International Journal of Applied and Natural Sciences (IJANS)
ISSN(P): 2319-4014; ISSN(E): 2319-4022
Vol. 4, Issue 2, Mar 2015, 1-8

International Academy of Science, Engineering and Technology
Connecting Researchers; Nurturing Innovations

SYNTHESIS OF 2, 5- DISUBSTITUTED-1, 3, 4- THIADIAZOLE DERIVATIVES AND EVALUATION OF THEIR ANTIBACTERIAL ACTIVITY

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ABSTRACT

In this work 2, 5- dimarcapto-1, 3, 4-thiadiazole[1] was synthesized from the reaction of hydrazine hydrate with carbon disulfide and then was converted into the hydrazino derivative [2], Reaction of compound [2] with pheny isocyanate, phenyliso thiocyanate, 4-chloro phenyliso thiocyanate leads to formation compounds[3-5] On otherhand treatment of compounds [1] with thiosemicarbazide gave compound[6], which upon refluxing with o ethyl chloro formate in dry benzene yielded derivative [11]. Moreover, Schiff Bases derivatives [7-10] have been synthesized by treatment of compound([2, 6]with various aromatic aldehyde

New synthesized compounds were characterized by their melting points, FT-IR and (1HNMR, 13C-NMR of some of them) spectra. The biological activity evaluated of the final products showed that some of these compounds possess good antibacterial activity.

KEYWORDS: 1, 3, 4-Thiadiazole, Schiff Bases, Carbamates, Fused Heterocyclic Rings

INTRODUCTION

The chemistry of heterocyclic compounds has been an interesting field of study for a long time[1-7]. Heterocyclic nucleus 1, 3, 4-thiadiazole constitutes an important class of compounds for new drug development. The synthesis of novel thiadiazole derivatives and investigation of their chemical and biological behaviour have gained more importance in recent decades. During the recent years there has been intense investigation of different classes of thiadiazole compounds, many of which possess extensive biological activities. Among of these compounds having 1, 3, 4 - thiadiazole nucleus are known to possess anti-inflammatory [8], analgesic[9], antimicrobial [10l, anticanser [11], antifungal[12], antimycobacterial[13], anticonvulsant[14], antidiabetic[15, antiviral[16] activities. So far, modification of the thiadiazole ring have proven highly effective with improved potency and lesser toxicity. The present review highlights the recently synthesized thiadiazole possessing important biological activities.

EXPERIMENTAL

Instruments

Melting point determination: Uncorrected melt ing points were determined in open capillary on SMP30 Melt ing point (Stuart, Germany). TLC was performed on aluminium plates coated with silica gel 60F254 (20cm x 20cm). Layer thickness 0.2 mm..

Fourier Transform Infrared (FT-IR) : is the most important tools for determining the various functional group and the possible chemical structure. The important advantage of FT-IR over other technique is that it gives fingerprints (3300-650 cm-1) information about the structure (functional group, bonding with each other) of molecules easily, no two

