Synthesis and Characterization of New Heterocyclic Compounds Containing 2-Amino -1,3,4 -Thiadiazole -5-Mercapto Ring

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Abstract

In this study, 2- Amino – 1,3,4- Thiadiazole -5- Thiol derivatives were synthesized by many reactions. Compound (1) was cyclized by the reaction of thiosemicarbazide with carbon disulfide. The compound **(1)** was reacted with formaldehyde and secondary amines in methanol furnished Mannich bases **(2-7)** . The last step of this study was prepared the derivativse **(8,9 and 10)** by the condensation of 1-((5-amino-1,3,4-thiadiazol-2-ylthio)methyl)indoline-2,3-dione compound **(2)** with aromatic aldehydes . The newly synthesized compounds were characterized by their spectral (IR, 1H-NMR) data.

KEYWORDS: Mannich bases, Schiff bases, anticancer,2-Amino -1,3,4-Thiadiazole 5-Thiol, Analgesic, anti HIV .

Introduction

Schiff bases are used as substrates in the preparation of a number of industrial and biologically active compounds via ring closure, cycloaddition and replacement reactions [1]. Moreover, Schiff bases derived from various heterocycles have been reported to possess cytotoxic [2], anticonvulsant [3], antiproliferative [4], ntimicrobial [5], anticancer [6], and antifungal activities [7]. Mannich bases have gained importance due to their application in pharmaceutical chemistry. They have been encountered with antibacterial [8], anticancer [9], analgesic and anti-inflammatory [10], anticonvulsant [11], antimalarial [12], antiviral [13], and CNS depressant activities [14]. 2-Amino -1,3,4 -Thiadiazole -5-Mercapto, has become a popular topic due to its various uses. The chemistry of 2-Amino -1,3,4 -Thiadiazole -5-Mercapto and its derivatives is particularly interesting because of their potential application in medicinal chemistry. 2-Amino -1,3,4 -Thiadiazole -5-Mercapto and its derivatives are very important compounds due to their antifungal properties [15]. Schiff and Mannich bases of 2-Amino -1,3,4 -Thiadiazole -5-Mercapto derivatives are reported to show variety of biological activities like antibacterial [16], antifungal [17], anticonvulsant [18], anti HIV [19], antidepressant [20], and antiinflammatory [21] activities. These biological data prompted us to synthesize new compounds were characterized by IR, 1H -NMR spectral data

Material and Methods:

General

Melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra discs (KBr) were recorded with a Shimadzu *FTIR*-8400, ^{1}H NMR spectra were recorded with a Varian Gemini spectrometer at 300 MHz and 200 MHz with TMS as internal standard. Chemical shifts are reported in δ scale (ppm) relative to TMS as a standard, and the coupling constants (*J* values) are given in Hz.

Preparation of 2-Amino-5- mercapto-1, 3, 4-thiadiazole(1):

A solution of thiosemicarbazide (9.0g, 0.178 mol) and ahydrous Sodium carbonate (10.6 g, 0.1 mol) in ethanol was placed in 250 ml round bottomed flask fitted with reflux condenser. Carbon disulfide (15.2g, 0.2 mol) was then added and the mixture was stirred for 1h. at room temp. After being refluxed for 7h, the reaction mixture was then allowed to cool, then most of the solvent removed via evaporization under reduced pressure by rotary evaporator. Water (60ml) was added to the residue and the mixture acidified carefully by conc. hydrochloric acid. The crude pale yellow residue was filterd and washed with distilled cold water. Then recrystallized from ethanol to give pale greenish- yellow needles of 2-amino-5- mercapto-1,3,4-thiadiazole [22] **.**

IR and 1H NMR Spectra of Compound(1): IR (KBr): , 3340,3251 (NH_2) ,3128 (N-H), 1608 (C=N), 2584 (-SH), 1550 (C=S) cm^{-1}.

Preparation of Mannich Bases compounds(2-7):

.Equimolar quantities (0.01 mol), of 5-Amino-1,3,4-thiadiazol-2- thiol and the respective compounds having secondary amine were dissolved in methanol (30 ml) in a beaker under perfect ice-cold condition and stirred constantly [23][24]. To this solution, formaldehyde (0.01 mol) was added drop by drop , and heated to reflux for 3 h the content was kept overnight in the freezer. The corresponding crystals of mannich base of, 5-Amino-1,3,4,-2-Thiol , The resultant solid was dried and purified by crystallization from appropriate solvents Table 1.

