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SPECTROSCOPIC AND STRUCTURAL STUDY OF A SERIES OF PIVALOYLTHIOUREA DERIVATIVES

(Spektroskopi dan Kajian Struktur Satu Siri Terbitan Pivaloiltiourea)

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Abstract

A series of pivaloylthiourea derivatives, *N*-(2-nitrophenyl)-*N'*-(pivaloyl)thiourea **(I)**, *N*-(3-nitrophenyl)-*N'*-(pivaloyl)thiourea **(II)** and *N*-(4-nitrophenyl)-*N'*-(pivaloyl)thiourea **(III)** were synthesised and characterised by typical spectroscopic methods and single crystal X-ray diffraction. The IR spectra show the important stretching bands for ν(N-H), ν(C=O), ν(C-N) and ν(C=S) at around 3300 cm^{-1}, 1600 cm^{-1}, 1300 cm^{-1} and 700 cm^{-1}, respectively. There are two vital chromophores, C=O and C=S were observed in the UV spectra with maximum absorption at 230 nm and 290 nm, respectively. The crystal structures of **(II)** and **(III)** have been determined by single crystal X-ray diffraction analysis. Both of the molecules adopt *cis-trans* configuration with respect to the position of the phenyl and pivaloyl groups relative to the thiono S atom, across their C-N bonds. There is an intramolecular hydrogen bond, N-H···O in both molecules that lead to the formation of a pseudo-six-membered ring. In the crystal lattice, the molecules are linked by intermolecular hydrogen bonds N-H···S, C-H···S and N-H···O forming dimer **(II)** and 3-dimensional network **(III)**. ^{1}H NMR spectra show chemical shift at δ_H 12.70 – 12.88 ppm and δ_H 10.84 – 10.94 ppm were assigned for both NH proton. Whereas, the chemical shift for ^{13}C NMR analysis for C=O and C=S presence at δ_C 179-180 ppm.

Keywords: Thiourea derivatives, Pivaloylthiourea, Crystal structure.

Abstrak

Satu siri terbitan pivaloiltiourea iaitu *N*-(2-nitrofenil)-*N'*-(pivaloil)tiourea **(I)**, *N*-(3-nitrofenil)-*N'*-(pivaloil)tiourea **(II)** and *N*-(4-nitrofenil)-*N'*-(pivaloil)tiourea **(III)** telah berjaya disintesis dan dilakukan pencirian dengan menggunakan kaedah spektroskopi dan kristalografi hablur tunggal sinar-X. Spektra IR menunjukkan regangan penting bagi ν(N-H), ν(C=O), ν(C-N) dan ν(C=S) masing-masing pada julat 3300 cm^{-1}, 1600 cm^{-1}, 1300 cm^{-1} dan 700 cm^{-1}. Terdapat dua kromofor penting dapat diperhatikan di dalam spektra UV iaitu merujuk kepada C=O dan C=S dengan penyerapan maksimum pada 230 nm dan 290 nm setiap satunya. Struktur hablur **(I)** dan **(III)** telah ditentukan dengan analisis kristalografi hablur tunggal sinar-X. Kedua-dua molekul menunjukkan konfigurasi *cis-trans* bagi kedudukan kumpulan fenil dan pivaloil terhadap kumpulan tiono C=S pada ikatan C-N masing-masing. Terdapat ikatan hidrogen intramolekul N-H···O pada kedua-dua molekul yang membentuk pseudo gelang berahli enam. Pada kekisi hablur, molekul-molekul dihubungkan dengan ikatan-ikatan hidrogen N-H···S, C-H···S dan N-H···O yang membentuk dimer **(II)** dan rangkaian 3-dimensi **(III)**. Spektra ^{1}H NMR menunjukkan anjakan kimia pada δ_H 12.70 – 12.88 ppm dan δ_H 10.84 – 10.94 ppm bagi kedua-dua NH proton. Manakala, anjakan kimia untuk analisis ^{13}C NMR bagi C=O dan C=S pada δ_C 179-180 ppm.

Kata kunci: Terbitan thiourea, Pivaloiltiourea, Struktur hablur

Introduction

The studies on chemical and structural properties of thiourea derivatives have received much attention due to the their wide potential application in pharmaceutical, agriculture and industrial [1-4]. The group N-C=S itself is considered as chemotherapeutic interest and responsible for the pharmacological activity [5]. The thiourea derivatives have been shown to exhibit antitubercular, antithroid, anthelmintic, antibacterial, antifungal, antioxidant, antimalaria, anticorrosion, insecticidal and rodenticidal properties [6-10]. In addition, some derivatives are biologically active, denature proteins and inhibit the formation of micelles [11].