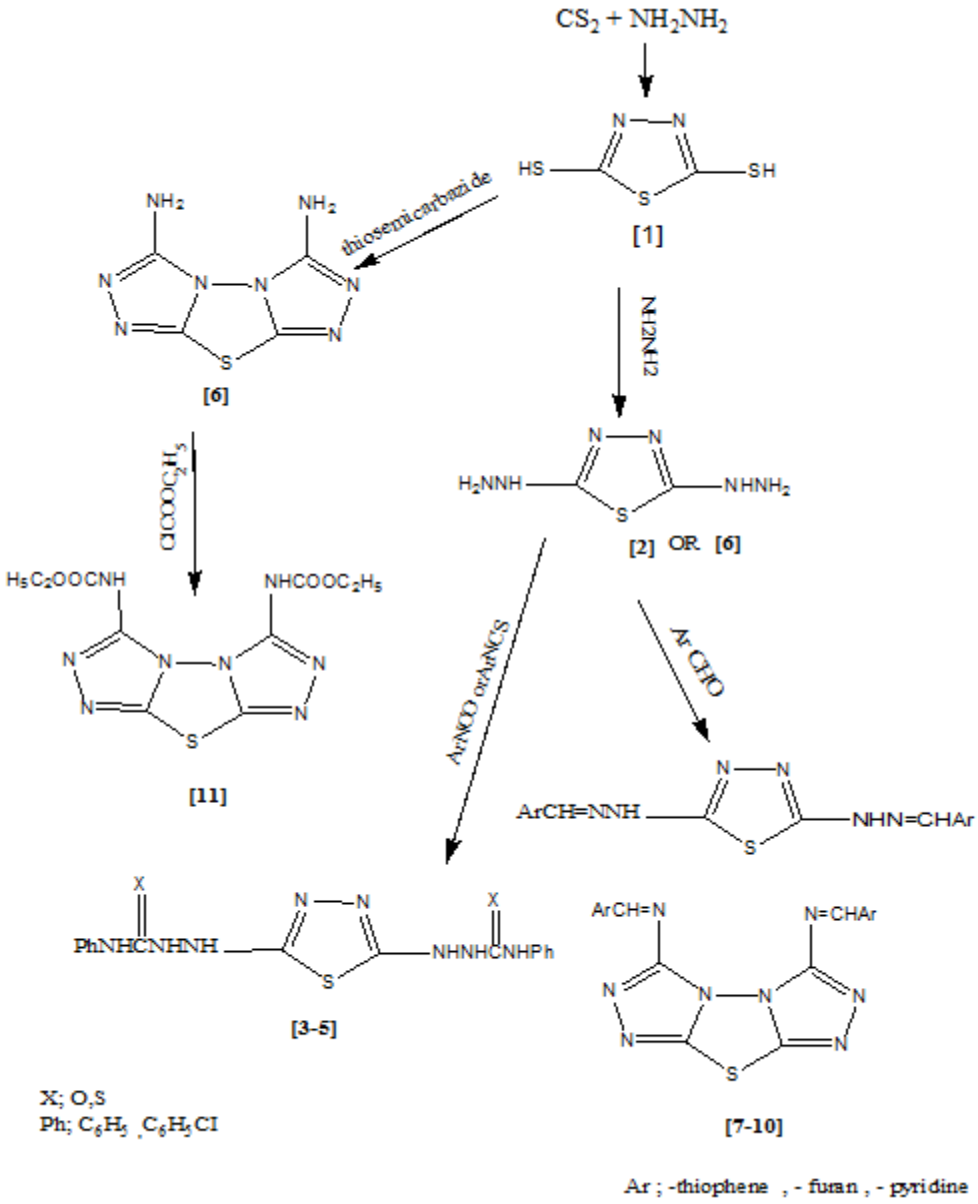
compounds have identical fingerprint region. This technique is based upon the molecular vibration of the compound such that each and every bond will vibrate at the different frequency. FTIR spectra were recordedon FTIR 8400 s Shimadzu spectrophotometer in Al-Mustansiriyah University, College of Sciences.

^{1}H -, ^{13}C-NMR were recorded on Bruker 300 MHz spectrophotometer, University of Al-albayt, Jordan using DMSO as a solvent

Ultra violet spectra were recorded using Shimadzu (UV-Vis)-160 recording spectrophotometer using ethanol as a solvent in Al-Mustansiriyah University, College of Science.

General Procedures

All compounds were synthesized according to scheme (1).



Synthesis of, 2, 5-dimercaptol-1, 3, 4- thiadiazole [1]

This compound was synthesized by previously described method. [17, 18]

A mixture of (99%) hydrazine hydrate (0.1 mol, 5g, 4.5 ml) and carbon disulfide (0.2 mol, 15g, 20ml) with dry pyridine (30 mL) was refluxed for 5 hrs, Then the excess solvent was then distilled off, and the resulting solid was separated out by adding (25 mL) of water and (5 mL) of hydrochloric acid. The mixture was then filtered and the solid was recrystallized from ethanol, The physical properties (yellow, m.p 163-165 ^{0}C ;lit.162-164^{0}C yield=72% ;lit .77.8%).

