Synthesis and Theoretical Characterization of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione Using Experimental and Quantum Chemical Calculations

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ABSTRACT

The aim of the study was to synthesize 4- (p-tollyl) -5- (thiophene-2-yl) -2,4-dihydro-3H-1,2,4-triazole-3-thione and detect its experimental and the quantum chemical properties. 4-(p-tollil)-5-(tiyofen-2-il)-2,4-dihidro-3H-1,2,4-triazole-3-tiyon was synthesized using by the nucleophilic sübstitüsyon reaction. The synthesized title compound has been characterized both experimentally and theoretically using quantum chemical calculations and spectral techniques. The molecular geometry, vibrational frequencies, and 1H and 13C NMR chemical shifts of the title compound in the ground state were calculated using the density functional method (B3LYP) with the 6–311G(d, p) basis set. It was seen that the calculated infrared and nuclear magnetic resonance values were compatible with the experimental values. To determine conformational flexibility, the molecular energy profile of 4- (p-tollyl) -5- (thiophene-2-yl) -2,4-dihydro-3H-1,2,4-triazole-3-thione was obtained by DFT calculations with respect to the selected torsion angle, which was varied from 180°to +180°in steps of 20°. In addition, the HOMO- LUMO energies of this conformational structure were calculated.

1. Introduction

Triazoles are one of the most of important class of heterocyclic compounds that exhibit a broad spectrum of pharmacological activities. They have two isomer groups based on the different position of the nitrogen atoms: As 1,2,3 triazoles and 1,2,4 triazoles have a wide range of drugs as essential heterocyclic structural components anticonvulsants [1], antimalarial [2], antiproliferative [3], anticancer [4] immune-nostimulants [5] and antidiabetic [6] are biologically very important. These diverse properties of the triazole core have led researchers to develop new triazole derivatives with promising biological activities. Biological research of 1,2,4-triazoles has been instrumental in demonstrating various pharmacological properties such as anticancer, antituberculosis. Various drugs have the triazole moiety, which highlights its importance, and recent advances by various researchers have delineated the importance of the triazole nucleus. To give a few examples of these; Beutle's study showed that various nucleoside-based triazole derivatives such as cladribine and gemcitabine, which natural nucleosides, can be used as anticancer agents [7]. Chandrasheka et al. showed that 4-isopropyl thiazole-4-phenyl-1,2,4-triazole derivative compounds exhibited strong antituberculosis activity compared to standard drugs [8]. The

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fact that triazoles and their derivatives have such important properties causes the study of triazoles. The aim of this study is to synthesize 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione, which is thought to be useful in at least one of these areas. It is aimed to examine experimentally and theoretically.

2. Materials and Methods

2.1. Experimental

50 ml of absolute ethyl alcohol and 10 mmol of thiophene-2-carbohydrazide were added to a 100 ml glass flask. After the reaction started, 10 mmol p-tollyl isothiocyanate was added. After about 3 hours, solid thiosemicarbazide began to form. 15 mmol potassium hydroxide was added to the solid formed and dissolution started. The reaction was stopped after six hours and the pH was brought to 3-4 with hydrochloric acid. The resulting solid was crystallized from a water-alcohol mixture. The structure of the obtained product was elucidated by spectral techniques. The reaction of the obtained compound is shown in Figure 1. Yield 68%
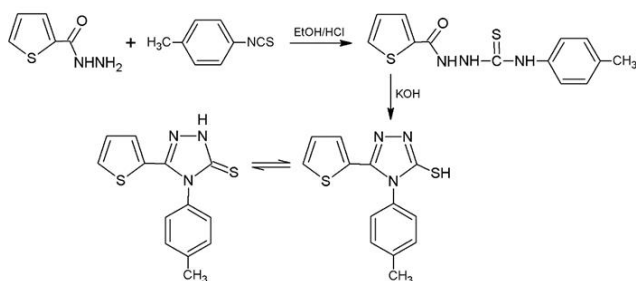

Figure 1. The reaction for the synthesis of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione.

2.2. Computational methods

Gaussian 09W package program and Density Functional Theory (DFT) method were used in the theoretical calculations of this study [10-11]. Energy values were obtained by using the 6-311G(d,p) basis set in the calculations. The boundary orbitals of the molecule, geometric optimization and infrared spectra were obtained by the Density Functional Theory (DFT) method. The GIAO (Gauge-Independent Atomic Orbital) [12-14] method was used to determine the NMR chemical shift values of the synthesized compound. The optimized form of

synthesized 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione is given in Figure 2.
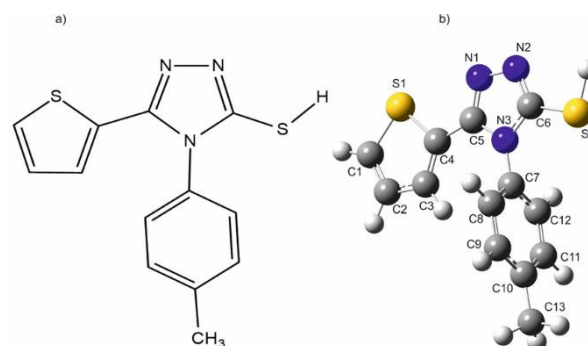

Figure 2. (a) Experimental form of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thion (b) Theoretical form of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione.