Therefore, the structural and some spectral properties of the title compounds; *N*-(2-nitrophenyl)-*N'*-(pivaloyl)thiourea **(I)**, *N*-(3-nitrophenyl)-*N'*-(pivaloyl)thiourea **(II)** and *N*-(4-nitrophenyl)-*N'*-(pivaloyl)thiourea **(III)** (Figure 1) are discussed in this paper.

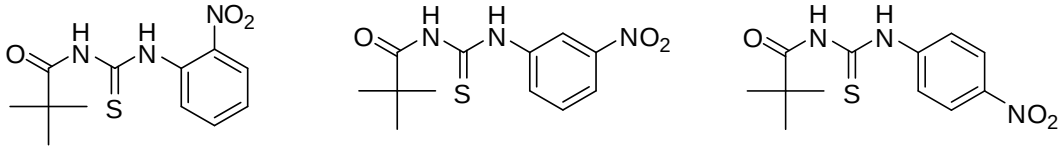

Figure 1: Molecular structural representations of *N*-(2-nitrophenyl)-*N'*-(pivaloyl)thiourea **(I)**, *N*-(3-nitrophenyl)-*N'*-(pivaloyl)thiourea **(II)** and *N*-(4-nitrophenyl)-*N'*-(pivaloyl)thiourea **(III)**.

Materials and Methods

All chemicals and solvents are in analytical grade and were used without further purification as received. Infrared spectra were recorded with Perkin Elmer 100 spectrometer in the region of 400 – 4000 cm^{-1} using the conventional KBr pellet method for solid samples. UV spectra were recorded using UV-Visible Spectrophotometer Shimadzu model 1601PC and methanol as a solvent in the concentration 10^{-6}M. The wavelength range lies at 200-400 nm. Single crystals data were collected using Bruker SMART APEX 4K CCD with a graphite monochromated Mo Kα radiation source. ^{1}H and ^{13}C NMR spectra in DMSO-d_6 as solvent were measured with a Bruker AVANCE III 400 MHz spectrometer (400.11 MHz for ^{1}H and 100.61 MHz for ^{13}C) at room temperature.

Synthesis of (I), (II) and (III).

A solution of pivaloyl chloride (5.0 g, 4 mmol) and ammonium thiocyanate (3.15 g, 4 mmol) in acetone (10 ml) were stirred for *ca.* 10 minutes. *o*-nitroaniline **(I)** / *m*-nitroaniline **(II)** / *p*-nitroaniline **(III)** (2.37 g, 2 mmol) in 10 ml of acetone was added dropwise. The solution mixture was put at reflux for 1 h. The resulting solution was poured into a beaker containing some ice cubes. The yellow precipitate was filtered off and underwent product isolation.

***N*-(2-nitrophenyl)-*N'*-(pivaloyl)thiourea (I) ($C_{12}H_{15}N_3O_3S$)**

Yield 73%; m.p. : 58.4-59.2 ˚C; ^{1}H NMR (DMSO-d_6, 400.11 MHz): δ_H 1.28 (s, 9H, CH_3), δ_H 7.03 (d, 1H, J_{HH} = 8.40 Hz, Ar), δ_H 7.53-7.57 (m, 1H, J_{HH} = 7.80 Hz, Ar), δ_H 7.76-7.79 (m, 1H, J_{HH} = 7.60 Hz, Ar), δ_H 8.079 (d, 1H, J_{HH} = 8.00 Hz, Ar), δ_H 10.94 (s, 1H, NH), δ_H 12.79 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100.61MHz): δ_C 26.61 (CH_3), δ_C 40.41 (C), δ_C 125.26, 125.83, 128.27, 130.82, 144.61, 146.65 (Ar), δ_C 180.67 (CS), δ_C 181.59 (CO). Anal. Calcd : C, 57.23; H, 5.37; N, 14.94 %. Found : C, 57.21; H, 5.33; N, 14.89 % .

