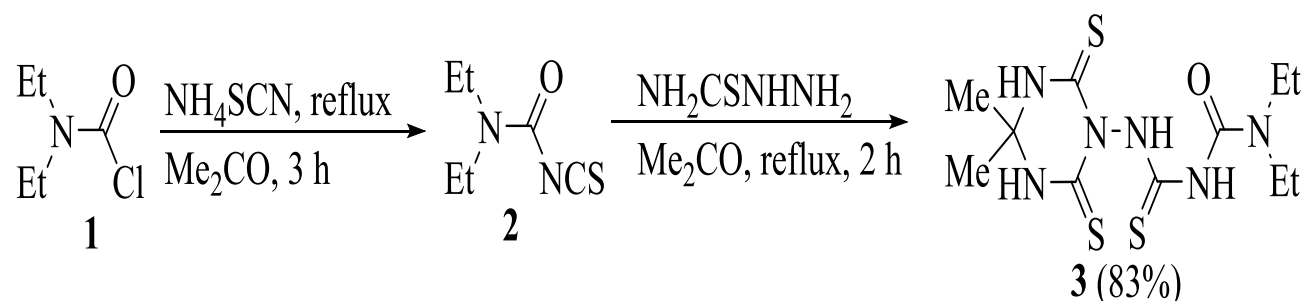
Results and Discussion

Synthesis and Characterization of 3

The reaction of diethylcarbamic chloride (**1**; one mole equivalent) and ammonium thiocyanate (two mole equivalents) in acetone under reflux for 3 h gave intermediate **2** *in*

situ. The reaction of **2** with thiosemicarbazide (one mole equivalent) in acetone under reflux for 2 h gave **3**³⁰ in 83% yield (Scheme 1). The structure of **3** was confirmed by NMR, IR, and elemental analyses. The FTIR spectrum (Fig.-1) showed characteristic stretching and bending bands at 3307, 2880, 1661, 1588, 1529, 1448, 1124, and 877 cm^{-1} , which were assigned to $\nu(\text{N-H})$, $\nu(\text{C-H})$, $\nu(\text{C=O})$, $\delta(\text{N-H})$, $\nu(\text{C-C})$, $\delta(\text{C-H})$, $\nu(\text{C-N})$, and $\nu(\text{C=S})$, respectively. No peaks around 2650 cm^{-1} due to $\nu\text{S-H}$ were observed, indicating the presence compound in its thion form.

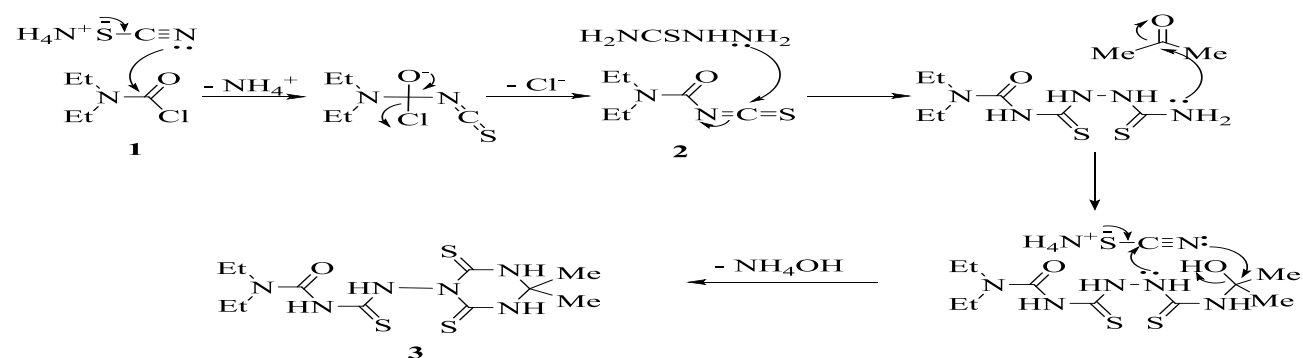
The ¹H NMR spectrum of **3** (Fig.-2) revealed the presence of three exchangeable singlets at 9.91, 7.99 and 7.52 ppm, which corresponded to the four NH protons. In addition, a quartet (2.90 ppm; $J = 6.8$ Hz) of the CH₂ segment and triplet (1.16 ppm; $J = 6.8$ Hz) of the CH₃ group corresponding to the two ethyl protons were observed. The two methyl protons appeared as a singlet at 1.88 ppm. The ¹³C NMR spectrum (Fig.-3) showed two peaks at 185.31 and 178.78 ppm, corresponding to the two C=S carbons. The carbonyl group was observed at 152.2 ppm. All of the expected carbons were observed (see experimental section for details).



