Research Article

A Microwave-assisted Synthesis of Some New Benzothiazines Derivatives and their Antimicrobial Activity

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ABSTRACT

The two convenient method for the synthesis of Cyclohexanone on Claisen-Schmidt condensation and Aldol condensation with various aromatic aldehydes in presence of dilute Sodium hydroxide affords the corresponding 2,6- diarylidene cyclohexanones (1)- Further, these compounds (1) were subjected to cyclocondensation with thiourea, catalyzed by aqueous potassium hydroxide to form 4-aryl-8-arylidene-2-imino-5,6-dihydro-4H,7H-(3,l) benzothiazines (2). The structures of synthesized compounds were characterized by their spectral analyses and Antimicrobial properties.

Keywords: Comparative method, Benzothiazines, Antimicrobial activity.

INTRODUCTION

The rapid Microwave-assisted organic synthesis is a fast developing area in synthetic organic Chemistry.[1-3] Thiazines are an important class of heterocyclic compounds being studied by many researchers and reported to possess a wide spectrum of biological properties such as antibacterial[4], antifungal, antimycobacterial, anthelminthic, anti-HIV, herbicidal, pesticidal,[5] analgesic, anti-inflammatory[6], antiserotinin, and anticonvulsant[7], activities. Moreover, thiazine nucleus is a pharmacophore of cephalosporins that occupy a very important place in the field of antibiotic[8], and the antifungal activity of thiazine nucleus is due to the presence of thiourea linkage in its structure[9]. In view of these observations, a series of new 4-aryl-8-arylidene-2-imino-5,6-dihydro-4H,7H-(3,l) benzothiazines (Scheme-1) with an aim to obtained potential antibacterial and antifungal agents were synthesized.

The synthesis of Cyclohexanone on Claisen-Schmidt condensation and Aldol condensation with various aromatic aldehydes in presence of dilute Sodium hydroxide affords the corresponding 2,6-diarylidene cyclohexanones (1)- Further, these compounds (1) were subjected to cyclocondensation with thiourea, catalyzed by aqueous potassium hydroxide to form 4-aryl-8-arylidene-2-imino-5,6-dihydro-4H,7H-(3,l) benzothiazines (2). The structures of synthesized compounds were characterized by their spectral analyses and Antimicrobial activity.[10-12]

MATERIALS AND METHODS

All melting points were determined in open capillary tubes using a liquid paraffin bath and are uncorrected. The purity of compounds was checked by TLC. UV (λ max', nm) spectra were obtained on a Shimadzu visible spectrophotometer. IR (v max' cm-^{1}) spectra were run on a Shimadzu 8700 spectrophotometer in potassium bromide pellets. ^{1}H NMR spectra were taken on an Amx-400 spectrophotometer in $CDC1_3$ using tetramethylsilane as reference. Mass spectra were recorded on a Finigan Mat spectrophotometer by GC-MS.

General procedure for the preparation of 2,6-diarylidene cyclohexanones

A mixture of 10% sodium hydroxide (30 mL), ethyl alcohol (50 mL), cyclohexanone (0.01 mol) and aromatic aldehyde (0.02 mol) was stirred at 20-25°C for 2 h. Later, the reaction mixture was kept in an ice chest overnight. The product was filtered, washed with ice cold water followed by ice-cold ethanol, dried and recrystallized from dimethyl formamide. The physical data of these synthesized compounds (1a-d) compounds **l(a-h)** is given in Table-1. UV of **1a**: 393, IR of **1b**: 1658 v(C=O) 1593,1556,1504,1458 v(aromatic), 831 v(C=C); ^{1}H NMR of l**a**: δ1.5-2.0 (m, CH_2,2H), δ2.7-3.1 (m, $(CH_2)_2$,4H), δ7.2-7.6 (hj, ArH, 10H), δ 7.9 (s, 2 x methine, 2H).

Conventional Method

General procedure for the preparation of 4 aryl-8-arylidene-2-imino-5,6-(dihydro-4H,7H-(3,1) benzothiazines

A mixture of 2,6-diarylidene cyclohexanone (0.01 mol); thiourea (0.015 mol) and potassium hydroxide (0.01 mol) dissolved in 10 mL of water was refluxed in isopropyl alcohol for 14 h. Later, the solvent was removed under reduced pressure and the residue obtained was treated with ice-cold water, filtered, dried and recrystallized from ethanol. The physical data of these synthesized compounds.

Spectral Analyses of compounds **2(a-h)** is given in table 1. UV of **2a**: 286, IR of **2b:** 3436 v(imine), 3193 v(cyclic NH), 1604 v(C=N>, 1506, 1475 v(aromatic), 1028 v(C=N).