***N*-(3-nitrophenyl)-*N'*-(pivaloyl)thiourea (II) ($C_{12}H_{15}N_3O_3S$)**

Yield 78%; m.p. : 68.7-69.1 ˚C; ^{1}H NMR (DMSO-d_6, 400.11 MHz): δ_H1.27 (s, 9H, CH_3), δ_H 7.67 - 7.71 (m, 1H, J_{HH} = 8.20 Hz, Ar), δ_H 7.97 (d, 1H, J_{HH} = 8.00 Hz, Ar), δ_H 8.10 (d, 1H, J_{HH} = 7.60 Hz, Ar), δ_H 8.74 (s, 1H, Ar), δ_H 10.84 (s, 1H, NH), δ_H 12.70 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100.61MHz): δ_C 26.61 (CH_3), δ_C 40.40 (C), δ_C 119.58, 121.29, 130.40, 131.61, 139.66, 148.0065 (Ar), δ_C 180.50 (CS), δ_C 180.63 (CO). Anal. Calcd : C, 57.23; H, 5.37; N, 14.94 %. Found : C, 57.27; H, 5.29; N, 14.92 % .

***N*-(4-nitrophenyl)-*N'*-(pivaloyl)thiourea (III) ($C_{12}H_{15}N_3O_3S$)**
Yield 77%; m.p. : 142.9-143.6 °C; ^{1}H NMR (DMSO-d_6, 400.11 MHz): δ_H 1.27 (s, 9H, CH_3), δ_H 8.04 (d, 2H, J_{HH} = 8.80 Hz, Ar), δ_H 8.25 (d, 2H, J_{HH} = 8.80 Hz, Ar), δ_H 10.88 (s,1H, NH), δ_H 12.88 (s,1H, NH). ^{13}C NMR (DMSO-d_6, 100.61MHz): δ_C 26.57 (CH_3), δ_C 40.43 (C), δ_C 124.62, 124.67 (Ar), δ_C 179.97 (CS), δ_C 180.75 (CO). Anal. Calcd : C, 57.23; H, 5.37; N, 14.94 %. Found : C, 57.20; H, 5.35; N, 14.98 % .

Results and Discussion

Infrared spectra

The IR spectra show important stretching bands for *v*(N-H), *v*(C=O), *v*(C-N) and *v*(C=S) in all compounds. A medium intensity bands presence at 3347.58 **(I)**, 3273.25 **(II)** and 3303.91 cm^{-1} **(III)** which corresponds to stretching *v*(N-H) (Figure 2). The stretching band of *v*(N-H) **(I)** has higher frequency compared to compounds **(II)** and **(III)** due to the position of electron withdrawing group near to the NH moiety. The strong absorption bands around 1690 cm^{-1} attributes to the stretching of *v*(C=O) and it is decreasing in frequencies compared with typical carbonyl absorption (1700 cm^{-1}) [12]. This is resulting from a conjugated resonance of phenyl ring and the formation of intramolecular hydrogen bonding with N-H [13]. The medium stretching vibration of *v*(C-N) bands are at 1345.88 **(I)**, 1342.19 **(II)** and 1317.85 cm^{-1} **(III)**. The medium bands around 740 cm^{-1} are assigned for stretching *v*(C=S) modes. From the infrared spectra analysis (Table 1) show that the thiourea moieties were formed for compounds **(I)**, **(II)** and **(III)** and in good agreement with previous studies [14-15].