Scheme 1: Synthetic route of **3**.

A suggested mechanism for the formation of **3** is shown in Scheme 2. The mechanism involves the reaction of **1** with ammonium thiocyanate to give intermediate **2**. The

reaction of **2** with thiosemicarbazide and one mole of acetone followed by reaction with a second mole of ammonium thiocyanate gave **3** as a final product (Scheme 2).



Scheme 2: The suggested mechanism for the formation of **3**.

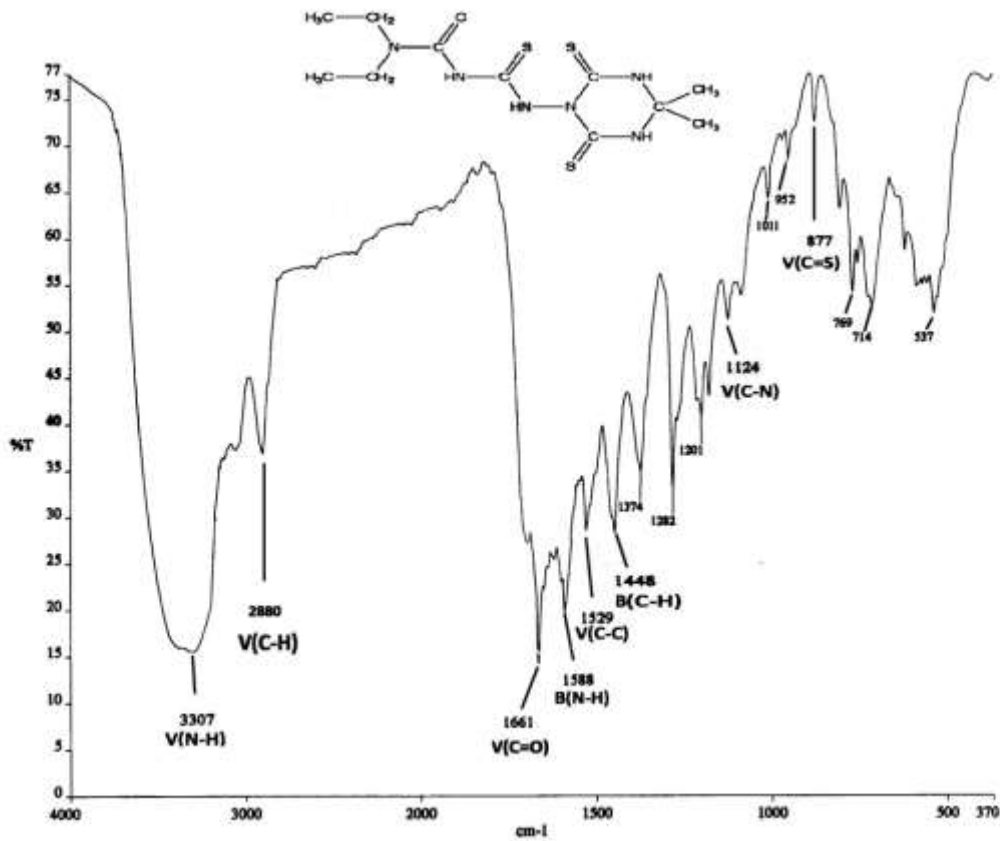


Figure 1: The FT-IR spectrum of 3.