***Synthesis of, 2, 5-dihydrazino -1, 3, 4- thiadiazole* [2]**

This compound was synthesized by previously described method [18]

To 2, 5-*dimercapto-1, 3, 4- thiadiazole [1] (1.5gm .0.01 mol)* dissolved in ethanol, hydrazine hydrate (5 ml, 0, 02 mol) was added droup wise with stirring and the mixture was then refluxed for (6 hrs). Liberation of H2S was assign ed by lead acetate strip, then, the excess solvent was distilled off. Filitered the resulting solid which was separated out on cooling and recrystalized from ethanol, The physical properties(yellow, m.p 201-202 ^{0}C ;lit.198-200^{0}C yield=66% ;lit .60%).

Synthesis of 2, 5-di (aryl hydrazone) -1, 3, 4- thiadiazoles [3- 5]

A mixture of compound [2], hydrazine hydrate (0.01 mol, 1.46g) and pheny isocyanate, pheny l or-chloro phynal iso thiocyanate (0.02 mol with 30 mL ethanol was refluxed for 8 hrs, The mixture was then filtered and the solid was recrystallized from ethanol The physical and spectral data of the synthesized compounds [3-5] are listed in table (1). The nomenclature of the tit led ompounds are listed in tables (4).

Synthesis of compound [6]

2, 5-dimercapto-1, 3, 4- thiadiazole [1] (1.5gm .0.01 mol) thiosemicarbazide (1.82gm, 0.02 mol) and absolute alcohol (40mL), the mixture was refluxed for 48 hrs. Liberation of H2S was assigned by lead acetate strip, cooled at room temperature and the solid was filtered, dried and recrystallized from methanol. The physical and spectral data of the synthesized compound [6] are listed in table (3). The nomenclature of the tit led compounds are listed in tables (4).

Synthesis of Schiff Bases [7-10]:

A solution of compound [2, 6] (0.01 mol) in dry benzene (10 mL)was added to solution of aromat ic aldehyde (0.01 mol) in dry benzene (10 mL) acidified with glacial acetic acid (1-2 drops). The reactants were heated by reflux for 4 hrs. The solvent was evaporated and the residue was washed with water, dried and recrystallized from ethanol. The physical and spectral data of the synthesized schiff bases are listed in table (2). The nomenclature of the tit led compounds are listed in tables (4).

Synthesis of compound [11]

(2.17 gm, 0.02 mole) of ethyl chloro formate was added drop – wise to asolution compound [6] (1.64 gm, 0.01 mol) in pyridine (40 mL). The reaction mixture was left at room temperature for on hour with occasional shaking. It was then pourd onto 100 ml ice water and the carbamated was filtered, washed with water, dilute hydrochloride acid, then water again and crystallized from aqueous ethanol. The physical and spectral data of the synthesized copound is listed in table (3). The nomenclature of the tit led compound is listed in tables (4).

RESULTS AND DISCUSSIONS

The starting compounds were synthesized by previously described methods[17,18], The FT-IR spectrum of compound [1] showed a medium intensity band at 1624 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 3051.49cm-1 and 2767.94 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. UV spectrum of compounds [1] showed an absorption λmax at 203-208 nm and 325-303 nm which attributed to (π-π *and n- π *).

Reaction between corresponded compound [1] and hydrazine hydrate afforded the hydrazino derivative (2) in good yield. The FT-IR spectrum of compound [2] showed t he disppearance of band at 2767.94 for C-SH with anew band at 3308, 3228 cm-1, 3153 and 1637 cm-1 which are assigned $NH_{2\ asy.\ sym.,}$ NH and C=N group respectively. UV spectrum exhibited two distinguishable maxima near 345 nm and 254 nm which clearly due to (π-π *and n- π *) transitions respectively.