IR and 1HNMR Spectra of 1-((5-amino-1,3,4-thiadiazol-2-ylthio)methyl)indoline-2,3-dione compound(2)**:** IR (KBr): , 3340,3251 (NH_2) , 1608 (C=N), 3015(C-H)Ar, 2974 (C-H)Ali, 1728 (C=O) , 1550 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d6) δ: 5.3 (S,2H,S-CH_2), 6.8-8.5(m,4H,Ar-CH) , 7.0-8.4(s,2H,NH_2).

IR and 1HNMR Spectra of 5-((1H-indol-1-yl)methylthio)-1,3,4-thiadiazol-2-amine compound(3)**:** IR (KBr): 3387,3228 (NH_2) , 1608 (C=N), 3015(C-H)Ar, 2974 (C-H)Ali,1566 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d6) δ: 5.2(S,2H,S-CH_2), 7.0-8.5(m,4H,Ar-CH), 7.3(s,2H,NH_2), 6.7(d,1H,CH-C=C), 7.9(d,1H,CH-C-N).

IR and 1HNMR Spectra of 5-((1H-imidazol-1-yl)methylthio)-1,3,4-thiadiazol-2-amine compound(4): IR (KBr):3340,3262(NH_2), 1612 (C=N), 3089(C-H)Ar, 2943 (C-H)Ali,1558(C=S)cm^{-1}. ^{1}H NMR (DMSO-d6) δ: 5.2(S,2H,S-CH_2), 7.7 (d,1H,CHN) 6.9(d,1H,CHN), 8.7(s,2H,NH_2), 8.9(s,1H,CH=N).

IR and 1H NMR Spectra of 5-(piperidin-1-ylmethylthio)-1,3,4-thiadiazol-2-amine compound(5): IR (KBr): 3271,3163 (NH_2), 2943(C-H)Ali, 1612 (C=N), 1558(C=S)cm^{-1}.

IR and 1HNMR Spectra of 1-((5-amino-1,3,4-thiadiazol-2-ylthio)methyl)-1H-indole-2-carboxylic acid compound(6): 3271,3163 (NH_2), 3015(C-H)Ar, 1651 (C=N) , 2927(C-H)Ali, 1570 (C=S)cm^{-1}. ^{1}H NMR (DMSO-d6) δ: 5.2(S,2H,S-CH_2), 11.04(S,1H,COOH), 8.5(s,2H,NH_2), 7.6(m,4H,Ar-CH),7.8(S,1H,C=C-CH2).

IR and 1HNMR Spectra of 5-(morpholinomethylthio)-1,3,4-thiadiazol-2-amine compound(7): 3278,3136(NH_2), 2958 (C-H)Ali, 1612 (C=N), 1562(C=S)cm^{-1}. ^{1}H NMR(DMSO-d6) δ:4.7(S,2H,S-CH_2),3.6(t,4H,O-CH_2CH_3), 7.00(s,2H,NH_2), 2.6(t,4H,NCH2CH2).

Preparation of Schiff Bases compounds(8-10): A mixture of compound (2) (0.003mol),and corresponding aryl aldehyde (0.003 mol) in absolute ethanol (15 ml) and drops of glacial acetic acid was refluxed for 8 h.. The mixture was cooled and collected by filtration and recrystallized by ethanol[25] .

IR Spectra of (E)-1-((5-(benzylideneamino)-1,3,4-thiadiazol-2-ylthio)methyl)indoline-2,3-dione compound (8): *3109(C-H) Ar,2927(C-H) Ali,1616 (C=N),1732(C=O).*

IR Spectra of (E)-1-((5-(4-hydroxybenzylideneamino)-1,3,4-thiadiazol-2-ylthio)methyl)indoline-2,3-dione compound (9):*3070 (C-H) Ar ,2974 (C-H) Ali ,1600(C=N),1735 (C=O).*