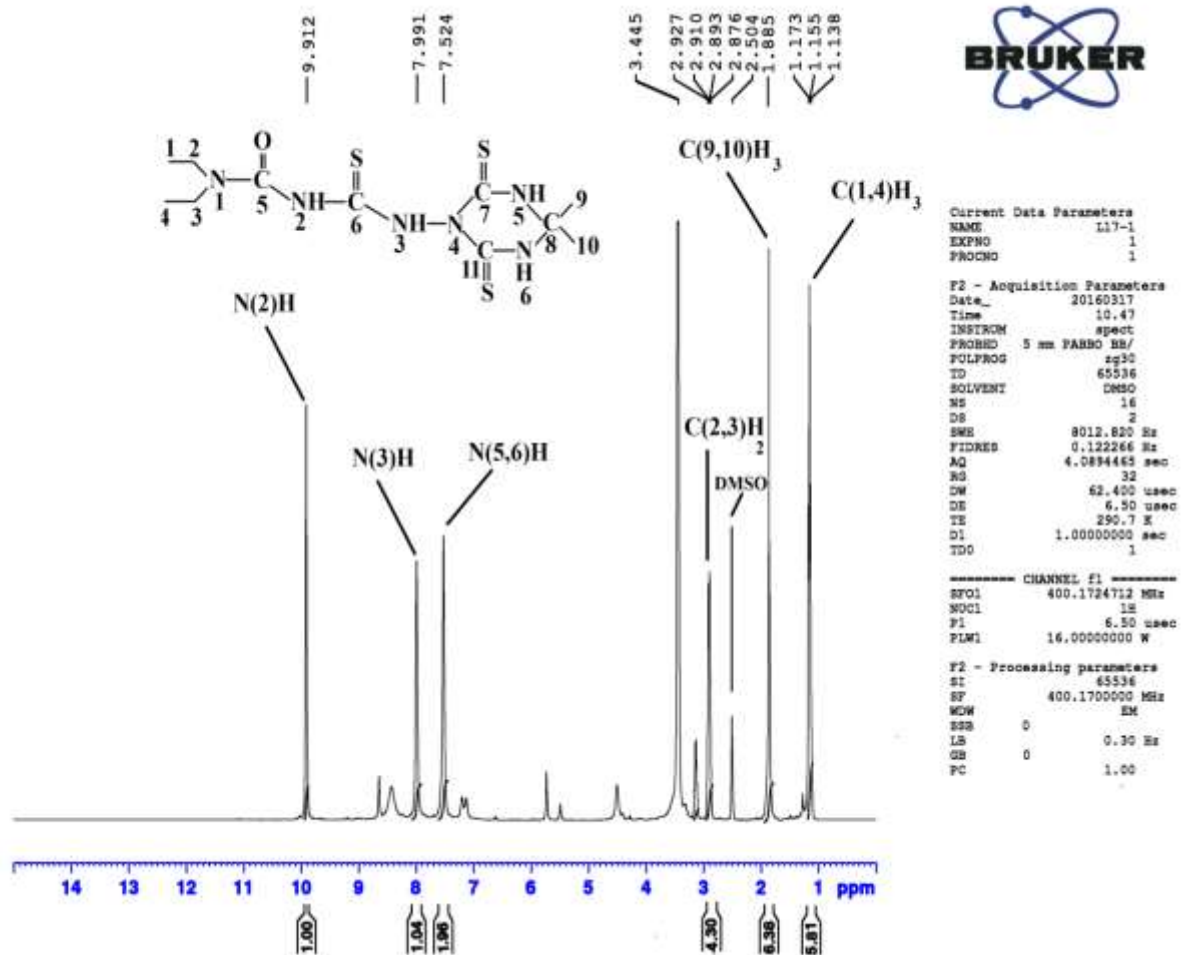