3. Results and Discussion

3.1. Conformation Isomer

Conformation analysis is a widely used method for determining the stability of conformations resulting from possible rotations in organic compounds, investigating the stability reasons of stable conformations, and examining intramolecular interactions [15]. In the 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione structure, the bond between the thiophene ring and the triazole ring has free rotation. Therefore, in order to observe this bond energy change by rotation, a conformation analysis at the B3LYP/6-311G(d,p) level was calculated to obtain the most stable optimized structure by rotating it around itself at 20 degree angles at each step. In Figure 3, the energy profile obtained for the molecule is given. Structures with minimum (stable) and maximum (unstable) energy were shown in the dihedral angle-energy plot. Looking at the graph, although the most unstable structures were formed at angles of approximately -80 º and +72 º, the most stable structures were obtained at -179 º and +178 º angles.

Figure 3. Conformation of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione.
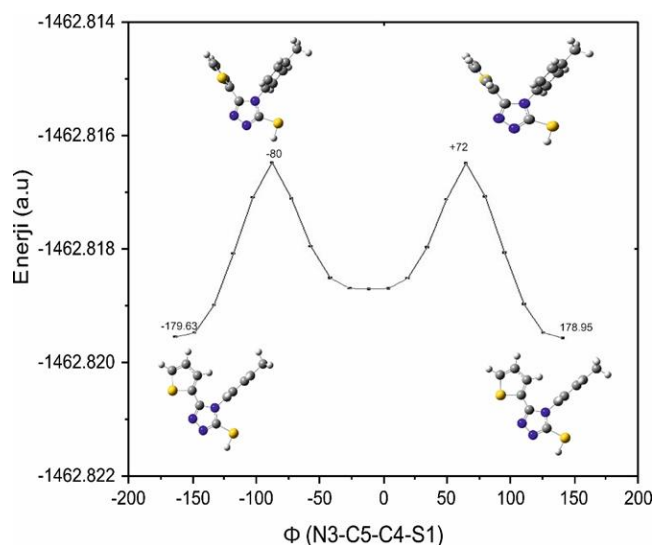

Figure 4. FT-IR spectrum of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione.

3.2. Infrared Spectroscopy (IR)

The vibrational frequencies of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thion were calculated theoretically and the obtained values were compared with the experimental values. When the spectra of the synthesized 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thion compound are examined, it is observed that the carboxylic acid hydrazide derivatives between 1650 and 1690 cm^{-1}. It was observed that the C=O tension vibration disappeared. In addition, in 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thion compound, CH3 stretch (symmetric and antisymmetric), out-of-plane There are CH bending, in-plane CH bending and aromatic CH stretching vibrations. Aromatic CH vibrational stresses are observed in the frequency range 3000-3100 cm^{-1} (in the form of multiple bands). In-plane CH bending vibrations appear as sharp peaks in the 1100-1500 cm^{-1} region. Out-of-plane bending vibrations are observed in the 860-1000 cm^{-1} region [16-17]. The theoretically calculated CH stretching vibrations in the aromatic and thiophene ring of the compound were observed in the range of 3186-3080 cm^{-1}, and experimentally in the frequency range of 3228-3063 cm^{-1}. CH in-plane bending vibrations were observed at 1071 and 1288 cm^{-1} experimentally at 1050 and 1250, out-of-plane bending vibrations were observed theoretically at 825 and 863 cm^{-1} and experimentally at 725 and 846 cm^{-1}. Other vibration values of the synthesized structure are shown in Table 1 and infrared spectrum in Figure 4.
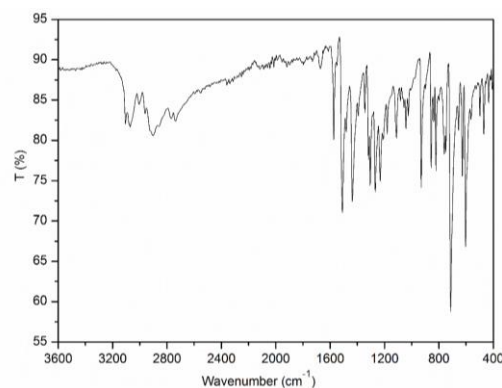
Table 1. Comparison of experimental and calculated vibrational frequencies of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione.

