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SYNTHESIS AND ANTIMICROBIAL ACTIVITY EVALUATION OF SOME NOVEL IMIDES AND SCHIFF BASES CONTAINING 1,3,4-THIADIAZOLINE RING

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ABSTRACT

A novel imides and Schiff bases containing 1,3,4-thiadiazoline ring were synthesized by many steps reaction. The reaction of 4-bromoacetophenon and 4-bromobenzaldehyde with thiosemicarbazide gave thiosemicarbazone $[1]_{a,b}$, afterward cyclization reaction of compound [1] with the acetic anhydride in presence of pyridine led to formation 1,3,4-thiadiazoline compounds $[2]_{a,b}$. These compounds $[2]_{a,b}$ were converted to 2-amino-1,3,4- thiadiazolines $[3]_{a,b}$ by hydrolysis of amide NHCOMe group to amine group using hydrazine hydrate. The new imides $[4]_{a-h}$ and Schiff bases $[5]_{a-h}$ were obtained by the reaction of compounds [3] with different anhydrides and aldehydes, respectively, scheme (1). New synthesized compounds were characterized by their melting points, FT-IR and ^{1}HNMR (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-Thiadiazoline, Thiosemicarbazone, Imides, Schiff Bases

INTRODUCTION

Heterocycles bearing nitrogen and sulphur atoms constitute an important part of biologically significant compounds[1]. The heterocyclic products having three heteroatoms in the five membered ring have been synthesized in the past decades because of their broad range of pharmacological behaviors [2].Thiadiazolines belongs to the above category of heterocyclic compounds having wide spectrum of biological[3-8] and technological applications [9].Among the few general routes to obtain 1,3,4-thiadiazolines, one of the most employed is that of heterocyclization of thiosemicarbazones prepared from aldehydes and ketones under acylation conditions (acetic anhydride and pyridine)[10]. The reaction between an aldehyde or a ketone with substituted thiohydrazides[11] led to formation thiadiazolines. Kaleta*et al*[12]found that 1,3-dipolar cycloaddition between chlorodiazabutadiene and thiourea yielded 4-amidine-1,3, 4-thiadiazolines. However, the preparation of this heterocyclic ring is mostly achieved by heterocyclization of thiosemicarbazones[13]. Thus the thiadiazoline nucleus has attracted much interest in the development of pharma-cologically active compounds. Since the thiadiazoline moiety seems to be a possible pharmacophore in various pharmacologically active agents, therefore, we decided to synthesize new compounds with this functionality as possible antimicrobial agents.

EXPERIMENTAL

Instruments

Uncorrected melting points were determined in open capillary on SMP30 Melting point (Stuart, Germany). TLC was performed on aluminium plates coated with silica gel $60F_{254}$ (20cm x 20cm). Layer thickness 0.2 mm. The IR

spectra were recorded on FTIR 8400 s Shimadzu spectrophotometer using KBr disk. ^{1}HNMR were recorded on Bruker 300 MHz spectrophotometer, University of Al-albayt, Jordan using DMSO as a solvent with TMS as an internal standard.

General Procedures

All new imides and Schiff bases compounds were synthesized according to scheme (1).

Preparation of 4-bromobenzaldehydethiosemicarbazone[1]$_a$ and 4-bromoacetophenone thiosemicarbazone [1]$_b$.[14] In 50 mL round bottom flask, the thiosemicarbazide (0.91 gm, 0.01mol)was added toa solution of the 4-bromoacetophenone (1 gm, 0.01mol) or 4-bromobenzaldehyde (1.85 gm,0.01 mol)in absolute ethanol (20mL). The reactants were heated by reflux for 5 hrs. The product was cooled to room temperature, the solid was filtered, dried and recrystallized from ethyl acetate.[1]$_a$; yield 88 % ; color, white; m.p. 217-220 ^{O}C.[1]$_b$; yield 73 % ; color, white; m.p. 189-191C^0