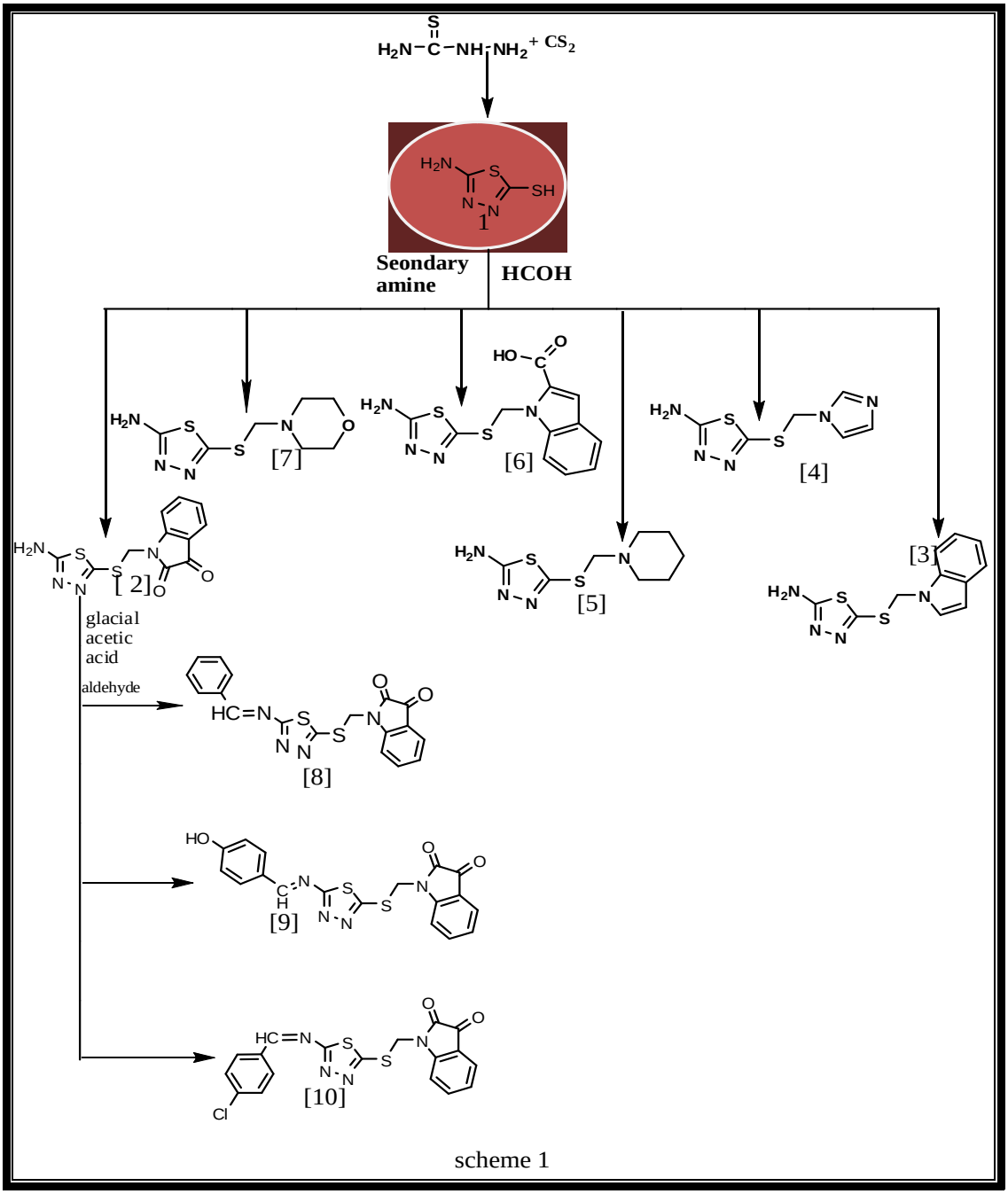
IRSpectraof(Z)-1-((5-(4-chlorobenzylideneamino)-1,3,4-thiadiazol-2-ylthio)methyl)indoline-2,3-dionecompound (10): 3109(C-H) Ar,2924(C-H) Ali,1616 (C=N),1735(C=O).

Table.1. Physical and Analytical data of the synthesized compounds (1-10)

Com. No.	Molecular Formula	M.P °C	Color	Recrystalized Solvent	Yield (%)
1	$C_2H_3N_4S_2$	230-232	Greenish-yellow	Ethanol	66%
2	$C_{11}H_8N_4O_2S_2$	112-114	Orange	Ethanol	78%
3	$C_{11}H_{10}N_4S_2$	100-102	Deep Yellow	Ethanol	83%
4	$C_6H_7N_5S_2$	146-148	Gray	Ethanol	45%
5	$C_8H_{14}N_4S_2$	90-92	White	Ethanol	55%
6	$C_{12}H_{10}N_4O_2S_2$	110-112	Light Brown	Ethanol	63%
7	$C_7H_{12}N_4OS_2$	199-201	Brown	Ethanol	83%
8	$C_{18}H_{12}N_4O_2S_2$	112-114	Yellow	Ethanol	47%
9	$C_{18}H_{12}N_4O_3S_2$	200-202	Red	Ethanol	67%
10	$C_{18}H_{11}ClN_4O_2S_2$	155-157	Orang	Ethanol	55%

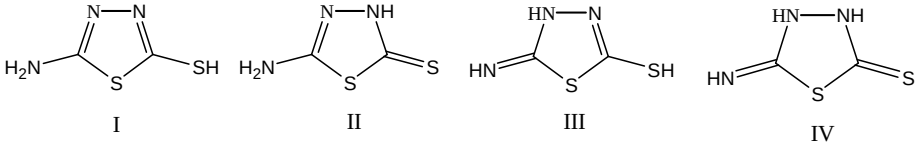
Results and Discussion

Compounds [1-10] were synthesized as shown in scheme 1.Some physical properties for this compounds were listed in table 1.