Symbols	Experimentally with FT-IR (cm-1)	Calculated B3LYP/6-311,G(d,p)
υ CH, Tyf	3186	3228,3210,3208
υ_s CH, Ar	3100	3063,3086,3083,3063
υ_{as} CH, Ar	3080	3062,3083
υ_{as} CH3	2970	3045,3024
υ SH	2610	2583
υ C=C, Ar	1620	1656,1613,1228
υ C=C, Tyf	1520	1548,1639,
υ C=N, Trz	1570	1565,1580,1393,1492
δ CH3	1445	1484,1417
δ CH3	1425	1482
δ CH, Ar	1050	1071,1089
δ CH, Tyf	1250	1288
α (Ar + CH3)	885	963
α CH3	890	943
α CH, Tyf	846	863,810
α CH, Ar	725	825,844

υ, strain; δ, in-plane bending; α, out-of-plane bending; s, symmetrical; ace, asymmetrical; Ar, aromatic, Tyf, Thiophene;   Trz,Triazole

3.3. Nuclear Magnetic Resonance Spectroscopy (NMR)

The most characteristic peak of the synthesized 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thion compound was theoretically at 14.06 ppm experimentally. It is the SH/NH peak seen as singlet at 14.00 ppm. The presence of this peak is an important parameter for the formation of the compound. Next to this characteristic peak of SH/NH, hydrogens in the p-tollyl group attached to the 1,2,4-triazole ring -ortho-positions resonate theoretically at 7.20 and 7.25ppm, experimentally at around 7.29ppm, while protons in the -meta position resonate as a doublet. theoretically 6.60 and 6.63 ppm, and experimentally 6.73 and 6.97 ppm, it gave a doublet signal. In addition, the protons of the methyl group attached to the p-tollyl group theoretically gave a singlet signal at 1.80, 1.95 and 2.00 ppm, experimentally at 2.39 ppm. Finally, the protons in the thiophene ring can be evaluated as follows; The proton adjacent to the sulfur atom resonated in low field due to the electron negativity of the sulfur atom compared to the other protons in the ring, giving an experimental signal at 7.64 ppm theoretically at 7.41 ppm, while other protons gave an experimental signal at 7.36 ppm and theoretically at 6.90 ppm. The experimental and theoretically calculated ^{1}H and ^{13}C-NMR spectrum values of the compound are given in Table 2. In addition, the ^{1}H-NMR and ^{13}C-NMR spectra of the compound are shown in Figure 5 and Figure 6.

Table 2. Theoretical and experimental 1H and13C isotropic chemical shifts (with respect to TMS, all values in ppm) for the title compound.

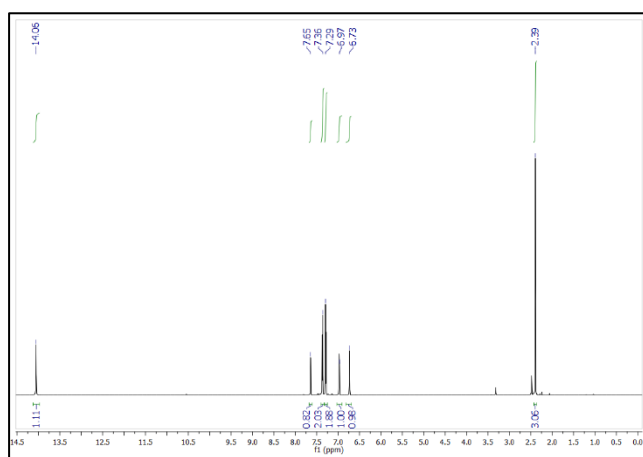| Atom	Teoretical (B3LYP) 6-311G(d,p)	Experimental(ppm) (DMSO-d$_6$)
C1	139.2	132.9
C2	127.5	127.3
C3	129.4	128.1
C4	135.3	130.6
C5	149.0	146.5
C6	165.6	169.2
C7	134.4	130.3
C8	131.9	128.8
C9	132.5	129.2
C10	144.2	140.3
C11	132.7	129.2
C12	131.2	128.8
C13	18.3	21.3
3H(thiophene)	6.90, 6.90 and 7.41	7.36, 7.36 and7.64
3H(CH$_3$)	1.80, 1.95 and 2.00	2.39
4H(Ar-H)	6.60, 6.63,7.20 and 7.25	6.73, 6.97, 7.29 and 7.29
1H(SH)	14.00	14.06

Figure 5. ^{1}H-NMR spectrum of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione.
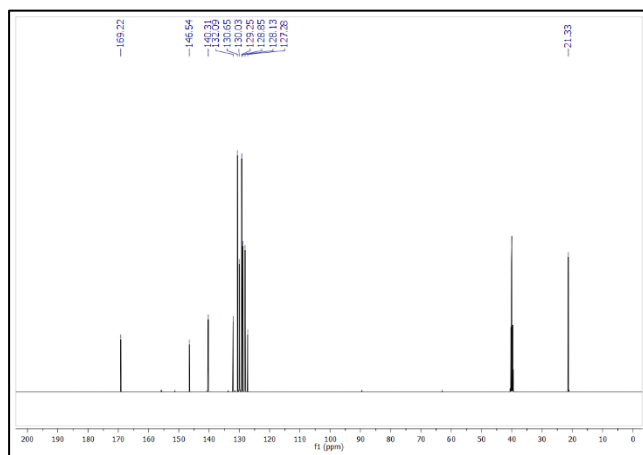

Figure 6. ^{13}C-NMR spectrum of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione.