Synthesis of 4-acetyl-2-acetamido-5-(4`-bromophenyl)-1,3,4-thiadiazoline[2]$_a$ and 4-acetyl-2-acetamido-5-(4`-bromophenyl)-5-methyl-1,3,4-thiadiazoline[2]$_b$[15]: Thiosemicarbazone [1] (0.25 mmol) was dissolved in 1:1 pyridine: acetic anhydride (1mL) and the reactants were heated by reflux for 3 hrs. The product was cooled in ice – water bath and acidified with 10 % HCl. The formed precipitate was filtered, washed with water, dried and recrystallized from ethanol.**[2]$_a$**; yield: 76 %; color: brown; m.p. 243-246 ^{O}C.**[2]$_b$**; yield: 69 %; color: brown yellowish; m.p. 206-208 ^{O}C.

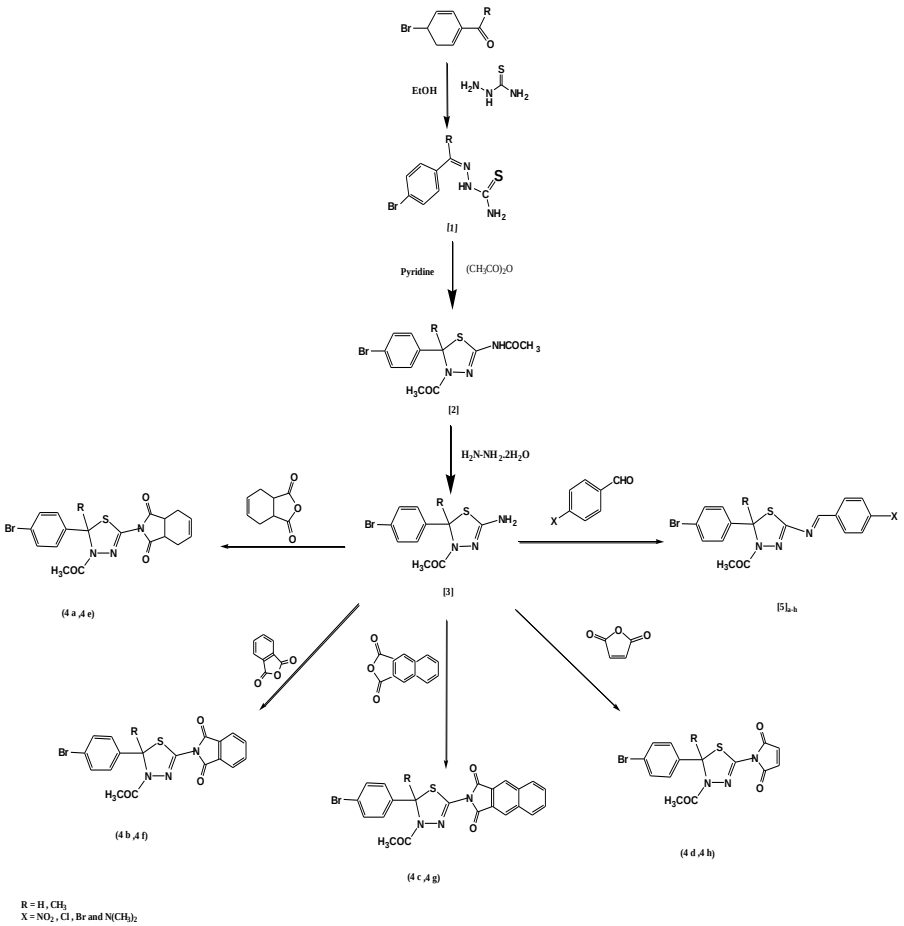


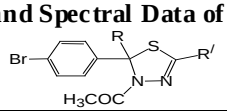
Figure 1: Synthetic Route of Imides [4]$_{a-h}$ and Schiff Bases[5]$_{a-h}$ Containing 1,3,4-Thiadiazoline Ring

Synthesis of 4-acetyl-2-amino-5-(4-bromophenyl)-5H -1,3,4-thiadiazoline $[3]_a$ and4-acetyl-2-amino-5-(4-bromophenyl)-5-methyl-1,3,4-thiadiazoline $[3]_b$: A mixture of 1,3,4-thiadiazoline [2] (0.01 mol) and hydrazine hydrate 80% (30 mL) was stirred at room temperature for 4 hrs. The resulted precipitate was collected by filtration and recrystallized from water. **$[3]_a$**; yield: 69 %; color: off-white; m.p.: 190 -193 ^oC. **$[3]_b$**; yield: 71 %; color: off-white; m.p.: 140-142 ^oC.

