Research Article

Synthesis and Characterization of 4-aryl-8-arylidene Thiazines Derivatives using Microwave Irradiation

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ABSTRACT

The microwave irradiation 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 corresponding2,6-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 studies and Antimicrobial activity.

Keywords: Microwave-assisted Synthesis of Benzothiazines and Antimicrobial activity.

INTRODUCTION

The rappid 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 [4-9], and reported to possess a wide spectrum of biological properties such as antibacterial [10], antifungal [11],antimycobacterial [12] ,anthelminthic [13],anti-HIV[14], herbicidal, [15], pesticidal[16],analgesic, [17], anti-inflammatory [18], antiserotinin [19] ,and anticonvulsant [20], activities. Moreover, thiazine nucleus is a pharmacophore of cephalosporins that occupy a very important place in the field of antibiotics[21] ,and the antifungal activity of thiazine nucleus is due to the presence of thiourea linkage in its structure 22. 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 synthesize.

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. ^{l}H NMR spectra were taken on an Amx-400 spectrophotometer in $CDC1_3$ using tetramethylsilane as rofe-ence. 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 mixtwe 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).

Microwave- irradiation Method

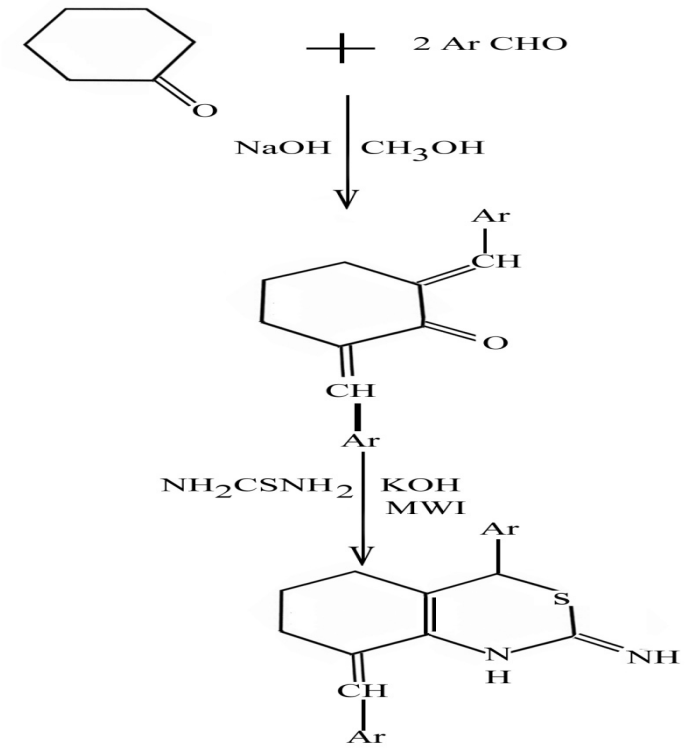
General procedure for the preparation of 4~aryl-8-arylidene-2-imino-5, 6-(dihydro -4H,7H-(3,1) benzothiazines[24]

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 treatedwith 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 Tqble-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, lH), δ 6.9-7.3(m,ArH,8H), **:** δ 7.6£Cs,methine, 1H).



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

Table 1: Characteristics Data of Synthesized Compounds of Thiazines (1a-h)

Compd.	Ar	M.F.	M..W.	M.P. °c	Yield (%)
la	Phenyl	$C_{20}H_{18}O$	274	116-118	74
1b	p-Methoxyphenyl	$C_{22}H_{22}2O_3$	334	158-160	84
1c	3,4-Dimethoxyhenyl	$C_{24}H_{26}O_5$	394	142-144	86
1d	3,4,5-Trimethoxyphenyl	$C_{26}H_{30}O_7$	454	210-212	95
1e	p-Chlorophenyl	$C_{20}Hi_6OCl_2$	342	150-152	86
1f	p-Tolyl	$C_{22}H_{22}O$	302	172-174	93
1g	2,3,4-Trimethoxyphenyl	$C_{26}H_{30}O_7$	454	180-182	94
1h	2-Furfurly	$C_{16}H_{14}O_3$	254	146-148	77

Table 1: Characteristics Data of Synthesized Compounds of Thiazines using Microwave Technique. (2a-h)

Compd.	Ar	M.F.	M..W.	M.P. °c	Yield /Time
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	3,4-Dimethoxyhenyl	$C_2SH_{2g}N_2O4S$	452	223-225	78/12
2d	3,4,5-TYimeflioxyphenyl	$C_{27}H_{32}N_2O6S$	512	213-215	86/12
2e	p-Chlorophenyl	$C_{2,}H_{18}N_2SC1_2$	400	235-236	94/12
2f	p-Tolyl	C:yH24N_2S	360	218-220	96/12
2 g	2,3,4-Trimethoxyphenyl	$C_{27}H_{32}N_2O_6S$	512	187-189	97/12
2h	2-Furfurly	$C_{;7}H_{16}N_2O_2S$	312	179-181	88/12

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).

Table 2: Antibacteial and Antifungal Activiy of Thiazines (2a-h)

Compound	Antibacterial activity				Antifungal 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	21	21	20	15	13	13
2d	17	17	14	12	10	11
2e	23	24	20	20	16	14
2f	23	23	16	17	14	13
2g	18	17	11	13	9	11
2h	23	21	17	15	14	13
Ampicillin	38	32	33	30	-	-
Amphotericin B	-	-	-	-	18	16

RESULTS AND DISCUSSION

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.

The compounds **l(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 la from cyclohexanone was indicated by its UV spectrum. The cyclohexanone exhibited λ max' at 262. The compound **la** 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 **la** 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 **la.**

The compounds **2(a-h**) were prepared by cyclocoadensation of **l(a-h)** with thiourea. The formation of **2a** from **la** 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 Amphotsricin B.

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