Also, reaction of the compound [2] with phenyl isocyanate, phenyl or chloro phenyl iso thiocyanate in ethanol gave compounds [3-5], The structural assignments of these compound [3-5] is based on it is spectral analysis showed in table (1), These spectra showed the disappearance of NH_2 bands and appearance of new stretching absorption bands at (2294-3171 cm-1), (1664) and (1656-1626 cm-1) belong to NH, C=O amide group and C=N group respectively. UV spectrum exhibited two distinguishable maxima near 355 -322 nm and 259-266 nm which clearly due to (π-π *and n- π *) transitions respectively.

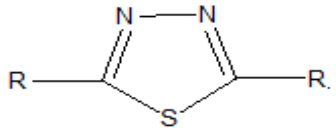
Compound [6] was prepared by refluxing of compound [1] with thiosemicarbazide in absolute ethanol for 8 hours. The compound was characterized by its melting points, FTIR, UV ^{1}H- NMR and^{13}C -NMR spectroscopy. The FTIR spectrum of compound[6] indicated the disappearance of C-SH band at (2767cm-1) and appearance of $NH_{2\ asy.\ sym}$ bands at (3354, 3261 cm^{-1}) and C=N band at (1635 cm^{-1}). UV spectrum revealed distinguished peaks at 361, 278 nm for (n- π *) and 245, 228 nm for (π-π *). 1H-NMR spectra of prepared compound was obtained in DMSO-d6 as solvents and with TMS as internal standard. The chemical shifts showed signal at δ 7.8613 for 4H protons of NH_2.The ^{13}C-NMR spectrum of compound[6] showed the signal at 149.400 ppm for carbon atom in triazole ring, while the signal at 158.116ppm for carbon atom in thiadiazole ring

Condensation of the copounds (2, 6) with aryl aldehydes in dry benzene gave the Schiff, s bases (7-10). The formation of these Schiff bases was indicated by the presence in their FTIR spectra of the azomethine (CH=N) stretching band at 1630-1650cm-1, combined with the disappearance of the NH_2 stretching bands, other bands showed in table (2) .The UV spectra of the Schiff bases mostly showed two intense maxima at 283-334 nm and 222-282 nm which belong to ((π-π *and n- π *) trasitions respectively. The 1 HNMR spectrum of compound [8] showed two singlet signal of CH=N group and NH group at δ (7.73 ppm and 7.21 ppm), A multiplet doublets appeared at δ (7.94-8.83) were due to eight aromat ic protons. ^{13}C-NMR spectrum of compound[8] showed the two signal at 124.177ppm, 148.530 ppm for carbon atoms in pyridine ring, while the signal at 159.224ppm for carbon atoms azomethanen (= CH) and the signal at 138.431ppm for carbon atoms in thiadiazole ring with(CH-C in pyridine ring)

Compound [11] was synthesized by previously described method[19], but the most suitable one which was adopted in this wok is the reaction of amino compound[6] with ethyl chloro formate[20, 21]. Structure of this products were confired

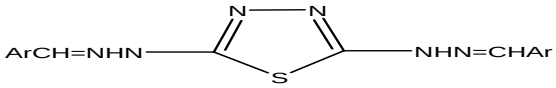
by its melting points and FTIR spectroscopy, FTIR spectrum of compound[11] indicated the disappearance of $NH_{2\ asy.\ sym}$ bands at (3354, 3261 cm^{-1}) and appearance of medium NH stretching band at (3279, 3082 cm^{-1}), medium C=N band at (1604 cm^{-1}). and strong C=O band at (1730 cm^{-1}). UV spectrum revealed distinguished peaks at 353 nm for (n- π *) and 277nm for (π-π *).