Scheme 1. Synthetic pathway for preparation of compounds **1** and **10**.

Compound **(1)** was characterized by its melting point and by FTIR spectrum, melting point was recorded (230-232) C^0 and the reported m.p was (230-232) C◦ [18]. The FTIR spectrum of compound (1) showed a medium intensity band at 1608 cm-1 that could corresponds with (C=N) bond in the vicinity of 1,3,4-thiadiazole ring. In this spectrum there are two other characteristic bands at 3128cm-1 and 2584.22 cm-1 due to (N-H, thion form) and (S-H) stretching vibrations, respectively. That means compound 1 can exist in the thiol and thion form.



The compound **(1)** was conveniently converted in to 2- amino-1,3,4- thiadiazole - 5-substituted –thiol **(2-7)** by condensing it with different secondary amines in absolute methanol .

Compound **(2)** was characterized by FTIR and 1HNMR spectroscopy, FTIR spectrum shows strong absorption band at 1728 cm-1 due to carbonyl group and bands at 2974.84 cm-1 and 2939.61 cm-1 for aliphatic (CH2) group and 3340,3251cm-1 for (NH2) group . Disappearance of S-H and N-H absorption bands was also detected. 1HNMR spectrum of compound (2) showed singlet signal at δ=5.3 ppm belong to (SCH2) and singlet signal at δ =2.50 ppm..

FTIR spectrum of compound **(3)** shows characteristic absorption bands at (3387,3228)cm-1 for (NH2) group and bands at 2974cm-1 for aliphatic (CH2) group. Disappearance of S-H and N-H absorption bands was also detected .

1HNMR spectrum of compound **(3)** showed singlet signal at δ=5.2 ppm belong to (SCH2) ,singlet signal at δ =7.3 ppm belong to(NH_2), multiplet signal at δ = 7.0 ppm belong to (4H) in benzene ring .

FTIR spectrum of compound **(4)** shows characteristic absorption bands at (3340,3262)cm^{-1} for (NH2) group and bands at 2943cm-1 for aliphatic (CH2) group. Disappearance of S-H and N-H absorption bands was also detected .

1HNMR spectrum of compound **(4)** showed singlet signal at δ=5.2 ppm belong to (SCH2) and singlet signal at δ =8.7 ppm belong to(NH_2) .

FTIR spectrum of compound **(5)** shows characteristic absorption bands at (3271,3163)cm^{-1} for (NH2) group and bands at 2943cm-1 for aliphatic (CH2) group. Disappearance of S-H and N-H absorption bands was also detected .

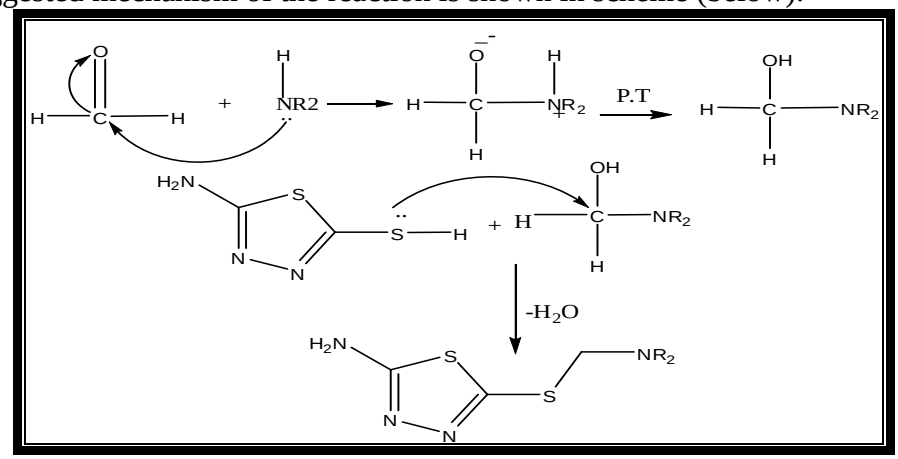
Compound **(6)** was characterized by FTIR and 1HNMR spectroscopy, FTIR spectrum shows strong absorption band at 1728.78 cm-1 due to carbonyl group for acetic acide and bands at 2927.00 cm-1 for aliphatic (CH2) group and (3271-3163)Cm^{-1} for NH_2 groub. Disappearance of S-H and N-H absorption bands was also detected.

