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Synthesis of Some 6-Aryl-1,2,4,5- Tetrazine-3-thione Compounds Derived from Thiocarbohydrazide

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***Abstract*- Carbon disulfide was reacted with hydrazine hydrate (80%) to obtained thiocarbohydrazide (1) and the latter reacted with different substituted benzaldehyde to afford 6-aryl-1,2,4,5-tetrahydro tetrazine-3-thione(2-6) via condensation reaction. Compounds 6-aryl-1,2,4,5-tetrazine-3-thione (7-11) were also obtained directly through the oxidation reaction of compounds (2-6) in presence of hydrogen peroxide (4%). The structure of the newly compounds were confirmed by available spectroscopic methods.**

***Keywords*- 1, 2, 4, 5- Tatrazine, Thiocarbohydrazide, Condensation reaction, Oxidation reaction.**

I. INTRODUCTION

1, 2, 4, 5-Tetrazine derivatives have a high potential for biological activity possessing a wide range of antiviral [1], antifungal [2], anti inflammatory [3] and antitumor [4] properties. Additionally, these compounds have been widely used as pesticide and herbicide [5]. As well as, it used recently in amino acids formation as a binder for peptide bonds [6] In this presentation, 1,2,4,5-tetrazines were prepared from unique compound known thiocarbohydrazide (1) which on the other hand it have as widespread use in heterocyclic chemistry, its used widely as a good synthon to form different types of heterocyclic compounds such as triazoles[7], thiadiazoles[8] and tetrazines [9]. Actually, thiocarbohydrazide used to obtaind a special type of organometallic compounds [10]. Furthermore, it showed an applications in industrial field [11] and biological field as antibacterial[12], antitumer [13], antifungi[14] and good drugs for epilepsy desease. Herien in this presentation simple and direct reactions were take place starting from the formation of thiocarbohydrazide (1) which then played as good synthon to obtained 6-aryl-1,2,4,5-tetrahydro tetrazine-3-thione compounds (2-6) and the latter converted by direct oxidation to 6-aryl-1,2,4,5-tetrazine-3-thione compounds (7-11) in presence of hydrogen peroxide (4%) as oxidizing agent.

II. EXPERIMENTAL SETUP

Melting points (M.P.) were measured on Stuart SMP10.MeltingPoint apparatus and are uncorrected. Proton-Nuclear Magnetic Resonance (^{13}C & ^{1}H-NMR) spectra were recorded using, Bruker DMX-500 NMR Spectrophotometer (300MHz); with TMS as internal standard, and DMSO-d_6 as solvents; Jordan, University of Al-Bayt. [(s) singlet; (d) doublet; (m) multiplet]. Infrared (FT-IR) spectra were recorded as (KBr) disc using a Thermo Mattson300 Infrared Spectrophotometer. Ultraviolet (UV) spectra were performed on ShimadzuUV-160Ultraviolet–Vissible Spectrophotometer using methanol as a solvent.

A. Synthesis of Thiocarbohydrazide (1) [15]:

(13 ml, 0.22 mole) of carbon disulphide was added drop wise to vigorously stirred solution (24 ml, 0.44 mole) of hydrazine hydrate (85%) in (15 ml) dis. water during (30 minutes). Then the temperature of the reaction was raised to (100-110°C) and the reaction mixture was refluxed for (2 hrs.), then cooled in ice bath to (0° C). The precipitated thiocarbohydrazide was filtered off, washed with ethanol followed by diethyl ether and then air dried. the product thus obtained was recrystallized from minimum amount of hot water. Yield (76%), M.p.(169-170°C), FT- IR(cm^{-}

[1]): NH_2 (3306), NH (3274,3203), N-N (1489), C-N (1384) and C=S (1282). U.V DMSO $\lambda max_{(nm)}$ (355,272).

B. Synthesis of 6-aryl-1,2,4,5-tetrahydro tetrazine-3-thione (2-6) [16]:

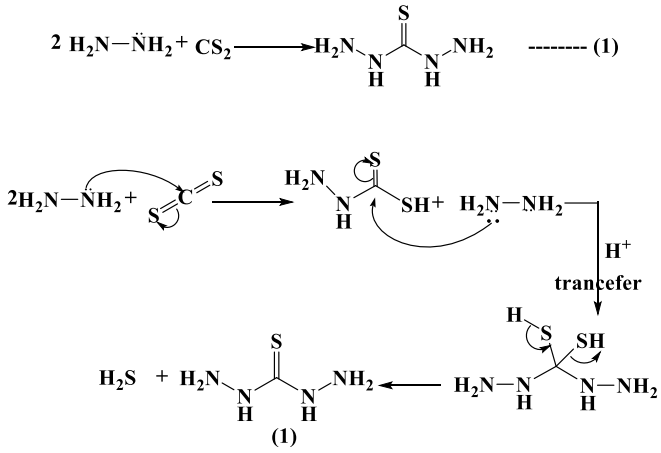
A solution of thiocarbohydrazide (1.06g , 0.01 mole) and (20 ml) glacial acetic acid was taken in round bottomed flask (100ml), followed by adding a solution of substituted benzaldehyde (0.01 mole) in absolute ethanol (15) drop wise with stirring at room temperature for (2-3 hrs.) until a white-yellowish precipitate was obtained which was calculated by filtration and washed with water and ether and finally it was recrystallized with ethanol. Table (1).