Synthesis ofimides $[4]_{a-h}$: Acyclic anhydride (0.01 mol) was added to solution of compound [3] (0.01 mol) in dry dioxane (15 mL). The reaction mixture was refluxed for 5 hrs, and the resulted solid was obtained by removal of the solvent. The residue was recrystallized from ethanol. The physical and spectral data of the synthesized imides are listed in table (1).

Synthesis of Schiff Bases $[5]_{a-h}$: A solution of compound [3] (0.01 mol) in dry benzene (10 mL)was added to solution of aromatic aldehyde (0.01 mol) in dry benzene (10 mL) acidified with glacial acetic acid (2-3 drops). Thereactants 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 titled compounds are listed in tables (3).

Table 1: Structure, Physical and Spectral Data of the Synthesized Imides $[4]_{a-h}$.



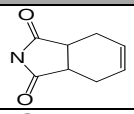
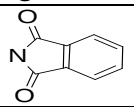
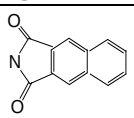
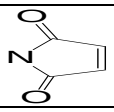
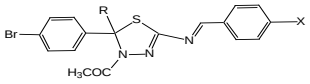
Comp. No.	R	R/	M.P.(C^0)	Color	Yield (%)	FT-IR Frequencies (cm^{-1})				
						υ C-H aliph.	υ C=O imide asy., sy.	υ C=O Amide	υ C=C arom.	υ C-N asy., sy.
$[4]_a$	H		166-168	White	48	2935-2847	1976,1870	1683	1585,1479	1170,750
$[4]_e$	CH_3		196-198	White	49	2934-2859	1735,1703	1684	1506-1469	1072,750
$[4]_b$	H		170-173	Pale brown	56	2929-2887	1776,1708	1676	1581,1475	1172,790
$[4]_f$	CH_3		320-323	Brown	66	2972-2899	1739,1700	1660	1599,1494	1165,788
$[4]_c$	H		155-157	Yellow	37	2944-2836	1720,1689	1669	1576,1477	1138,786
$[4]_g$	CH_3		160-162	Pale yellow	51	2976-2856	1772,1739	1689	1583,1481	1122,775
$[4]_d$	H		176-179	Pale yellow	60	2976-2856	1772,1739	1689	1583,1481	1134,783
$[4]_h$	CH_3		220-224	Brown Yellowish	74	2953-2926	1730,1697	1685	1595,1487	1118,750

Table 2: Structure, Physical and Spectral Data of the Synthesized Schiff Bases $[5]_{a-h}$.



Comp. no.	R	X	M.P.(C^0)	Color	Yield (%)	FT-IR Frequencies (cm^{-1})				
						υ C-H aliph.	υC=Oamide	υ C=N	υC=C arom.	Other
$[5]_a$	H	NO_2	289-291	Yellow	62	2943-2841	1597,1485	1627	1683	4-NO_2:1517,1379
$[5]_e$	CH_3		220-225	Pale-yellow	58	2974-2939	1597,1519	1597	1681	4-NO_2:1519,1383
$[5]_b$		Cl	251-253	Pale-yellow	41	2933-2898	1575,1480	1611	1687	4-Cl: 960
$[5]_f$	CH_3		242-245	dark-yellow	33	2928-2841	1581,1483	1593	1671	4-Cl : 931
$[5]_c$	H	Br	226-229	Yellow	43	2997-2943	1583,1481	1626	1685	
$[5]_g$	CH_3		223-225	Yellow	40	2980-2941	1585,1481	1624	1656	
$[5]_d$	H	NMe_2	232-235	Orange	78	2982-2802	1602,1521	1620	1683	4-NMe_2: 814
$[5]_h$	CH_3		168-170	Orange-Yellowish	73	2991-2820	1595,1487	1614	1681	4-NMe_2: 812

