



SYNTHESIS AND CHARACTERISATION STUDIES OF NOVEL THIOUREA AMINO ACID DERIVATIVES

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ABSTRACT

Three novel compounds of *N*-methylbenzoyl thiourea derivatives, namely 3-mercapto-*N*-(2-methylbenzoyl)thioureido)-*N'*-propanoic acid [**1**], 3-mercapto-*N*-(3-methylbenzoyl)thioureido)-*N'*-propanoic acid [**2**] and 3-mercapto-*N*-(4-methylbenzoyl)thioureido)-*N'*-propanoic acid [**3**], were successfully synthesised with moderate yield. All of these compounds were fully characterised using ultraviolet (UV), infrared (IR) and Multi-nuclear Magnetic Resonance (NMR). IR spectra showed the important bands of interest such as $\nu(\text{C}=\text{S})$, $\nu(\text{C}-\text{N})$, $\nu(\text{C}=\text{O}_{\text{carboxylic}})$, $\nu(\text{C}=\text{O}_{\text{amide}})$, and $\nu(\text{N}-\text{H})$ have been observed at around 700 cm^{-1} , 1200 cm^{-1} , 1700 cm^{-1} , 1600 cm^{-1} and 3000 cm^{-1} respectively. Two chromophores, C=S and C=O, have been observed in the UV spectra at 280nm and 230 nm, respectively. Compound [**1**] and [**3**] were characterised by NMR (^1H and ^{13}C). The resonances for $\delta_{\text{H}}(\text{OH})$, $\delta_{\text{H}}(\text{NH})$ -1 and $\delta_{\text{H}}(\text{NH})$ -2 presence at around δ_{H} 11ppm, 10ppm and 5 ppm, respectively. Whilst in ^{13}C , the signal for $\delta(\text{C}=\text{S})$, $\delta(\text{C}=\text{O}_{\text{carboxylic}})$ and $\delta(\text{C}=\text{O}_{\text{amide}})$ can be observed at around 180ppm, 170ppm and 167ppm, respectively.

Keyword: Thiourea, *N*-methylbenzoyl and amino acid

ABSTRAK

Tiga sebatian baru terbitan *N*-metilbenzoil tiourea, asid-3-mercapto-*N*-(2-metilbenzoil) tioureido)-*N'*-propanoik [**1**], asid-3-mercapto-*N*-(3-metilbenzoil)tioureido)-*N'*-propanoik [**2**] and asid-3-mercapto-*N*-(4-metilbenzoil)tioureido)-*N'*-propanoik [**3**], telah berjaya disintesis dengan hasil yang baik. Kesemua sebatian telah dicirikan menggunakan inframerah (IR), ultra lembayung (UV) dan Resonan Magnetik Nukleus (RMN). Spektra inframerah menunjukkan jalur penyerapan yang penting seperti $\nu(\text{C}=\text{S})$, $\nu(\text{C}-\text{N})$, $\nu(\text{C}=\text{O}_{\text{karboksilik}})$, $\nu(\text{C}=\text{O}_{\text{amida}})$, dan $\nu(\text{N}-\text{H})$ dapat diperhatikan pada 700 cm^{-1} , 1200 cm^{-1} , 1700 cm^{-1} , 1600 cm^{-1} and 3000 cm^{-1} . Dua kromofor, C=S dan C=O, boleh dilihat di dalam spektra UV pada penyerapan maksimum 280nm dan 230nm. Sebatian [**1**] dan [**3**] telah dicirikan menggunakan RMN (^1H and ^{13}C). Nilai resonan bagi $\delta_{\text{H}}(\text{OH})$,

$\delta_{\text{H}}(\text{NH})$ -1 dan $\delta_{\text{H}}(\text{NH})$ -2 berada pada δ_{H} 11 ppm, δ_{H} 10 ppm and δ_{H} 5 ppm. Manakala di dalam ^{13}C , resonan bagi $\delta(\text{C}=\text{S})$, $\delta(\text{C}=\text{O}_{\text{karboksilik}})$ and $\delta(\text{C}=\text{O}_{\text{amida}})$ boleh dilihat dalam lingkungan δ_{C} 180 ppm, δ_{C} 170 ppm and δ_{C} 167 ppm.