3.4. Frontier Molecular Orbitals (FMOs)

Boundary orbitals, the highest energy filled molecular orbital (HOMO) and the lowest energy vacant molecular orbital (LUMO), have an important place in the explanation of chemical reactions. Since most of the chemical reactions occur by gaining or losing electrons, HOMO and LUMO are effective in the chemical interactions in the structure of the molecule. Since the received electron will be placed in the LUMO orbital, the smaller the energy of this orbital, the easier it will be to take the electron. Since the given electron will be in the HOMO orbit, the higher the energy of this orbit, the greater the tendency to donate electrons. Electrons in HOMO are the first to be separated during ionization [18]. The HOMO-LUMO graph of the compound is given in Figure 7. When calculating the HOMO and LUMO energy values of the molecule, the energy difference between the ground and first excited levels is -4.626 eV. If the HOMO-LUMO of the same molecule is re-excited, the calculated energy difference is -5.837 eV. In excited and ionic molecules, the dispersion of electron density, that is, activation, will make the molecule weaker and therefore the interaction between the molecules will also weaken. This is the reason for the decrease in the energy difference between HOMO-LUMO when the molecule is excited to higher levels [19].
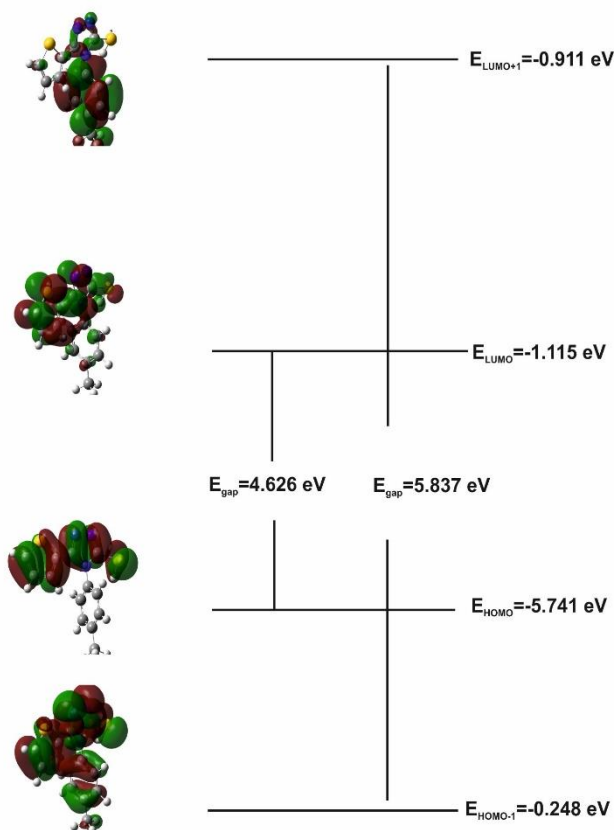
$E_{LUMO+1}=-0.911$ eV

$E_{LUMO}=-1.115$ eV

$E_{gap}=4.626$ eV $E_{gap}=5.837$ eV

$E_{HOMO}=-5.741$ eV

$E_{HOMO-1}=-0.248$ eV

Figure 7. By method B3LYP/6-311G(d,p) of 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione calculated HOMO and LUMO energies.

4. Conclusions

In this work, 4-(p-tollyl)-5-(thiophen-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thion synthesized by reaction of thiophene-2-carbohydrazide and p-tollyl isothiocyanate. Its compound structure was elucidated by characterizing it by spectroscopic methods such as FT – IR, ^{1}H-NMR and ^{13}C-NMR. In addition, quantum mechanical methods were used to obtain information about its electronic structure, and the obtained data were found to be compatible when compared with experimental methods. By calculating the conformation analysis of the compound, it was observed that the most unstable state was formed at angles of approximately -80 º and +72 º, and the most stable state was obtained at angles of -179 º and +178 º. By calculating the HOMO and LUMO energy values of the obtained structure, the energy difference between the ground state and first excited levels of the molecule is -4.626 Ev, If the HOMO-LUMO of the same molecule is re-excited, the calculated energy difference was calculated as -5.837 eV, and the high energy gaps in both cases showed that the molecule had a stable structure.

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