C. Synthesis of 6-aryl-1,2,4,5-tetrazine-3-thione (7-11) [17]:

In a round bottomed flask (100ml) hydrogen peroxide (4%, 50 ml) was added drop wise with stirring to a solution of compounds (2-6) (0.0018 mole in 10 ml ethanol). The reaction mixture was then refluxed for (2 hrs.) at (60°C) and then kept to stand at room temperature . The resulting product was washed with a small portion of distilling water and dried. Finally,It was purified by racrystallization from ethanol. Table (2).

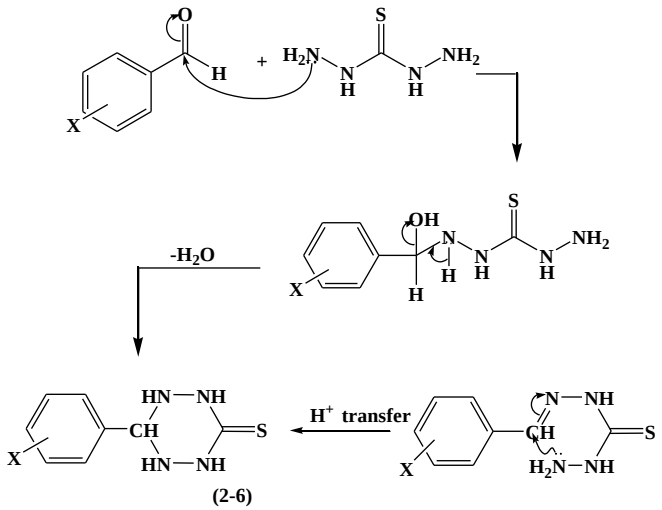
III. RESULTS AND DISSCUSION

Firstly, thiocarbohydrazide (1) was prepared as shown in equation (1) and Scheme (1)[18] in good yield (76 %) [15]. This compound gave three special absorption bands in FT-IR spectra at 3306, (3274 and 3203) and 1282 cm^{-1} refered to three functional groups NH_2, NH and C=S respectively in addition to the N-N functional group at 1489 cm^{-1} and C-N functional group at 1384 cm^{-1}. While in U.V spectra it gave two types of electronic transition represented by $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ at (355 & 272 nm)respectively [19].



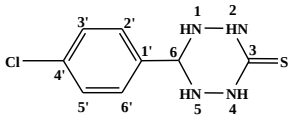
Scheme (1)

Thiocarbohydrazide (1) used as a good precursor to form symmetrical tatrazine represented by compounds 6-aryl-1,2,4,5-tetrahydro tetrazine-3-thione compounds (2-6) through cyclocondensation reaction with substituted benzaldehyde in acidic media , and these compounds were isolated in good yield (Table I). The reaction started by the formation of schiff base through the action of the electron pair of primary amino group in thiocarbohydrazide on the carbonyl group in substituted benzaldehyde followed by proton transfer which lead to the intracyclization reaction between the second primary amino group and schiff base to obtained compounds (2-6) as shown in (Scheme 2) [11].



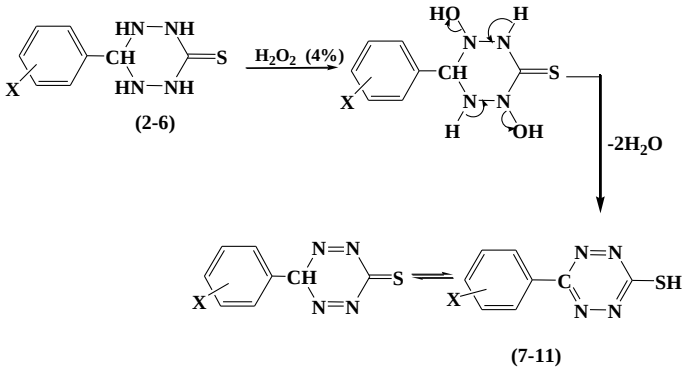
Scheme (2)

Compounds (2-6) were characterized by FT-IR spectra which they showed a stretching vibration bands at (3111-3190cm^{-1}), (1588- 1597cm^{-1}), (1513-1589cm^{-1}) and (1244-1255cm^{-1}) refer to NH, C=C, C=Nand C=S respectively. The absence of the NH_2 absorption band gave an indication to form the six memberd ring. Whereas, in U.V spectra they show (λ_{max}) at (304-373 nm), (253-337nm) due to the electronic transitions $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ respectively[19]. On the other hand, ^{1}H NMR spectrum of compound (2) (CDCl3): showed proton signals at 1.98 ppm (s, CH ,1H), 3.4 ppm (s,NH,4H) and at 7.3-8.0 ppm (m, 4H, -Ar-H) respectively, table III.