Kata kunci: Thiourea, *N*-metilbenzoi dan asid amino

INTRODUCTION

Thiourea and its derivatives have attracted great deal of interest for their numerous biological properties such as antifungal, antiviral, antitumor agents, as well as inhibitors for nitric oxide (NO) production as potential therapeutic agents (del Campo *et al.*, 2002; Venkatachalam *et al.*, 2005; Li *et al.* 2006; & Kim *et al.*, 2007). Thiourea is also may be applied in electrochemistry, as corrosion inhibitors and in agriculture (Agnieszka *et al.*, 2005; Shetty *et al.*, 2007 & Zheng *et al.*, 2004).

Thiourea derivatives can act as good ligand in metal complexes. In recent studies, thiourea derivatives coordinate to metal by N and S atoms. It is also showed that these derivatives can act as monodentate and bidentate ligand (del Campo *et al.*, 2002; Shetty *et al.*, 2007; Piro *et al.*, 2002; & Ferrari *et al.*, 2007).

In this study, three new compounds were successfully synthesised, 3-mercapto-*N*-(2-methylbenzoyl) thioureido)-*N'*-propanoic acid [**1**], 3-mercapto-*N*-(3-methylbenzoyl) thioureido)-*N'*- propanoic acid [**2**] and 3-mercapto-*N*-(4-methylbenzoyl)thioureido)-*N'*-propanoic acid [**3**], varying its methyl substituent position, at ortho-meta-para position in the phenyl ring (Figure 1)

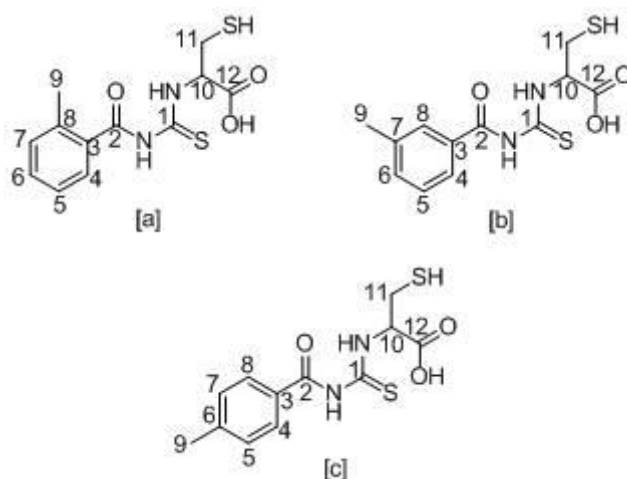


Figure 1: [a] compound **1**, [b] compound **2**, and [c] compound **3** with numbering scheme for NMR spectral assignment.

MATERIALS AND METHOD

All analytical grade reagents and solvents used are purchased and used as received. The UV spectra were recorded by UV-Visible Spectrophotometer Shimadzu model UV-1601PC using methanol as a solvent in 1 cm quartz cell in the sample concentration of 10^{-6} M. The IR spectra were recorded using Perkin Elmer Spectrum 1000 using KBr pellet. The ^1H and ^{13}C NMR spectra were obtained with Jeol JNM-ECP400 with the frequency of 399.78MHz and 100.54MHz, respectively from acetone- d_6 solutions and referenced against solvent resonances. A mixture of *N*-methylbenzoyl chloride (3g, 0.02mol) and ammonium thiocyanate (1.48g, 0.02mol) were put at reflux for 1 hour. Then, cysteine (5.8g, 0.02mol) was added to the mixture and further underwent reflux for another *ca.* 5 hours, the reaction was completed by the formation of yellow solution. The mixture was poured into beaker containing several pieces of ice. The yellowish precipitate obtained in the beaker was filtered, washed with little cold water and dried at room temperature. The crude products was recrystallised from ethanol to give pale yellow crystals in 50-60% yield for all the three synthesised compounds.

RESULT AND DISCUSSION

All the compounds exhibit as pale yellow crystals. The compounds have been characterised by UV/Vis, IR and NMR (^1H and ^{13}C). UV analyses show all of the compounds have two chromophores which are C=S and C=O presence at around 280 nm and 230nm respectively indicating the absorption band of resulting from $n \rightarrow \pi^*$ transition.