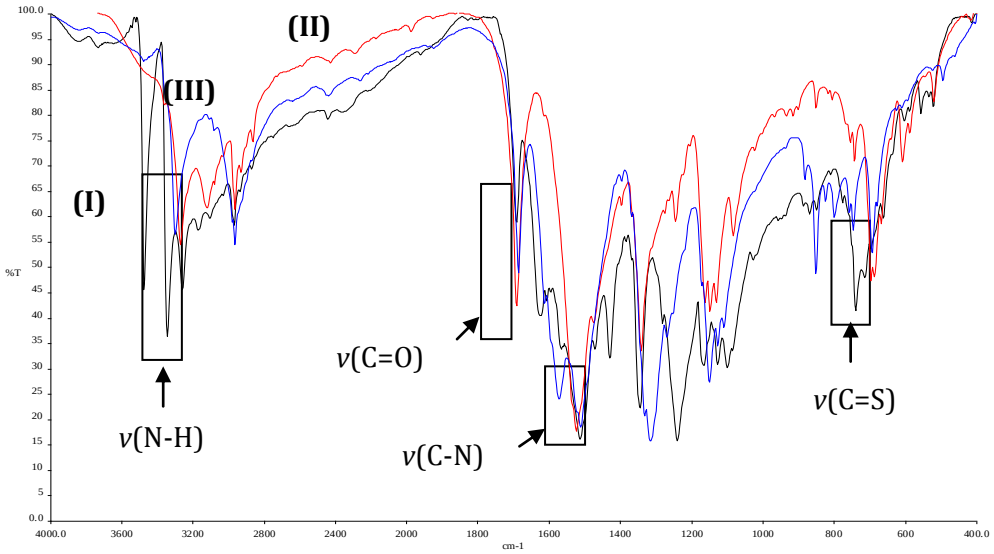

Figure 2: The FTIR spectra of compounds **(I)**, **(II)** and **(III)**.

Table 1: IR absorption data for compounds **(I), (II)** and **(III).**

Compounds	Wavenumber (cm^{-1})			
	v(N-H)	*v*(C=O)	*v*(C-N)	*v*(C=S)
(I)	3347.58	1692.94	1345.88	741.57
(II)	3273.25	1692.58	1342.19	744.34
(III)	3303.91	1686.45	1317.85	747.62

Ultraviolet spectra

UV absorption for compounds **(I)**, **(II)** and **(III)** exhibit n → π* and π → π* transition (HUMO→LUMO). The UV spectra show two important bands for chromophores carbonyl (C=O) and thione (C=S) groups. All compounds show maximum absorption bands at 230 nm and 290 nm were assigned for chromophores C=O and C=S respectively. There is a presence of NO_2 band in *para* position **(III)** with maximum absorption 330 nm (Figure 3). Table 2 shows the maximum absorption for each compounds; **(I)**, **(II)** and **(III)** from the UV spectra analysis.

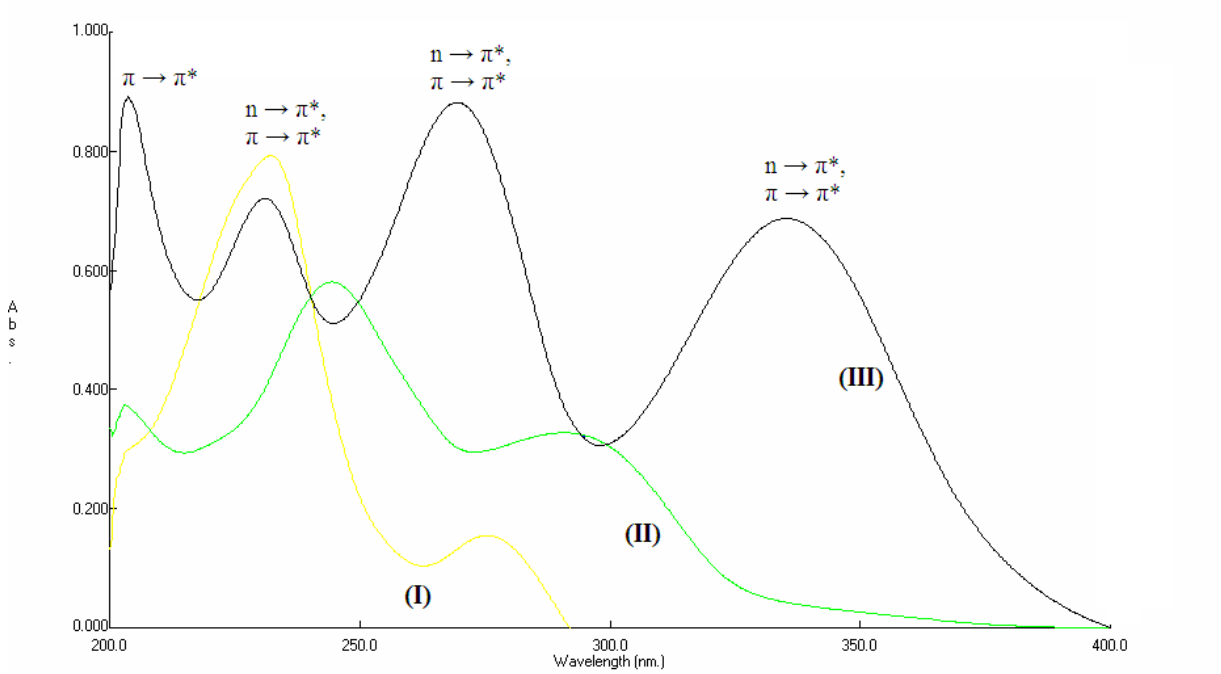

Figure 3: The UV spectra of compounds **(I)**, **(II)** and **(III).**

Table 2: UV absorption maximum of compounds **(I)**, **(II)** and **(III).**

Compounds	λ^{max} (nm)			Transition
	C=O	C=S	NO_2	
(I)	232.2	275.2	-	n → π*, π → π*
(II)	244.4	290.6	-	n → π*, π → π*
(III)	231.6	269.4	335.4	n → π*, π → π*