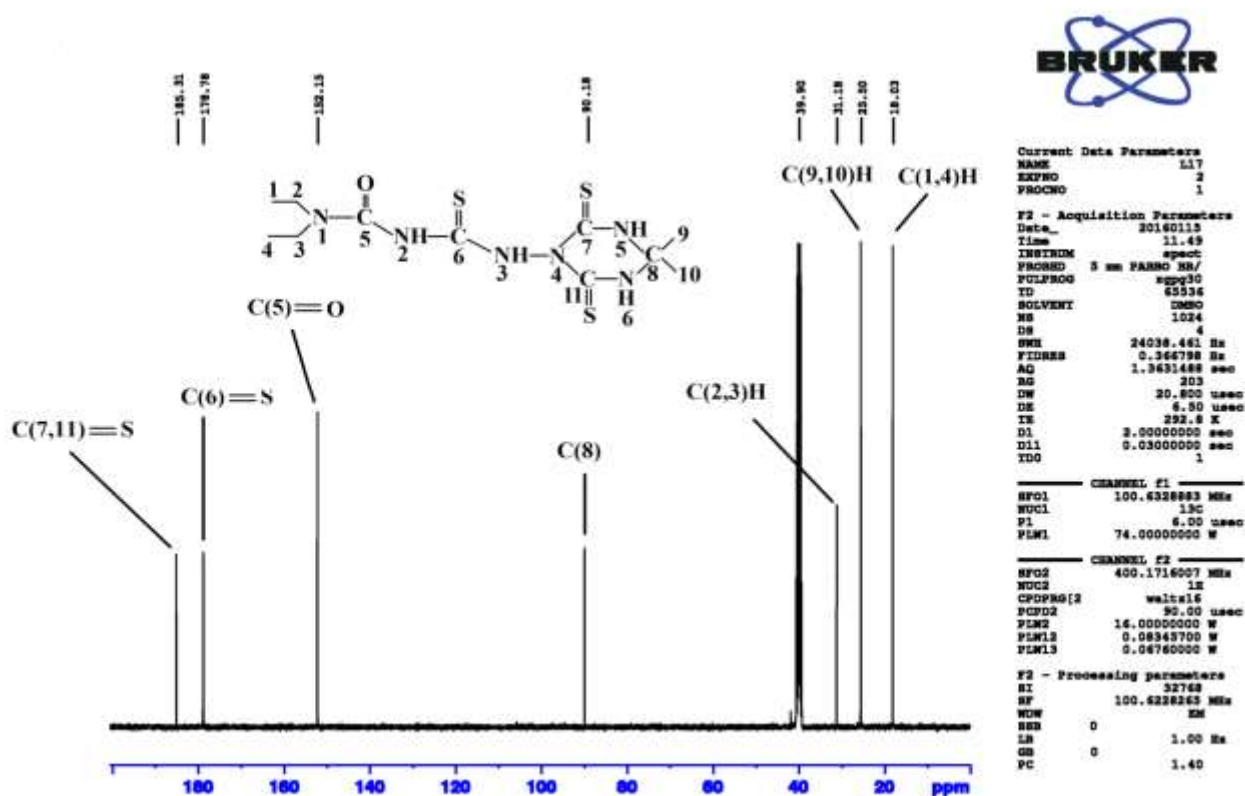