Table 3: Nomenclature of the Synthesized Imides $[4]_{a-h}$ and Schiff Bases $[5]_{a-h}$

Comp. No.	Nomenclature
$[4]_a$	4- acetyl -2-(1,2,5,6-tetrahydrophthalimido)-5-(4`-bromophenyl)-1,3,4-thiadiazoline
$[4]_b$	4-acetyl-2-phthalimido-5-(4`-bromophenyl)-1,3,4-thiadiazoline
$[4]_c$	4-acetyl-2-naphthalimido-5-(4`-bromophenyl)-1,3,4-thiadiazoline
$[4]_d$	4-acetyl-2-maleicimido-5-(4`-bromophenyl)-1,3,4-thiadiazoline
$[4]_e$	4-acetyl-2-(1,2,5,6-tetrahydrophthalimido)-5-methyl-5-(4`-bromophenyl)-1,3,4-thiadiazoline
$[4]_f$	4-acetyl-5-methyl -2-phthalimido-5-(4`-bromophenyl)-1,3,4-thiadiazoline
$[4]_g$	4-acetyl-5-methyl-2-naphthalimido-5-(4`-bromophenyl)-1,3,4-thiadiazoline
$[4]_h$	4-acetyl-5-methyl-2-maleicimido-5-(4`-bromophenyl)-1,3,4-thiadiazoline
$[5]_a$	4-acetyl-2-(4`-nitrobenzylideneamino)-5-(4``-bromophenyl)-1,3,4-thiadiazoline
$[5]_b$	4-acetyl-2-(4`-chlorobenzylideneamino)-5-(4``-bromophenyl)-1,3,4-thiadiazoline
$[5]_c$	4-acetyl-2-(4`-bromobenzylideneamino)-5-(4``-bromophenyl)-1,3,4-thiadiazoline
$[5]_d$	4-acetyl-2-(4`-N,N-dimethylbenzylideneamino)-5-(4``-bromophenyl)-1,3,4-thiadiazoline
$[5]_e$	4-acetyl-5-methyl-2-(4`-nitrobenzylideneamino)-5-(4``-bromophenyl)-1,3,4-thiadiazoline
$[5]_f$	4-acetyl-5-methyl-2-(4`-chlorobenzylideneamino)-5-(4``-bromophenyl)-1,3,4-thiadiazoline
$[5]_g$	4-acetyl-5-methyl-2-(4`-bromobenzylideneamino)-5-(4``-bromophenyl)-1,3,4-thiadiazoline
$[5]_h$	4-acetyl-5-methyl-2-(4`-N,N-dimethylbenzylideneamino)-5-(4``-bromophenyl)-1,3,4-thiadiazoline

RESULTS AND DISCUSSIONS

In the present work, we report the the synthesis of heterocyclic imides and schiff bases containing 1,3,4-thidiazoline ring $[4]_{a-h}$ and $[5]_{a-h}$ respectively. They derived from the reaction of 4-bromoacetophenone or 4-bromobenzaldehyde and thiosemicarbazide. The thiosemicarbazones$[1]_{a,b}$ were in a good yield in the first step and they were characterized by FT-IR spectroscopy. Three new stretching bands appeared in the (3165- 3441 cm^{-1}) due to NH_2 and NH group. A stretching vibration band of C=N group appeared at (1650 cm^{-1}). However, the spectra showed the disappearance of carbonyl stretching absorption of the starting materials. The resulted thiosemicarbazones $[1]_{a,b}$ were cyclized to 4-acetyl-2-acetylamino-5-(p-bromophenyl)-5-methyl(H)-1,3,4-thiadiazoline$[2]_{a,b}$ under acylationcondition (pyridine, acetic anhydride). The progress of the reactions were monitored by TLC technique until the disappearances of thiosemicarbazones. Physical and spectroscopic data of compounds $[2]_{a,b}$ confirmed the success of the cyclization reaction produced 1,3,4-thiadiazoline ring system. These spectra showed the disappearance of NH_2 bands and appearance of two new stretching absorption bands at (1631-1699 cm^{-1}) and (1616 cm^{-1}) belong to C=O amide group and C=N (indocyclic) group respectively. The cyclization mechanism may follow bath A or B orboth[16], scheme (2). The final step of the mechanism of formation of product [2] was the reaction between 2-amino group of the formed 1,3,4-thiadiazoline with excess anhydride.