^{1}H NMR of **2a:** δ 1.5-2.2 (m, (CH^, 4H).δ2.3-2.9 (m, CH_2, 2H), δ 4.9 (s,—CH—S, 1H), δ 6.5 (s, imine, 1H), δ 7.0 (s, cyclic NH, 1H), δ 7.2-7.5(m, ArH, 10H), δ 7.8 (s, methine, 1H). ^{1}H NMR of **2b:** δ 1.6-2.0(m, $(CH_2)_2$,4H), **:** δ 2-4-2.8

(m, CH_2,2H), **:** δ 3.8 (s, 1 X OCH_3,3H), δ 3.9 (s, 1 x OCH_3,3H), **:** δ 4.9 (s, CH—5,1H), **:** δ 6.5 (s, imine,1H) **:** δ , 6.7 (s, cyclic NH, IH), δ 6.9- 7.3(m,ArH,8H),**:** δ 7.6£Cs,methine, 1H).

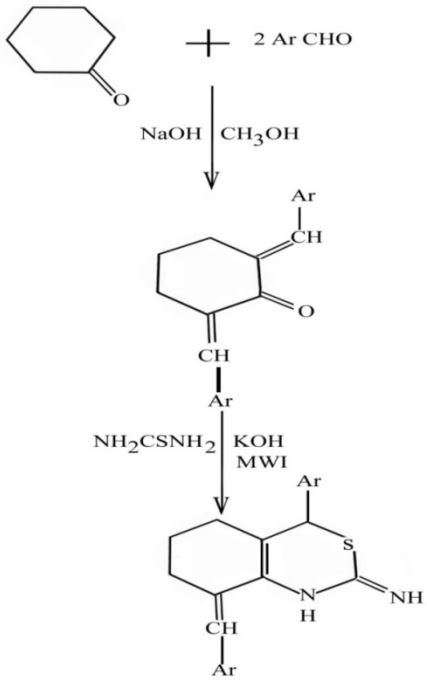
Microwave-irradiation Technique

General procedure for the preparation of 4 aryl-8-arylidene-2-imino-5, 6-(dihydro -4H,7H-(3,1) benzothiazines[24]

A mixture of 2,6-diarylidene cyclo- hexanone (0.01 mol); thiourea (0.015 mol) and potassium hydroxide (0.01 mol) dissolved in 10 mL of water and isopropyl alcohol , the contents were thoroughly mixed. The reaction mixture was subjected to microwave irradiation in a Laboratory or domestically available panasonic microwave oven having a maximum power 80-100 W and operated at 120 **±** 5°C for 10-12 min, after completion of the reaction, the solid product was separated out, the solvent was removed under reduced pressure and the residue obtained was treated with ice-cold water, filtered, dried and recrystallized from ethanol. The physical data of these synthesized compounds

Spectral Analyses of compounds **2(a-h)** is given in table 1. UV of **2a**: 286, IR of **2b:** 3436 v(imine), 3193 v(cyclic NH), 1604 v(C=N>, 1506,1475 v(aromatic), 1028 v(C=N).

^{1}H NMR of **2a:** δ 1.5-2.2 (m, (CH^, 4H).δ2.3-2.9 (m, CH_2, 2H), δ 4.9 (s,—CH—S, 1H), δ 6.5 (s, imine, 1H), δ 7.0 (s, cyclic NH, 1H), δ 7.2-7.5(m, ArH, 10H), δ 7.8 (s, methine, 1H). ^{1}H NMR of **2b:** δ 1.6-2.0(m, $(CH_2)_2$,4H), **:** δ 2-4-2.8 (m, CH_2,2H), **:** δ 3.8 (s, 1 X OCH_3,3H), δ 3.9 (s, 1 x OCH_3,3H), **:** δ 4.9 (s, CH—5,1H), **:** δ 6.5 (s, imine, 1H) **:** δ, 6.7 (s, cyclic NH, IH), δ 6.9- 7.3(m,ArH,8H),**:** δ 7.6£Cs, methine, 1H).



Scheme 1: Synthetic scheme of Benzothiazines derivatives (1a-h) & (2a-h)

RESULTS AND DISCUSSION

Antimicrobial activity

The newly synthesized 4-aryl-8-arylidene-2-imino-5,6-dihydro-4H,7H-(3,l) benzothiazines 2(a-d) were screened for *in vitro* antimicrobial activity using two Gram positive organisms, viz., *Staphylococcus aureus* and *Bacillus subtilis,* two Gram negative organisms, viz., *Escherchia coli* and *Pseudomonas aeruginosa* and two fungal organisms, viz., *Asperagillus niger* and *Candida albicans* by agar cup plate method at the concentration of 100 µg. The zone of inhibition was measured in mm and the values of antibacterial and antifungal activity of 2(a-h) were compared against standard references, ampicillin and amphotericin B, respectively (table 2).