X-ray Crystallographic Studies

Compounds **(II)** and **(III)** were obtained as a single crystal and suitable for single crystal X-ray diffractometer analysis (Table 3). Both of the molecules are discret and adopt *cis-trans* configuration with respect to *cis* position for phenyl and *trans* position for pivaloyl groups relative to the thiono S atom, across their C-N bonds (Figures 4 & 5). Compound **(II)** shows the plane of carbonyl-thiourea S1/C6/N1/N2/O1/C5 and 3-nitrophenyl are nearly planar with maximum deviation 0.077Å at O2 atom. The dihedral angle of this two plane is 85.64(7)°. However, the plane of carbonyl-thiourea S1/C6/N1/N2/O1/C5 and 4-nitrophenyl of compound **(III)** are more planar with maximum deviation of 0.045 Å at C6 atom. The dihedral angle between these plane is 28.32(8)°.

Table 3: Crystal data for compounds **(II)** and **(III)**.

Compound	**(II)**	**(III)**
Empirical formula	$C_{12}H_{15}N_3O_3S$	$C_{12}H_{15}N_3O_3S$
Formula mass (g mol^{-1})	281.33	281.33
Crystal system	Ortorhombic	Monoclinic
Space group	$Pna2_1$	$P2_1/c$
a(Å)	20.400(5)	6.258(2)
b(Å)	10.886(3)	10.959(4)
c(Å)	6.2120(15)	20.421(7)
α(°)	90	90
β(°)	90	99.697(10)
γ(°)	90	90
Volume ($Å^3$)	1379.5(6)	1380.5(8)
Z, density (calculated) (mg/m^3)	4, 1.355	4, 1.354
Absorption coefficients (mm^{-1})	0.242	0.242
F(000)	592	592
Crystal size (mm)	0.48 x 0.18 x 0.12	0.38 x 0.33 x 0.12
Crystal description	Slab	Slab
Crystal colour	Colourless	Colourless
θ Range (°)	2.00 – 27.48	2.02 – 27.49
Index ranges	$-21 \le h \le 26$ $-13 \le k \le 14$ $-7 \le l \le 7$	$-8 \le h \le 8$ $-14 \le k \le 14$ $-26 \le l \le 26$
Independent reflections	8152 / 3020 [R(int) = 0.0318]	15257 / 3157 [R(int) = 0.0401]
Maximum and minimum transmissions	0.9715 and 0.8926	0.9715 and 0.9136
Procession method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/ restrains/ parameters	3020 / 1 / 172	3157 / 0 / 175
Goodness-of-fit on F^2	1.070	0.905
Largest diff. peak ($eÅ^{-3}$)	0.281	0.490
Largest diff. hole ($eÅ^{-3}$)	-0.145	-0.027
R, wR	0.0416, 0.0945	0.0548 , 0.1183
R, wR (all reflection)	0.0617, 0.1029	0.0886 , 0.1314

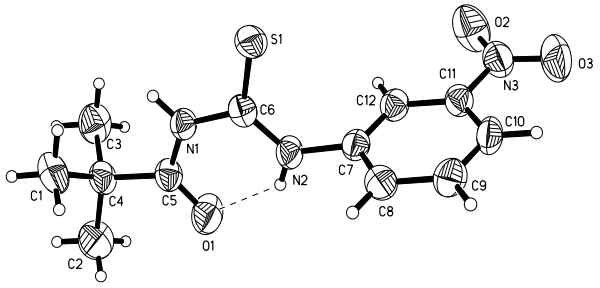

Figure 4: ORTEP drawing for **(II)** (ellipsoids are plotted at the 50% probability) with intramolecular hydrogen bond.

