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RESEARCH ARTICLE

STUDY ON SYNTHESIS OF SOME THIOUREA DERIVATIES CONTAINING THIAZOLE SCAFFOLD USING MICROWAVE OVEN.

Nguyen Thi Thanh Mai.
Faculty of Chemistry, Hanoi University of Industry, Hanoi, Vietnam.

***Corresponding Author:-* Nguyen Thi Thanh Mai.**

Abstract:

Thiourea and its derivatives represent a well-known important group of organic compound due to their diverse application in fields such as medicine, agriculture, coordination, and analytical chemistry,...In the present study, phenyl isothiocyanate and aromatic amines were milled in a porcelain crucible with lid and irradiated by using the MW irradiation power of 120W in several minutesto give the corresponding thioureas in high yields. Their biological activities were evaluated. They are screened for anti-bacterial activity against *Escherichia coli and Staphylococcus aureus* as well as screened for antifungal activity by agar diffusion method at 1 µg/ mL concentration in DMSO [2]... All the Structures of compounds were indentified by IR, ^{1}H-NMR,^{13}C-NMR spectra.

Key Words:- thioureas containg thiazole scaffold, solvent free.

Introduction:-

Thiourea is widely studied and claimed to be used in many applications such as pharmaceutical agents, pesticides, rodenticides, vulcanization accelerator, herbicides and scaffolds in organic synthesis. In the synthesis of thiourea [1,3]. Many studies reported on the direct reaction of isothiocyanate with amines after isolation to produce thiourea in good purity. Multisubstituted thioureas have gained more interest among researchers due to the increase of their pharmaceutical properties [5]. Our recent studies on thiourea reported that compounds that consist of more than one thiourea moiety possess better antimicrobial activities. It was due to the presence of more active sites of thiourea moieties containing C=S, C=O, and N-H groups [3]. In the present study, various thioureas containing thiazole scaffold were synthesized using microwave oven and their biological activities were evaluated.

Material And Methods:-

I. General experimetal procedures

Melting point was measured by using Thiele's apparatus in capillary and uncorrected. The FTIR-spectra were recorded on Magna 760 FT-IR Spectrometer (NICOLET, USA) in form of mixing with KBr and using reflex-measure method. ^{1}H-NMR (500 MHz), ^{13}C-NMR (125 MHz) spectra were recorded on an AVANCE AMX 500 FT-NMR Spectrometer (BRUKER, German) at 500.13 MHz, using DMSO-d_6 as solvent and TMS as an internal reference, δ in ppm. Bioassays were carried out in Hospital 19-8, Hanoi, Vietnam.

II. General procedure for synthesis of thioureas (2a-e).

A mixture of amine **1** (2 mmol) and phenyl isothioxyanat (2 mmol) was grinded in 5-mL. porcelain beaker. Then the mixture was put into a domestic microwave oven (the power output is 750 W). The adjustor of the microwave oven was set to the proper temperature (about 50 °C). The reactants were irradiated for a period of 5-7 min. The mixture became dark-yellow pasty in reaction process. The reaction was traced with thin-layer chromatography. The reaction mixture was cooled to room temperature, triturated with ethanol, filtered by suction and recrystallized with ethanol: toluene (1:1) to afford the title compounds (**2)** as ivory-white crystals [2].

Results:-

a) Synthesis of 1-phenyl-3-(2-(2',4',6'-trihydroxyphenyl)thiazol-5-yl)thiourea

^{1}H-NMR (DMSO-d6, δ, ppm): 12.05 (s, 1H, Ha) 11.5 (s,1H, Hb); 10.5 (s, 1H, Hd); 9,5 (s, 2H, Hc, He); 7.8 (d, 2H, d, *J* = 8.0, H-2", H6"); 7.3 (m, 2 H, H-3", H5"); 6.9 (m, 1H, H-4"); 6.5 (s, 1H, H-4); 5.5 (2H, H-5', H3'). ^{13}C-NMR (DMSO-d6, δ, ppm): 175.9 (C=S); 169.5 (C-2); 161.5 (C-4'); 159.2 (C-2', C-6'); 153.1 (C-5); 142.1(C-4); 126.3-135.1 (C- Ar); 85.5 (C-3', C-5').