The structures of new compounds prepared during the present investigation have been authentically established by their UV, IR, NMR and mass spectral studies. In the following section the spectral studies of some selected compounds were dealt.

Table 1: Characteristics Data of Synthesized Compounds of 2,6-diarylidene cyclohexanones (1a-h)

Compd	Ar.	M.F.	M.W	M.P. °C	Yields (%)
1a	Phenyl	$C_{20}H_{18}O$	274	116-118	74
1b	p-Methoxyphenyl	$C_{22}H_{22}2O_3$	334	158-160	84
1c	p-Fluorophenyl	$C_{20}H_{16}O_3$	310	148-149	79
1d	m-Tolyl	$C_{22}H_{22}O$	302	83-84	78
1e	Styryl	$C_{24}H_{22}O$	326	181-182	82
1f	1-Naphthyl	$C^{28}H_{22}O$	374	208-209	85
1g	p-Ethoxyphenyl	C_{24}H2603	362	145-146	81
1h	p-Isopropylphenyl	$C_{26}H_{30}O$	358	14G-141	85

Table 2: Characteristics Data of Synthesized Compounds of Benzothiazines using Conventional Technique (2a-h)

Compd.	Ar.	M.F.	M.W.	M.P. °C	Yields /Time % / hr.
2a	Phenyl	$C_{21}H_{20}N_2S$	332	192-194	75/14
2b	p-Methoxyphenyl	$C_{23}H_{24}N_2O_2S$	392	196-198	77/14
2c	p-Fluorophenyl	$C_{21}H_{18}N_2F_2S$	368	188-189	79/14
2d	m-Tolyl	$C_{23}H_{24}N_2S$	360	175-176	40/14
2e	Styryl	$C_{25}H_{24}N_2S$	384	192-193	75/14
2f	1-Naphthyl	$C_{29}H_{28}O_2S$	432	225-226	68/14
2g	p-Ethoxyphenyl	$C_{25}H_{28}N_2O_2S$	420	201-202	78/14
2h	p-Isopropylphenyl	$C_{27}.H_{32}N_2S$	416	192-193	88/14

Table 3: Characteristics Data of Synthesized Compounds of Benzothiazines using Microwave Technique (2a-h)

Compd.	Ar.	M.F.	M.W.	M.P. °C	Yields /Time % / hr.
2a	Phenyl	$C_{21}H_{20}N_2S$	332	192-194	87/12
2b	p-Methoxyphenyl	$C_{23}H_{24}N_2O_2S$	392	196-198	85/12
2c	p-Fluorophenyl	$C_{21}H_{18}N_2F_2S$	368	188-189	84/12
2d	m-Tolyl	$C_{23}H_{24}N_2S$	360	175-176	58/12
2e	Styryl	$C_{25}H_{24}N_2S$	384	192-193	84/12
2f	1-Naphthyl	$C_{29}H_{28}O_2S$	432	225-226	80/12
2g	p-Ethoxyphenyl	$C_{25}H_{28}N_2O_2S$	420	201-202	84/12
2h	p-Isopropylphenyl	$C_{27}.H_{32}N_2S$	416	192-193	92/12

Table 4: Anti-bacterial and Anti-fungal activity Benzothiazines (2a-h)

Compound	Anti-bacterial activity			Anti-fungal activity		
	S.aureus	*B. Subtilis*	*E.coli*	*P. aeruginosa*	*A. Niger*	*C. albicans*
2a	20	19	20	17	13	13
2b	24	22	20	21	14	14
2c	26	25	24	19	15	15
2d	17	15	13	12	11	11
2e	21	18	17	15	13	12
2f	21	19	20	18	14	11
2g	20	21	17	14	*12*	16
2h	17	18	13	10	*11*	11
Ampicillin	38	32	33	30	---	---
Amphotericin B	-	---	---	---	18	16

The compounds **I(a-h)** were prepared by reaction of cyclohexanone with aromatic aldehydes which is an example for Claisen-Schmidt condensation and Aldol condensation. The formation of Ia from cyclohexanone was indicated by its UV spectrum. The cyclohexanone exhibited **λ** max' at 262. The compound **Ia** exhibited **λ** max' at 393. This clearly indicates that the bathochromic shift was because of=CHAr chromophore. The formation of **1b** from cyclohexanone was indicated by its IR spectrum. The cyclohexanone exhibited v max' at 1715 (C=0). The compound **Ib** exhibited v max' at 1658 (C=O). The appearance of a band at 1658 is mainly due to the presence of two =CHAr chromophores[26]. This clearly indicates the formation of **Ib.** The formation of **Ia** was also confirmed by its ^{1}H NMR spectrum.