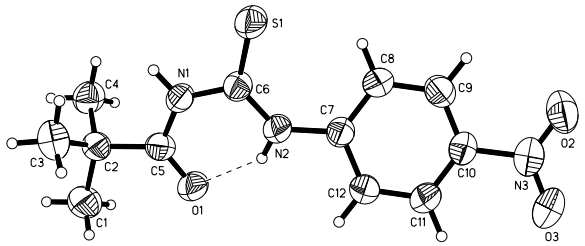

Figure 5: ORTEP drawing for compound **(III)** (ellipsoids are plotted at the 50% probability) with intramolecular hydrogen bonds.

The bond length and angles (Table 4) are in normal ranges [16] and comparable with other pivaloyl thiourea derivative compounds [17-22]. However, N1-C6 is longer than N2-C6 by 0.053 Å **(II)** and 0.059 Å **(III)**, similar to the other benzoylthiourea [23-25]. This differences are probably due to the intramolecular hydrogen bonding interaction [13]. The C=S and C=O bond distances for both compounds show the expected full double bond character, while the values of N1-C5, N1-C6, N2-C6 and N2-C7 bond lengths indicate partial double-bond character [26-27]. Thus, the position (i.e., *meta* or *para*) of nitro group on the aryl ring has no significant effect on the bond and angles of the thiourea moiety [28].

Table 4: Selected bond lenght (Å) and angles (˚) for compounds **(II)** and **(III).**

Compounds	Distances	Bond distances, (Å)	Distances	Angles distances, (˚)
(II)	S1-C6	1.668(2)	C6-N2-C7	123.2(2)
	O1-C5	1.222(3)	C5-N1-C6	128.0(2)
	N1-C5	1.377(3)	O2-N3-O3	123.7(3)
	N1-C6	1.386(3)	O2-N3-C11	118.3(2)
	O3-N3	1.217(3)	O3-N3-C11	118.0(3)
	N2-C6	1.327(3)	N2-C6-S1	124.6(2)
(III)	S1-C6	1.652(2)	C5-N1-C6	128.9(2)
	O1-C5	1.222(2)	C6-N2-C7	130.9(2)
	N1-C5	1.382(3)	O2-N3-O3	123.1(2)
	N1-C6	1.390(2)	O2-N3-C10	118.6(2)
	N2-C6	1.337(2)	N1-C6-S1	119.1(2)
	N2-C7	1.413(2)	O1-C5-C2	122.3(2)

There is an intramolecular hydrogen bond in both molecules**,** NH···O forming a pseudo-six-membered ring (Table 5). Compound **(II)** has longer distance of N2-H2···O1, 2.605(3) Å compare to **(III)**, the distance of N2-H2···O1 is 2.589(2) Å. This difference indicates an electronic effect and steric effect of the molecules (Valdés-Martínez *et al*., 1999).

Table 5: Intramolecular and intermolecular hydrogen bond distances (Å) and angles (˚) for compounds **(II)** and **(III).**

Compounds	D	A	D-H	H···A	D-H···A	D-H···A
Intramolecular						
(II)	N2	O1	0.86	1.92	2.605(3)	135˚
(III)	N2	O1	0.86	1.85	2.589(2)	143˚
Intermolecular						
(II)	N1	S1	0.86	2.76	3.582(2)	160˚
	N2	O2	0.86	2.52	3.197(3)	137˚
	C3	S1	0.96	2.83	3.742(3)	159˚
(III)	N1	S1	0.86	2.87	3.727(2)	174˚
	C4	S1	0.96	2.79	3.659(3)	151˚

In the crystal lattice, the molecules are linked by intermolecular hydrogen bonds N1-H1···S1, N2-H2···O2 and C3-H3···S1 **(II)** forming a dimer. Whereas for compound **(III)**, the intermolecular hydrogen bonds are N1-H1···S1 and C4-H4···S1 which formed a 3-dimensional network (Figures 6 & 7).