Table 1: Structure, Physical and Spectral Data of the Synthesized Compounds [3-5]



Com. no.	R	MP (C⁰)	Color	Yield%	UV(λmax EtOH)	FT-IR Frequencies (cm-1)					
						υ N-H.	υ C-H arom.	υ C-H(o.o.plane)	υC =Carom.	υC=N	Others
3	NHNHCONHPh	240-243	Pave yellow	56	355,259	3294,3213	3090	754,698	1595	1656	1693 υ C =O Amide
4	NHNHCSNHPh	185-187	yellow	55	354,259	3228,3186	3028	746,686	1552	1635	1274 υ c=s
5	NHNHCSNHPhCl	190-193	Dark yellow	50	325,257	3296,3171	3032	752	1550	1626	1274 υ c=s ,700 υ C -Cl

Table 2: Structure, Physical and Spectral Data of the Synthesized Schiff Bases [8-10]



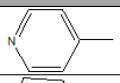
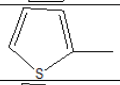
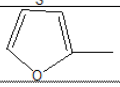
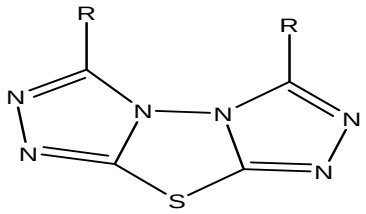
Comp. no.	Ar	MP (C⁰)	Color	Yield%	UV(λmax EtOH)	FT-IR Frequencies (cm-1)						
						υ N-H	υ C-H arom.	υ C-H alph	υ C-N	υ N- N	υ C=N	Others
8		194-196	Dark red	68	318,247	3086	3055	2980,2888	1336	1535	1626	
9		130-132	yellow	64	329,239	3099	3082	2978,2898	1354	1512	1610	719υ C-s.
10		140-143	Pave yellow	55	328,247	3160	3099	2940,2830	1348	1539	1604	1130 υ C-O

Table 3: Structure, Physical and Spectral Data of the Synthesized Compounds [8-10]



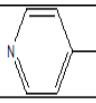
Com. no.	R	MP (C⁰)	Color	Yield%	UV(λmax EtOH)	FT-IR Frequencies (cm-1)				
						υ N-H	υ C-N	υ N- N	υ C=N	Others
6	NH2	194-196	Pale yellow	67	361,278	3354,3261	1334	1531	1635	
7		285-288	Dark red	70	404,273	-	1338	1527	1629	3041υ C-Harom. 2980,2861υC-Halph
11	$NHCOOC_2H_5$	250-253	white	65	353,277	3279	1348	1539	1604	1730 υ C=Oester

Table 4: Nomenclature of the Synthesized [3-11]

Comp. No.	Nomenclature
3	2, 5-bis(2-{[imino(phenyl)- λ^6-carbonylidyne]methyl}hydrazinyl)-1, 3, 4-thiadiazole
4	2, 5-bis(2-{[imino(phenyl)- λ^6-sulfanylidyne]methyl}hydrazinyl)-1, 3, 4-thiadiazole
5	2, 5-bis(2-{[imino(4-chlorophenyl)- λ^6-sulfanylidyne]methyl}hydrazinyl)-1, 3, 4-thiadiazole
6	bis[1, 2, 4]triazolo[3, 4-*b*:4', 3'-*d*][1, 3, 4]thiadiazole-3, 6-diamine
7	*N*, *N*'-bis(pyridin-4-ylmethylidene)bis[1, 2, 4]triazolo[3, 4-*b*:4', 3'-*d*][1, 3, 4]thiadiazole-3, 6-diamine
8	2, 5-bis(2-pyridine -4-yl)methylene hydrazinyl)-1, 3, 4-thiadiazole
9	2, 5-bis(2-thiophen -2-yl-methylene)hydrazinyl)-1, 3, 4-thiadiazole
10	2, 5-bis(2-furan -2-yl-methylene)hydrazinyl)-1, 3, 4-thiadiazole
11	diethyl bis[1, 2, 4]triazolo[3, 4-*b*:4', 3'-*d*][1, 3, 4]thiadiazole-3, 6-diylbiscarbamate