The presence of signals at 8 1.5-2.0 (m, CH_2,2H), §2.7-3.1 (m, $(CH_2)_2$,4H), 8 7.2- ?.6 (m, ArH, 10H) and 8 7.9 (s, 2 x methine,2H) clearly shows the formation of **Ia.** The compounds **2(a-h**) were prepared by cyclocoadensation of **I(a-h)** with thiourea. The formation of **2a** from **Ia** was indicated by its UV spectrum. The **λ** max' of **Ia** was 393. The **λ** max' of **2a** was 286. These indicate that the hypsochromic shift was attributed because of cyclocondensation. The formation of **2b** from **1b** was confirmed by its IR spectrum. The compound **Ib** exhibited v_{max} at 1658 (C**==**O). The compound **2b** exhibited v_{majl} at 3436 and 3193 (mine and cyclic NH). The absence of 1658 and presence of 3436 and 3193 in **2b** clearly indicates its formation. The formation of **2a** was confirmed by its ^{1}H NMR spectrum. The presence of signals at 8 1.5-2.2 (m, $(CH_2)_2$,4H), 8 2.3-2.9 (m, CH_2,2H), 8 4.9 (s, -CH—S, 1H), 8 6.5 (s, imine, 1H), 8 7.0 (s, cyclic NH, 1H), 8 7.2-7,5 (m, ArH, 10H), 8 7.8 (s, methine, 1H) clearly shows the formation of **2a**. The other compounds were also confirmed by their ^{1}H NMR spectra. The formation of **2a** was also elucidated by its mass spectrum.

The molecular ion peak of **2a** was observed at m/e 332, which was in good agreement with the calculated molecular weight of the compound. The compounds 2g and 2h were also confirmed by their mass spectra. The compounds 2(a-h) exhibited antibacterial activity against Gram + Gram -ve organisms. Among these compounds with *p*-methoxyphenyl **2b** substitutions showed the maximum activity against *S. aureus, B. subtilis, E. coli* and *Ps. aeruginosa,* respectively, while other compounds showed moderate and poor activity.

All thiazines 2(a-h) showed antifungal activity against *A. niger.* However, none of these compounds had greater activity than standard references, Ampicillin and Amphotericin B.

CONCLUSION

Microwave assisted synthesis of Thiazines was ecofriendly method for the synthesis of Thiazines. The Thiazines were obtained in high yield and high purity, comparative than traditional method. The Benzothiazines 2a-h were tested against Anti-bacterial and Anti-fungal activity and Spectral analyses for the confirmation of medicinal compounds.

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REFERENCES

1. Caddick S., Synthesis of Thiazines, Tetrahedron, 51, 1995, 10403.
2. Rathod A. K., Microwave-assisted syntheses, IJRRPAS, 2(1), 2012, 115-125.
3. Verma R.S.and Dahiya R., Biginelli syntheses, tetrahedron, Lett, 38, 1997, 2039.
4. Gupta R., Gupta A.K., Paul S., Antibacterial activity of microwave assisted derivatives, Indian journal j. chem., 34, 1995, B61.
5. Rathod A.K., Microbial activity of Imidazolyl pyrimidine, Int.J.PharmTech Res., 4(2), 2012, 852-859.
6. Kidwai, M., Goel. Y, Kumar R., Syntheses Thiazines derivatives, Indian J. chem, 37B, 1998, 174.
7. Kidwmigh M., Dave, R Venkatraman., Claisen condensation reaction by microwave irradiation, Indian chem., 41B, 2002, 2414.
8. Cyrille L., David. D., Alain R and Jean C.M., *Synthesis,* 2002, 403.
9. Rathod. A.K, Synthesis of benzothiazines under microwave method, IJPCS, 3, 2012, 1111-4.
10. Raghuvanshi P.B. and Doshi B.G., Antibacterial activity of thiazines pyrimidine, *Asian J. Chem.,* 5, 1994, 291.
11. Guiyu J., Chunyang C., Linato. L, Guofengj Z. characterization and synthesis of heterocyclic compounds, *Pesticide ScL,* 1, 1999, 15.
12. Bozsing D., Sonar P., Gigler G, Kovacs G., *Eu formulation of medicinal compounds, J. Med. Chem.,* 31, 1996, 663.

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