Figure 2: ¹H NMR spectrum of 3.

Figure 3: ^{13}C NMR spectrum of 3.

Description of the Geometry of 3

The stable geometry of **3** was confirmed using the PM3 method implemented in the Hyperchem package (Fig.-4). Clearly, intermolecular H-bonding occurred between the hydrogen atom of N3 and the oxygen atom (O1). The total energy (-331423.53

kJ/mol) of the molecular modelling system was calculated after the geometry was fully relaxed. A non-flat conformation was the most stable geometry for **3**, due to the minimum angle and tensional strains.

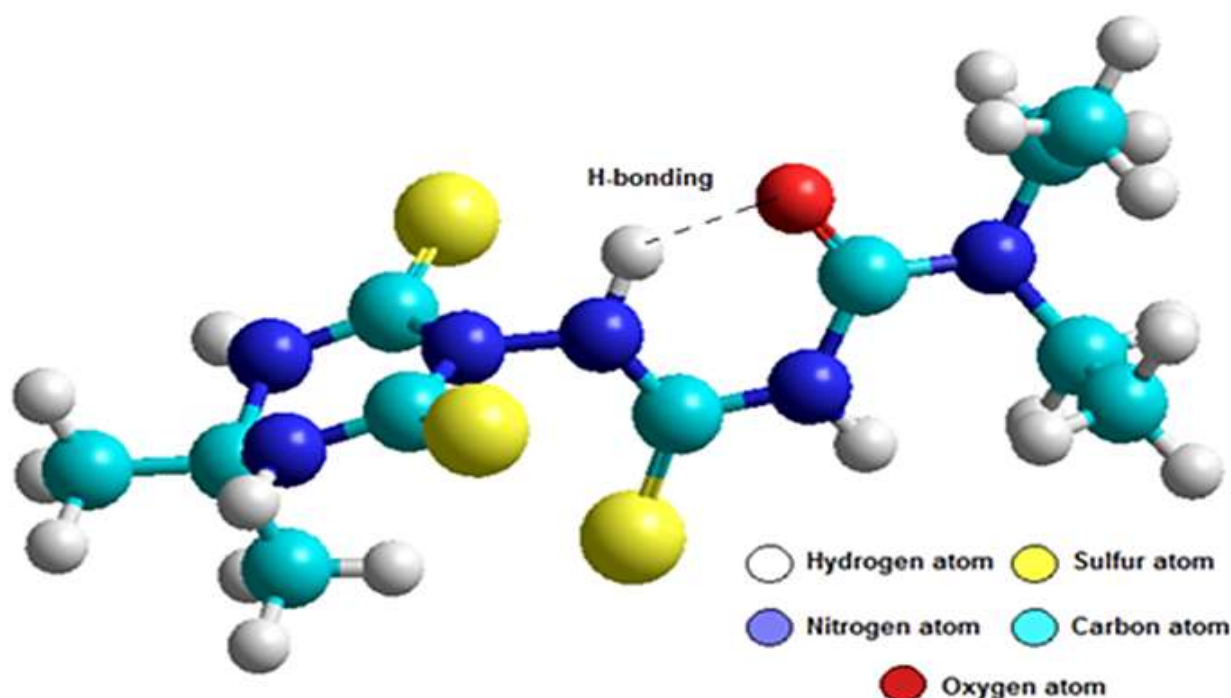


Figure 4: The confirmation of 3 using the PM3 method.

The title compound has six nitrogens, one oxygen, and three sulfur atoms. The calculations revealed that the charges on the nitrogen, oxygen, and sulfur atoms were -0.061 to $+0.08$, -0.376 , and -0.307 to $-0.234e/\text{atom}$, respectively. The average charge on the carbon atoms was $-0.070 e/\text{atom}$. The charge on the hydrogen atoms was about $+0.060 e/\text{atom}$. The variation

within the electronic density distribution in the title compound led to a dielectric constant ($1.21 D$). Fig.-5 shows the electrostatic potential maps of the molecular modelling system. It illustrates the charge distributions of three-dimensional molecules. These maps assist in the visualization of the variable charged regions of the molecule.

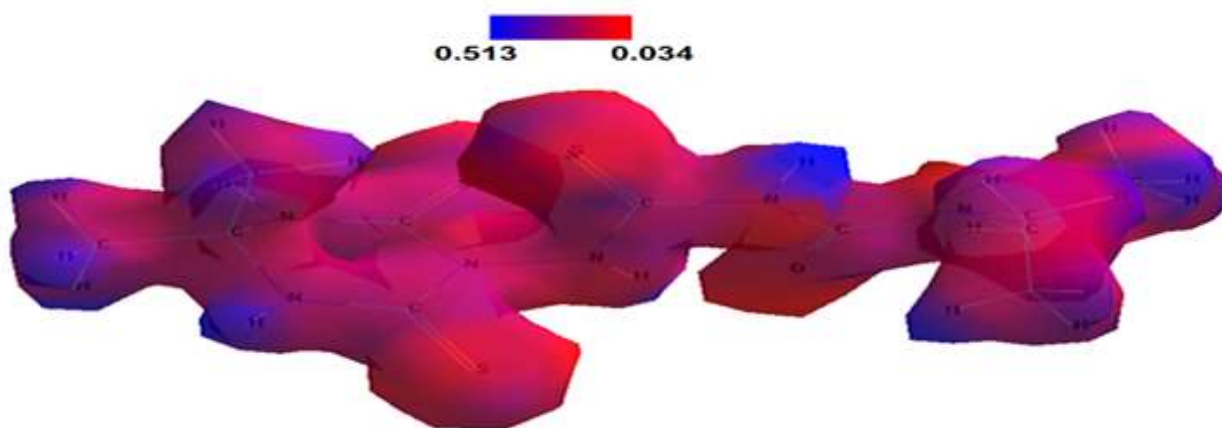


Figure 5: Electrostatic potential maps for 3 using PM3 method.

Notably, there was a difference in the distribution of electronic density and energy levels (HOMO = $-9.1667 eV$ and LUMO = $-1.7163 eV$). Such difference could lead to an

interaction with other reactive sites. The frontier molecular orbitals related to the electronic transition between molecular orbitals HOMO \rightarrow LUMO is shown in Fig.-6.