Treatment of the product [2] with hydrazine hydrate at room temperature led to libration of amine group at position 2 of 1,3,4-thiadiazoline ring and formation of 4-acetyl-2-amino-5-(p-bromophenyl)-5-methyl(H) -1,3,4-thiadiazoline[3]. The structural assignments of this compound [3] is based on it is spectral analysis (FTIR and 1HNMR spectroscopy). FTIR spectra showed two absorption bands at (3325-3425 cm^{-1}) for asymmetrical and symmetrical (NH_2) group. The ^{1}H NMR spectrum of compound $[3]_b$ showed two singlet signals at δ (2.45 ppm and 1.88 ppm) due to six protons of two (CH_3) groups at $NCOCH_3$ and C-5. Two protons of NH_2 group apperared as a singlet at δ (6.51 ppm). The four aromatic protons of p-substituted benzene ring appeared as two doublets in the region δ (7.32 – 7.52 ppm).

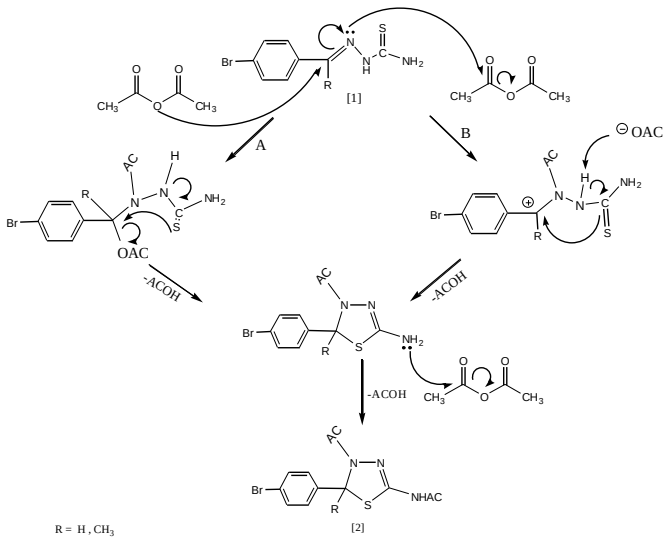


Figure 2

The imides $[4]_{a-h}$ were synthesized from the reaction of compound [3] with different cyclic anhydrides in 1:1 ratio, scheme (1). IR showed the disappearance of absorption bands of amino group and the appearance of new band at (1689-1776 cm^{-1}) which is attributed to the symmetrical and asymmetrical stretching of (C=O imide), table (1). The ^{1}HNMR spectrum of imide $[4]_a$ showed a quartet signal at δ (4.38 ppm) due to two symmetrical cycloolefinic protons, while the cyclic two methylene groups appeared as a symmetrical triplet equivalent to four protons at δ (3.24 ppm). The four aromatic protons signals appeared as a symmetrical two doublets at δ (7.6-8.12 ppm). The Schiff bases $[5]_{a-h}$ were resulted from the reaction of compound [3] with different aromatic aldehydes in a 1:1 mole ratio. The FTIR of the synthesized imines showed the characteristic absorption bands of imine group C=N at (1593-1627cm^{-1}), table (2), while the ^{1}HNMR spectrum of $[5]_e$ showed a singlet signal of CH=N group and two singlet signals at δ (2.56 ppm and 1.91 ppm) for six protons of two methyl groups at $NCOCH_3$ and C-5. A multiplet signal appeared at δ (7.32-8.41) were due to eight aromatic protons.