ANTIMICROBIAL ACTIVITY TEST

The antimicrobial potency of the synthesized copounds [4 - 11] were evaluated. Four types of bacteria were used (+ve and –ve). Some of the tested compounds demonstrated an encouraging activity such as (6, 7, 8, 9, 10, 11) table (4)

Table 4: Inhibition Zones of Titled Compounds [3-11]

Compound Code (1000 ppm).	Inhibition Zone (mm.)			
	Gram Positive		Gram Negative	
	Staphylococcus Sciuri	*Streptococcus Aeidominimus*	*E. Coli e*	*Pseudomonas Fluorensce*
[3]	-ve	-ve	-ve	-ve
[4]	-ve	-ve	-ve	-ve
[5]	-ve	-ve	-ve	-ve
[6]	-ve	19	-ve	-ve
[7]	20	24	-ve	7
[8]	-ve	13	-ve	12
[9]	16	-ve	-ve	6
[10]	-ve	19	-ve	8
[11]	21	-ve	-ve	-ve

REFERENCES

1. Nargund, L .V. G ., Reddy, G.R.N. and Haripasad, V " ***Ind. J. Chem***., 35, 499 **(1996)**
2. Demirdas, N., Demirdas, A., Karaoglo, S.A and Celik, E ", ***Arkivoc***, 75 (i) **(2005).**
3. Zhang, L.X., Zhang, A.J., Chen, X.X., Lie, X.X., Nan, X., Y., Chen, D.Y. nd Zhang, Z.Y. " ***Molecule,*** 7681 **(2002).**
4. Masry El-, Fahmy A.H.,, H.H.and, S.H. bdwahed, " ***Molecule*** 5, 1429 **(2000).**
5. Sharba, A.H.K., AL-Bayati, R.1., Aouad M. and Rezki, N., *Molecules*, 10(9), 1161-1168 **(2005).**
6. Sharba, A.H.K., AL-Bayati, R.l., Rezki, N. and Aouad M", *Molecules*, 10 (9), 1153-1160**(2005)**
7. Alexandra T., Denisa H., LaurIan V.Cristina M., Valentin Z "*Pharmacy* 86 – Sup. no. 1, **(2013)**

8. Bala S, Kamboj S, Kumar A.'. *J Pharm Res*. 3(12):2993-2997**.(2010)**
9. Vashi.B.S, Mehta.D.S and Shah.V.H: '. *Ind. J. Chem*, 53B, 111-115, **(1999)**
10. Mohd. R., Asif.H and Ravinesh.M. *Euro. J. of Med. Chem.*, 54, 855–866, **(2012).**
11. Mishra.V.K and Rahel S.C, Bis Heterocyclic as possible fungicides: *Ind. J. Chem*, (Lx, Sep):876-870 **(1983)**.
12. Mistry KM, Desai KR.. *Euro. J. Chem*. 1(4):189-193**.(2004)**
13. Loscher. W.,, " *Euro. J. of Pharm. Sci.*, . 342, 1–13, **(1998).**
14. Patttan.S. R, Kittu, B.S. Sastry, B.S, Jadav, S.G, Thakur D.K., Madamvar S.A and Shinde H.B... *Ind. J. Chem* 50B, 615-618 **(2011)**
15. Chhonker YS, Veenu B, Hasim SR, Kausik N, Kumar D, Kumar P. *Euro. J. Chem*. 6 (S1) : 342-346 **(2009).**
16. Mustafa M. Abdulrasool, Alaa H. Jawad, Jawad K. Shneine *Inter. J. of Appl. Sci. and Tech. 2 (10), **(2012)***
17. (Jumat, N., EmadY, A. H. and Hiba I., *Aust. J. Basic & Appl. Sci.*, 4, 2016-2021. (2010).
18. Metcalf, R.L, Fukuto, T.R, and Winton, M.Y.J ;Econ.Entomol 55, 889, (1965)
19. Armstrong, V.C., and Moodie, R.B. ; J. Chem. Soc., Sec B 934, (1969)
20. Moayed S. ; j. Raf.Sci 20(1), 1-7, (2007)