All of the compounds show important stretching in IR spectra such as $\nu(\text{C}=\text{S})$, $\nu(\text{C}=\text{O}_{\text{carboxylic}})$, $\nu(\text{C}=\text{O}_{\text{amide}})$, $\nu(\text{C}-\text{N})$ and $\nu(\text{N}-\text{H})$ which can be observed around 700 cm^{-1} , 1200 cm^{-1} , 1700 cm^{-1} , 1600 cm^{-1} and 3000 cm^{-1} , respectively which data comparison by several previous reports has been done (Yang *et al.*, 2007; Arslan *et al.*, 2007; & El-Bahy *et al.*, 2003). All compounds show almost the same characteristics especially for $\nu(\text{C}=\text{S})$, $\nu(\text{C}=\text{O}_{\text{carboxylic}})$, $\nu(\text{C}=\text{O}_{\text{amide}})$, $\nu(\text{C}-\text{N})$ and $\nu(\text{N}-\text{H})$ (Table 1). However, Compound **2** shows some significant wavelength value, illustrate that the position of methyl as electron donating group at phenyl ring plays certain role for the absorption band in the infrared spectra. Compound **2** which have *meta*- substitution of methyl, shifted to lower frequency region compared to other members in the group. Absorption band for N-H is in range of $3100\text{-}3400\text{ cm}^{-1}$, was observed as broad signal due to the intramolecular hydrogen bonding (Tadjarodi *et al.*, 2007) between N-H and C=O (Yusof *et al.*, 2007; & Ngah *et al.*, 2005)

Table 1: Selected infrared absorption bands for compound **1**, **2** and **3** (cm⁻¹).

Compound	$\nu(\text{N-H})$	$\nu(\text{C=O}_{\text{carboxylic}})$	$\nu(\text{C=O}_{\text{amide}})$	$\nu(\text{C-N})$	$\nu(\text{C=S})$
1	3139.30	1697.42	1609.31	1261.62	740.11
2	3430.68	1704.26	1631.33	1349.45	750.00
3	3270.67	1689.00	1603.28	1245.40	739.21

These compounds were further characterised using ¹H and ¹³C NMR spectroscopy. The NMR spectra of compound **1** and **3** were in the agreement with the proposed structures and show no significant difference in chemical shifts for both compounds (Table 2). The carbon atoms for C=S, C=O_{carboxylic} and C=O_{amide} can be observed at around δ_{C} 182 ppm, δ_{C} 171 ppm and δ_{C} 168 ppm. Resonance for (NH)-1, (NH)-2, OH and CH₃ show as singlet peak, which can be observed at above δ_{H} 10.00 ppm, around δ_{H} 5.60 ppm, above δ_{H} 11 ppm and around δ_{H} 2.40 ppm, respectively. The CH₂ moiety was observed as triplet at around δ_{H} 3.90 ppm while CH resonance observed as doublet-of-doublet at slightly above δ_{H} 4.30 ppm. The aromatic protons are totally distinguishable from the other resonances in the structures, they exhibit as multiplet due to the overlapping and unresolved protons signals in the aromatic rings which can be observed at around δ_{H} 7.29-7.91 ppm.

Table 2: NMR (¹³C & ¹H) chemical shifts for compound **1** and **3**

Signals ($\delta_{\text{C/H}}$)	Compound 1 (ppm)	Compound 3 (ppm)
C1	182.05	182.24
C2	167.56	168.64
C (Ar, m)	126.61 – 138.00	129.13 – 145.07
C9	29.34	21.52
C10	56.76	56.87
C11	38.14	38.50
C12	171.94	171.26
(s, 1H, OH)	11.42	11.51
(s, 2H, NH)	10.47, 5.69	10.21, 5.67
(s, 3H, CH ₃)	2.44	2.39
(t, 2H, CH ₂)	3.91	3.89
(dd, 1H, CH)	4.39	4.32
(m, 4H, Ar)	7.29-7.56	7.33-7.91

s: singlet, t:triplet, dd: doublet-of-doublet, m: multiplet

CONCLUSION

Three new thiourea derivatives featuring *N*-benzoyl and amino acid have been successfully synthesised and fully characterised by using typical spectroscopic methods namely UV, IR and NMR (^1H and ^{13}C). Although the varieties of substitution of the methyl group at the phenyl ring has been made, the spectroscopic results showed that all members in the series exhibit no significant different. However, with the exception of compound **2**, where it is shifted to lower frequency region in the IR compared to other members in the group. Further studies should be carried out to investigate this matter which may include single crystal X-ray crystallography, electrochemistry and computational studies. In addition, the variation of the substituents on the phenyl rings for an example should be considered for future studies in order to determine their electronic properties of this class of compounds.

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