1HNMR spectrum of compound **(6)** showed singlet signal at δ=5.2 ppm belong to (SCH2) and singlet signal at δ =8.5 ppm belong to(NH_2), multiplet signal at δ = 7.6 ppm belong to (4H) in benzene ring .

FTIR spectrum of compound **(7)** shows characteristic absorption bands at (3278,3136)cm^{-1} for (NH2) group and bands at 2958 cm-1 for aliphatic (CH2) group. Disappearance of S-H and N-H absorption bands was also detected .

1HNMR spectrum of compound **(7)** showed singlet signal at δ=4.7ppm belong to (SCH2) and singlet signal at δ =7.00 ppm belong to(NH_2).

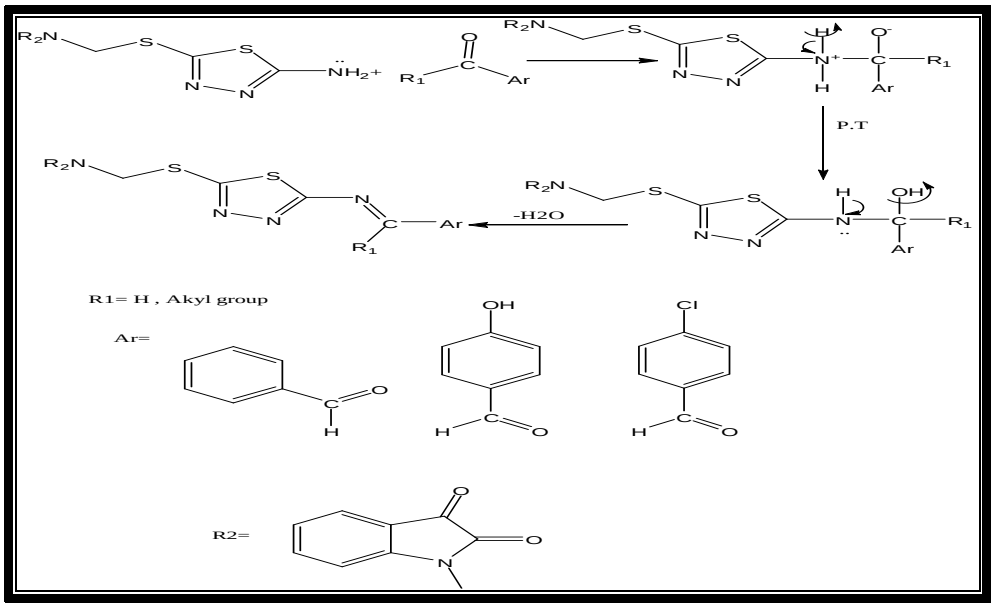
The suggested mechanism of the reaction is shown in scheme (below):



Scheme 2, Mechanism steps for the prepared compounds [2-7].

Condensation of compound **2** with aromatic aldehydes in absolute ethanol afforded the corresponding Schiff's bases **8-10** . (Scheme 1, Tables1). Compounds **(8-10)** were prepared from the reaction of compounds 2 with benzaldehyde , p-hydroxy benzaldehyde or p-chloro benzaldehyde . FTIR spectrum of compounds (8,9,10) show the disappearance of the absorption band of (NH2) group at (3340,3251) cm-1 and appearance of band sym., and asym., at (1616) cm-1which attributed to (C=N) azomethine group .

The suggested mechanism of the reaction is shown in scheme (below):



Scheme 3, Mechanism steps for the prepared compounds [8, 9 and 10].

CONCULSION

Thiadiazole are the most important classes of heterocyclic compounds and possess versatile type of biological activities; have exist anti-cancer, anti-tubercular, anti-bacterial, anti-fungal,anti-malarial, anti-inflammatory, anti-helmentic and anti-hypertensive activities. Thiadiazole heterocycles that have been reported to date illustrates different approaches to the challenge of preparing these bioactive products. In general, thiadiazole are prepared by appropriate rearrangements, ring opening and substitution reaction. Thiadiazole rings continues to grow,and the organic chemistry will provide more and better methods, more active, more specific and safer.

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