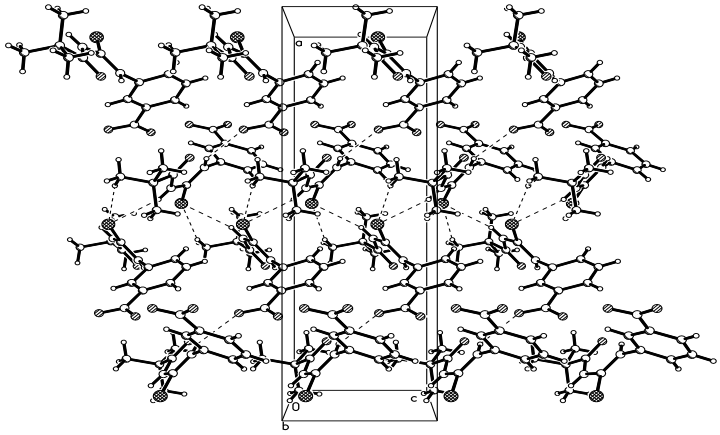

Figure 6: Packing diagram of **(II)**, viewed down the *b* axis. Dashed line denote the intermolecular hydrogen bonds.

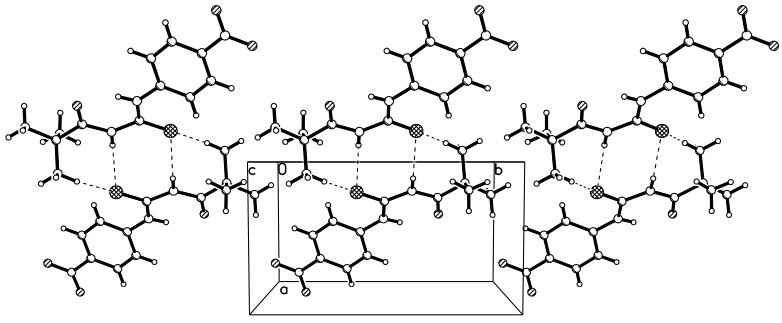

Figure 7: Packing diagram of **(III)**, viewed down the *c* axis. Intermolecular hydrogen bonds are indicated by the dashed line.

Nuclear Magnetic Resonance

The ^{1}H NMR and ^{13}C NMR spectra are similar and consistent with the structures obtained from single crystal X-ray analysis. The ^{1}H NMR spectra data showed a sharp singlet peak at δ_H 1.27 ppm **(II)**, **(III)** and 1.28 ppm **(I)** correspond to protons of $-CH_3$. There are multiplet signal at δ_H 7.03 – 8.74 ppm which corresponds to the aromatic protons on phenyl ring in **(I)**, **(II)** and **(III)**. The two most de-shielded signals are broad and is assigned to NH proton at δ_H 10.94, δ_H 12.79 ppm **(I)**, δ_H 10.84, δ_H 12.70 ppm **(II)** and δ_H 10.88, δ_H 12.88 ppm **(III)**. These signals are comparable to those found in the similar molecules as reported in previous occasions (Yang *et al*. 2007; Weiqun *et al.* 2004).

The ^{13}C NMR spectra show a signal for carbon methyl which was observed at δ_C 26.61 ppm **(I)**,**(II)** and δ_C 26.57 ppm **(III)**. Another signal for carbon bound to methyl group can be seen at δ_C 40.41 ppm **(I)**, δ_C 40.40 ppm **(II)** and δ_C 40.43 ppm **(III)**. Whereas, the aromatic carbons of the phenyl ring appear around δ_C 119-147 ppm for all compounds. The chemical shift of carbon atom for thione presence at δ_C 180.67 ppm **(I)**, δ_C 180.63 ppm **(II)** and δ_C 179.97 ppm **(III)**. In addition, carbonyl carbon exhibits as singlet at δ_C 181.59 ppm **(I)**, δ_C 180.63 ppm **(II)** and δ_C 180.75 ppm **(III)**. In general a chemical shifts for compounds **(I)**, **(II)** and **(III)** show no significant difference in proton and carbon NMR analysis.

Conclusion

In this report, the synthesis of three new pivaloyl thiourea compounds **(I)**, **(II)** and **(III)** have been carried out and characterised by spectroscopic methods namely infrared (IR), ultraviolet (UV-vis) and nuclear magnetic resonance analysis (NMR). The IR spectra show the important stretching bands for ν(N-H), ν(C=O), ν(C-N) and ν(C=S) for **(I)**, **(II)** and **(III)**. There are two vital chromophores identified as C=O and C=S which are believed responsible to the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition were observed in the UV spectra for all compounds. The structures of molecules **(II)** and **(III)** were determined by single crystal X-ray diffraction analysis. From the analysis, it is obvious that the position *meta* or *para* of nitro group on the aryl ring has no significant effect on the bond and angles of the thiourea moiety.

Acknowledgement

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