ANTIMICROBIAL ACTIVITY TEST

The antimicrobial potency of the synthesized imides $[4]_{a-h}$ and imines $[5]_{a-h}$ were evaluated. Four types of bacteria were used (+ve and –ve). Some of the tested compounds demonstrated an encouraging activity such as (4f, 5b, 5e), table (4).

Table 4: Inhibition Zones of Titled Compounds ([4]a-h and [5]a-h)

Compound Code (1000 ppm).	Inhibition Zone (mm.)			
	Staphylococcus Sciuri	*Streptococcus Aeidominimus*	*E. Coli*	*Pseudomonas Fluorensce*
	Gram Positive		Gram negative	
4a	_	13	_	8.6
4b		_	_	7.3
4c	15.1	_	_	12
4d	_	_	_	_
4e	_	11.7	_	9
4f	18.2	6	_	_
4g	8	_	_	_
4h	_	_	_	_
5a	_	12.3	_	_
5b	20.5	_	_	10
5c	15	_	_	9.4
5d	_	_	_	_

Table 4: Contd.,

5e	_	19.7	_	_
5f	_	12.2	_	_
5g	6.9	_	_	_
5h	_	_	_	_

CONCLUSIONS

In conclusion, series of new imides and Schiff bases containing 1,3,4-thiadiazoline ring$[4]_{a–h}$ and $[5]_{a-h}$, respectively, were synthesized in good yield and were characterized by different spectral studies and their antibacterial activity has been evaluated, some of these showed good antibacterial activity.

REFERENCES

1. Reddy C. S., Rao L. S., Devi M. V., Kumar, G. R. and NagarajA.,*Chinese Chemical Letters* **(2010)**.
2. Sancak K. and Unver, Y. Er M., *Turk. J. Chem*., *31*, 125**, (2007)**.
3. Chen Y. L., Chen I. L. Lu C. M., Treng, C. C., Tsao L. T. and Wang J. P., *Bioorg. Med. Chem.*, *11*, 3921-3927 **(2003)**.
4. Karegoudar P, Karthikeyan MS., Prasad DJ., Mahalinga M.,Holla BS., and Kumari NS.*Eur J Med Chem*., 43,261-267, **(2008).**
5. Rostom SA., El-Ashmawy IM., El RazikHA., Badr MH. And Ashour HMA., *Bioorg Med Chem*, 17,882-895, **(2009)**.
6. Vicini P., Geronikaki A., Incerti M., Zani F., Dearden J. and Hewitt M., *Bioorganic Med Chem*, 16, 3714-3724, (**2008**).
7. Chen Y. L., Lu C. M., Chen I. L., Tsao L. T. and Wang J. P.,*J. Med. Chem.*, *45*, 4689-4694,(**2002)**.
8. HuiXP., Chu CH., Wang Q. and Zhang Q.,*Indian J. Chem.*, (41B), 2176, (**2002**).
9. Franz J. E. and Dhingir O. P., in: *Comprehensive Heterocyclic Chemistry*, **(1984).**
10. Brousse B., Moglioni A., Alho M., Larena A., Moltrasio G. and Accorso N., *ARKIVOKE*, (x), 14-23,**(2002).**
11. Mohd Amir, Arun Kumar, Israr Ali, Khan SA, *Ind. J. Chem.*, 48B: 1288-1293, (**2009).**
12. Kaleta Z, Makowski BT, Soos T and DembinskiR, *Org. Lett*; 8, 1625-1628, (**2006**).
13. Martins Alho M. A.; D'Accorso N. B. *J. Heterocyclic Chem*., 34, 1415 (**1997**).
14. Nasser A., Idhayadhulla A., Kumar K. and Selvin J., *E-Journal of Chemistry*, 7(4), 1320-1325, (**2010**).
15. Ioana I., et al, *Clujul Medical*, 86, 28, (**2013**).
16. Rouge P., Brousse B., Moglioni A., Gozzi G., Larena A., Moltrasio G. and Accorso N., *ARKIVOKE*, (xii), 14-23, **(2005).**