b) Synthesis of 1-phenyl-3-(2-phenylthiazol-5-yl)thiourea

^{1}H-NMR (DMSO-d6, δ, ppm): 12.09 (s,1H, Ha) 11.3 (s, 1H, Hb); 8.1 (d, 2H, J = 7.8, H-2, H6; 7.5 (d, 2 H, *J* = 7.25, H-2", H- 6"); 7.20 - 7.55 (H- Ar); 6.5 (s, 1 H, H-4); ^{13}C-NMR (DMSO - d6, δ, ppm): 179.5 (C=S); 169.5 (C-2); 153.5 (C-5); 146.5 (C-4); 140.1 (C-1"); 126.5-133.5 (C- Ar).

c) Synthesis of 1-(2-(4-chlorophenyl)thiazol-5-yl)-3-phenylthiourea

^{1}H-NMR (DMSO-d6, δ, ppm): 12.1 (s, 1H, Ha) 11.3 (s, 1H, Hb); 8.05 (d, 2H, J = 7.5, H-2, H6; 7.7 (d, 2 H, *J* = 7.3, H-2", H-6"); 7.09 - 7.52 (H- Ar); 6.22 (s, 1 H, H-4); ^{13}C-NMR (DMSO-d6, δ, ppm): 180.0 (C=S); 169.3 (C-2); 151.5 (C-5); 146.5 (C-4); 140.1 (C-1"); 126.5 - 134.3 (C- Ar).

d) Synthesis of 1-(2-(4-bromophenyl)thiazol-5-yl)-3-phenylthiourea

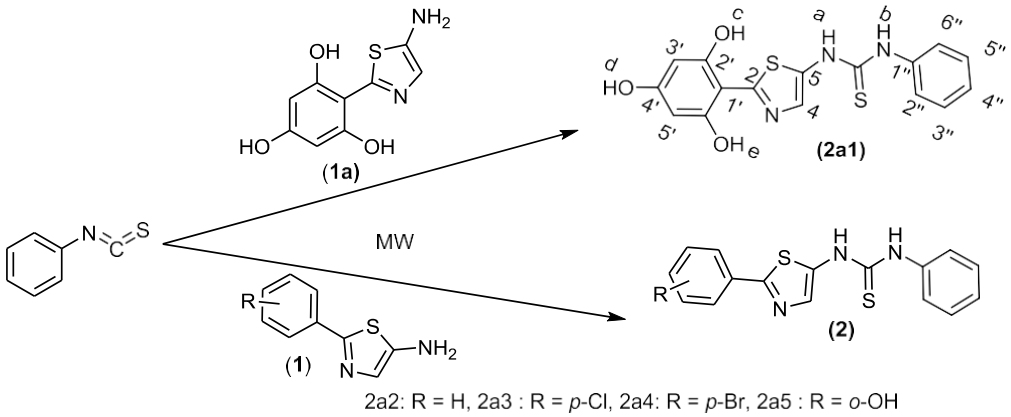
^{1}H-NMR (DMSO-d6, δ, ppm): 12.09 (s, 1H, Ha) 11.35 (s, 1H, Hb); 8.05 (d, 2H, J = 7.8, H-2, H6; 7.86 (d, 2 H, *J* = 7.3, H-2", H-6"); 7.09 - 7.72 (H- Ar); 6.2 (s, 1H, H-4); ^{13}C-NMR (DMSO-d6, δ, ppm): 179.9 (C=S); 169.5 (C-2); 151.2 (C-5); 143.5 (C-4); 139.5 (C-1"); 123.1 - 134.3 (C- Ar).