Additionaly, in ^{13}C-NMR spectra compound (2) showed a singlet band at 175.4 and 147.8 ppm (C_3 &C_6 in tetrazine ring),while the aromatic ring showed the following bands at 142.6 &133.5 ppm refer to ($C_{1'}$&$C_{4'}$) and at 129.3 &129.6 ppm refer to ($C_{3'}$,$C_{5'}$ & $C_{6'}$, $C_{2'}$) respectively (table III).

Finally, compounds (2-6) converted directly to compounds 6-aryl-1,2,4,5-tetrazine-3-thione (7-11) by treatment with hydrogene peroxide (4%) as oxidizing agent through an oxidation reaction by loosing two molecules of water (Scheme 3) [11] in good yields (Table 2).



Scheme (3)

This compounds were identify by FT-IR spectra which showed stretching vibration bands at (1602-1617cm^{-1}), (1550-1559cm^{-1}), (1521-1544cm^{-1}) and (1212-1294cm^{-1}) refer to (C=C), (N=N), (C=N) and (C=S) functional groups, the absence of NH absorption bands and appearance of N=N absorption band provide a clear indication of the composition of the desired compounds (7-11). On the other hand, these compounds showed two types of electronic transitions represented by $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ at (274-322nm) & (250-299nm) respectively [19]. On the other hand, ^{1}H NMR spectrum of compound (7) (CDCl3): showed absorption band at (3.7ppm) refer to (s,CH ,1H) and absorption bands at (7.4-8.0 ppm) refer to (m,4H,aromatic), table III.

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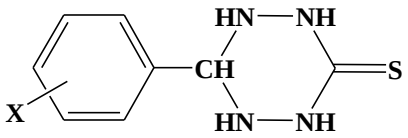
Table I

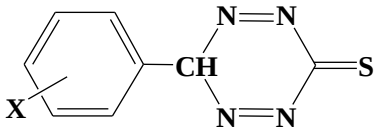
Physical and spectral data of compounds (2-6)



Comp. No.	FT-IR (KBr) , υ (cm^{-1})								*U.V DMf* $\lambda_{max(nm)}$
	X	**M.P. (°C)**	**Yield (%)**	**N-H**	**C=S**	**C=C**	**C=N**	**Others**	
2	p-Cl	193-194	74	3190	1248	1592	1513	C-Cl 875	337,352
3	p-Br	196-197	94	3125	1254	1590	1520	C-Br 871	336,353
4	P-NO_2	206-208	93	3111	1244	1594	1567	NO_2 sym.1558 asym.1344	253,315
5	N,N-diCH_3N	206-207	89	3132	1255	1597	1518	C-H 2987	278,373
6	o-OMe	203-204	34	3123	1250	1588	1589	C-O-C sym.1081 asym. 1286	268,304

Table II

The physical and spectral data of compounds (7-11)



Comp. No.	FT-IR (KBr) , υ (cm^{-1})								U.V DMf $\lambda_{max(nm)}$
	X	M.p. (°C)	Yield(%)	N=N	C=S	C=C arom.	C=N	Others	
7	p-Cl	179-180	65	1559	1294	1617	1539	C-Cl 626	263,322
8	p-Br	185-186	76	1559	1294	1617	1539	C-Br 550	250,313
9	P-NO_2	173-174	77	1588	1243	1616	1521	NO_2 sym. 1348 asym. 1540	260,274
10	N,N-diCH_3N	150-151	41	1556	1367	1615	1526	–	259,372
11	o-OMe	154-155	34	1550	1218	1602	1544	C-O-C sym. 1081 asym. 1286	299,312

Table III

^{1}H-NMR and ^{13}C-NMR data for compounds (2&7)

Compd. No.	^{1}H-NMR (δ,ppm)	^{13}C-NMR (δ,ppm)
2	δ1.98 (s, CH ,1H) δ 3.4 (s,NH,4H) and δ 7.3-8.0 (m, 4H, -Ar-H)	175.4,147.8, 142.6 &133.5
7	δ 3.7 (s,CH ,1H) δ 7.4-8.0 (m,4H,aromatic).	—