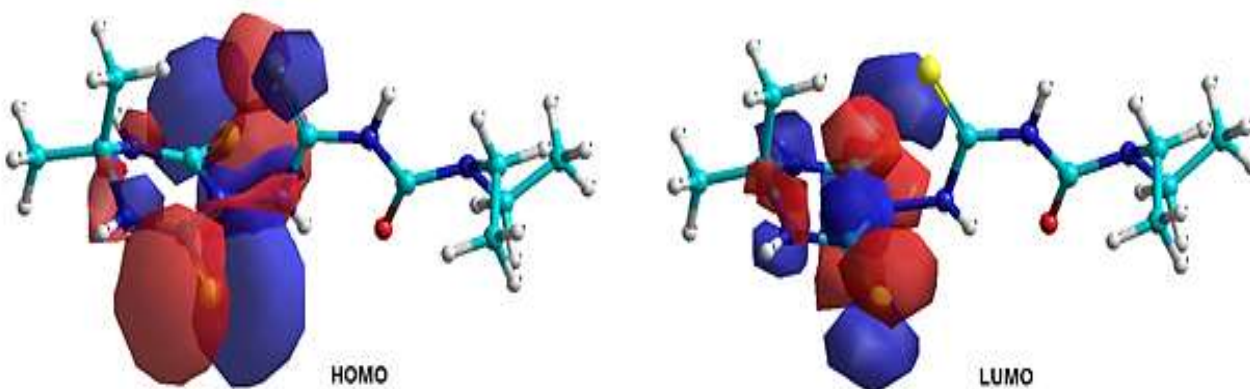


Figure 6: Frontier molecular orbital density distributions for 3 using PM3.

We also present the calculated HOMO-LUMO gap energy ($\Delta E = \text{LUMO} - \text{HOMO} = 7.4504 eV$) of **3**. The HOMO-LUMO gap energy ($\Delta E = \text{LUMO} - \text{HOMO} = 7.4504 eV$) in the title compound was high, due to the absence of conjugated systems. The iso surfaces of the HOMO were localized in compound **3** through the central double bonds on the ring system. The diethylaminocarbonylthiourea group, on the side chain of the triazinane, made a slight contribution to the electronic distribution of the HOMO in the molecular modelling system. In contrast, the LUMO distribution

was localized on the nitrogen, carbon, and sulfur atoms of the ring system in the molecular modelling system. The methyl and ethyl groups attached to the triazinane ring had no effect on the HOMO or LUMO distributions. The electron distributions of the HOMO and LUMO were not uniform over the entire molecule.

Materials and Methods

All reagents were purchased commercially and used without further purification. Solvents were distilled from appropriate drying agents according to standard protocols

immediately prior to use. Elemental analysis was carried out using a Carlo Erba 1108 Elemental Analyzer (Milan, Italy). The infrared (IR) spectrum was recorded as KBr pellet using a Perkin Elmer Spectrum GX spectrophotometer (Perkin Elmer, Waltham, MA, USA). NMR spectra (^1H , ^{13}C -NMR) were acquired in DMSO- d_6 solutions using a Bruker-400MHz for ^1H -NMR and 100.61 MHz for ^{13}C -NMR with tetramethylsilane (TMS) as an internal reference for ^1H NMR.

Synthesis of 3

A mixture of **1** (1.36 g, (10.0 mmol) and ammonium thiocyanate (1.52 g, 20 mmol) in acetone (40 ml) was stirred under reflux for 3 h. The solid obtained upon cooling was filtered. A solution of thiosemicarbazide (0.91 g, 10 mmol) in acetone (20 ml) was added to the filtrate. The mixture was heated under reflux for 2 h, and then left to cool to room temperature. The obtained solid was collected and dried to give **3** (1.33 g, 83%) as colorless crystals.³⁰m.p 220–221°C. ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.91 [s, 1 H, N(2)H], 7.99 [s, 1 H, N(3)H], 7.52 [s, 2 H, N(5,6)H], 2.90 [q, J = 6.8 Hz, 4 H, 2CH₂], 1.88 (s, 6 H, 2 CH₃), 1.16 (t, J = 6.8 Hz, 6 H, 2CH₃). ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 185.3[C(7,11)=S, 178.8], [C(6)=S], 152.1 (C=O), 90.1 [C(8)], 31.2 [C(2,3)H], 25.5[C(9,10)H], 18.0 [C(1,4)H]. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 3307, 2880, 1661, 1588, 1529, 1448, 1124, 877. Elemental anal. Cal cd for

$\text{C}_{11}\text{H}_{20}\text{N}_6\text{OS}_3$ (348.51): C, 37.91; H, 5.78; N, 24.11; S, 27.60. Found: C, 37.73; H, 5.41; N, 23.87; S, 27.65.

Theoretical Structure Determination

The total energy calculations and the corresponding structure optimizations for the most stable geometry were based on the semi-empirical molecular quantum calculations within the PM3 method³¹ and molecular mechanics within MM+ method as implemented in Hyperchem package version 7.52.³² No frozen core approximation was used for the calculations. All calculations were carried out in the gas phase at 25°C.

Conclusions

The title compound was synthesized in a high yield using a simple and convenient procedure in which one mole of acetone was involved in the cyclization to produce **3**. The molecular modelling system provided some useful information about the quantum chemical parameters.

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