e) Synthesis of 1-(2-(2-hydroxyphenyl)thiazol-5-yl)-3-phenylthiourea

^{1}H-NMR (DMSO-d6, δ, ppm):): 12.09 (s,1H, Ha) 11.35 (s, 1H, Hb); 10.1 (s, 1H, OH); 7.80 (d, 2H, *J* = 7.8, H-2", H-6"); 7.70 (d, 1 H, *J* = 7.5, H-6'); 7.55 (m, 2H- H-3", H-5"); 7.35 (m, 1 H, H-5'); 7.05 (m, 1 H, H-4") 7.02 (m, 2 H, H-3', H-5'); 6.2 (s, 1H, H-4); ^{13}C- NMR (DMSO-d6, δ, ppm): 179.9 (C=S); 169.5 (C-2); 156.5 (C-2'); 151.3 (C-5); 143.8 (C-4); 138.5 (C-1"); 121.8 - 134.3 (C- Ar).

Discussion:-

The derivatives of thioureas **(2, 2a)** could be easily synthesized by the addition of corresponding amine compounds (**1, 1a**) on phenyl isothiocyanate. We performed this reaction by executing in microwave oven in several minutes. The synthetic processes could be represented in Figure. We have found that nucleophile addition of amines to phenyl isothiocyanate has taken place fairly easily. Reaction yields were high in using MW oven, in 65-72%. All these obtained thioureas could be dissolved in common organic solvents (such as ethanol, methanol, toluene, benzene, DMF,…) and couldn't be dissolved in water. Their structure have been affirmed by spectroscopic data (such as IR, NMR). In the IR-spectra of these above thioureas, stretching band of C=S bond in thiourea linkage have appeared in region of 1062-1064 cm^{-1}, furthermore, N–H bonds in thioureas have absorption band in region of 3622-3410 cm^{-1}, specified for stretching vibration of those bonds. In the ^{1}H-NMR spectra of these thioureas there are the resonance signals which are specifed for protons in thiourea -NH groups at =11.08-12.09 ppm. Some resonance signals are in region 7.625-8.350 ppm belong to some aromatic protons in amino component. In the ^{13}C-NMR spectra, it's could be noticed that number of carbon atoms in spectra and this one in molecular formulas of each thiourea were identical each other. It's could can be parted the spectra of these thioureas into three regions as follows: magnetic resonance signals of the C=S bonds have appeared in the low-field region of δ = 179.5 - 180.2 ppm, 179.5 - 180.2 ppm belong to thiazole scaffold140.1 - 169.5 ppm, and121.5 - 134.8 ppm belong to aromatic.



Scheme 1:- Synthetic reaction of thiourea compounds **2a-e**.

Table1:- Responese of various micro-organisms to some novel selected substituted thioureas.

Entry	R	Diameter of zone inhibition (mm		
		Staphylococcus aureus	*Escherichia coli*,	*C. Albicans*
2a	2,4,6-OH	28	25	19
2b	H	22	15	0
2c	*p*-Cl	25	23	18
2d	*p*-Br	26	25	21
2e	*o*-OH	25	28	22
Ref	-	35[a]	35[b]	45[c]

Ref = [a)] amicillin; [b)]methincillin; [c)]clotrimazole

Compounds **(2)** were screened for their antibacterial and antifungal activities in vitro antibacterial, antifungal by disc diffusion method. All thioureas **(2)** have significant biological activities against *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*. Compounds **2a** showed highest antibacterial activity against *Staphylococcus aureus*. Almost all compounds **(2)** have remarkable biological activity, except compound **2b** which exhibited no antifungal activity.(Table 1)

Conclusions:-

The ^{1}H- and ^{13}C-NMR spectra of some thioureas have been recorded and discussed. The magnetic signals in their NMR spectra show the relationships between the structure and positions of the substituted groups. All the newly synthesized thioure containing thiazole scaffold derivatives have good to moderate anti-bacterial and anti-fungal activity, they can be used for the development of new drugs for treatment of bacterial and fungal diseases.

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