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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF BENZOTHIAZINES COMPOUNDS USING MICROWAVE TECHNIQUES

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ABSTRACT

A convenient 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, dihydro- catalyzed by aqueous potassium hydroxide to form 4-aryl-8-arylidene-2- imino-5,6-4H,7H-(3,l) benzothiazines(2). The structures of synthesized compounds were characterized by their spectral studies and the antimicrobial activity of Synthesized compounds

KEYWORDS: Green Chemistry approaches Synthesis,,Benzothiazines, Antimicrobial activity

INTRODUCTION

The utilization of green chemistry technique dramatically reducing chemical waste and reaction timeas has recently been proven in organic syntheses and chemical transformation.The Microwave-assisted organic synthesis is a fast developing area in synthetic organic Chemistry[1-3] Benzothiazines 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. ^{1}H NMR spectra weretaken 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-d)** is given in Table-1. UV of **1a**: 393, IR of **1d**: 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). Mass of **Ic:** 360 (M*), 227,133,94.

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 cyclo - hexanone (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 compounds

Spectral Analyses,: of compounds **2(a-d)** is given in Tqble-1. UV of **2a**: 286, IR of **2d:** 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 **2d:** 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)

Microwave- irradiation 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 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

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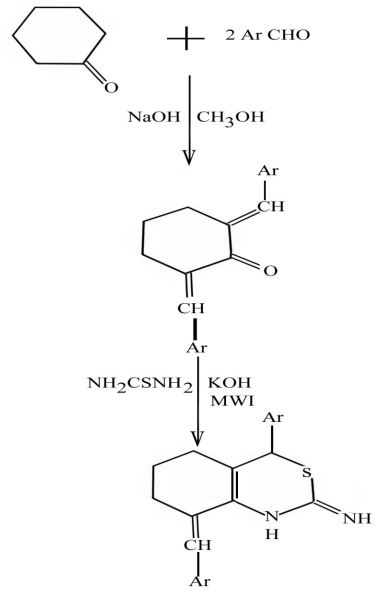

Scheme,1: Synthetic scheme of Benzothiazines derivatives

Compd.	Ar	M.F.	M.W.	M.P. °C	Yield (%)
la	Phenyl	$C_{20}H_{18}O$	274	116-118	74
1b	m-Nitrophenyl	$C_{20}H_{16}N_2O_5$	364	206-208	69
1c	p-Dimethylaminophenyl	$C_{24}H_{28}N_2O$	360	82-84	56
1d	p-Methoxyphenyl	$C_{22}H_{22}2O_3$	334	158-160	81

TABLE 1: CHARACTERISTICS DATA OF SYNTHESIZED COMPOUNDS OF BENZOTHIAZINES (1a-d)

Compd.	Ar	M.F.	M.W.	M.P. °c	Yield /Time (%) /Hr
2a	Phenyl	$C_{21}H_{20}N_2S$	332	192-194	74/14
2b	m-Nitrophenyl	$C_{21}H_{20}N_2S$	422	190-191	78/14
2c	p-Dimethylaminophenyl	$C_{2j}H_{3o}N_4S$	418	110-112	40/14
2d	p-Methoxyphenyl	$C_{23}H_{24}N_2O_2S$	392	196-198	72/14

TABLE 2: CHARACTERISTICS DATA OF SYNTHESIZED COMPOUNDS OF BENZOTHIAZINES UNDER CONVENTIONAL TECHNIQUES (2a-d)

Compd.	Ar	M.F.	M.W.	M.P. °c	Yield /Time (%) /min
2a	Phenyl	$C_{21}H_{20}N_2S$	332	192-194	87/12
2b	m-Nitrophenyl	$C_{21}H_{20}N_2S$	422	190-191	91/12
2c	p-Dimethylaminophenyl	$C_{2j}H_{3o}N_4S$	418	110-112	61/12
2d	p-Methoxyphenyl	$C_{23}H_{24}N_2O_2S$	392	196-198	85/12

TABLE 3: CHARACTERISTICS DATA OF SYNTHESIZED COMPOUNDS OF BENZOTHIAZINES USING MICROWAVE TECHNIQUES (2a-d)

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-d) were compared against standard references, ampicillin and amphotericin B, respectively (Table-4).

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	16	16	15	14	11	NA
2c	17	18	17	16	10	NA
2d	24	22	20	21	14	14
Ampicillin	38	32	33	30	--	--
Amphotericin B	--	--	--	--	18	16

TABLE-4 : ANTIBACTEIAL AND ANTIFUNGAL ACTIVIY OF (2a-d)

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-d) 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 1d from cyclohexanone was indicated by its IR spectrum. The cyclohexanone exhibited v max' at 1715 (C=0). The compound Id 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 Id. 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-d) were prepared by cyclocoadensation of l(a-d) with thiourea. The formation of 2a from la was indicated by its UV spectrum. The λ max' of la was 393. The λ max' of 2a was 286. These indicate that the hypsochromic shift was attributed because of cyclocondensation. The formation of 2d from 1d was confirmed by its IR spectrum. The compound Id exhibited v_{max} at 1658 (C==O). The compound 2d exhibited v_{majl} at 3436 and 3193 (mine and cyclic NH). The absence of 1658 and presence of 3436 and 3193 in 2d 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-d) exhibited antibacterial activity against Gram + Gram -ve organisms. Among these compounds with *p*-methoxyphenyl 2d 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-d) showed antifungal activity against *A. niger.* Among these *c*ompound with p-dimethylaminophenyl substitution **2c** showed the least activity. The compounds except 2b and 2c, also showed activity against *C. albicans.,* while others compounds showed moderate and poor activity. However, none of these compounds had greater activity than standard references, Ampicillin and Amphotsricin B.

CONCLUSION

A convenient method for the synthesis of 4~aryl-8-arylidene-2-imino-5, 6-(dihydro -4H,7H-(3,1) benzothiazines were prepared under mild and environmentally benign reactions conditions using green chemistry methodology has been reported. The reactions can be carried out in the flask within the least possible time in contract with the literatures multistep methods. Considering the easy availability of the starting materials, the speed of the reactions and simplicity of the work up the present method appears to be useful.

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REFERENCES

1. Caddick S..,Tetrahedron. 1995,51,10403,
2. Rathod A.K. et al,IJRRPAS, 2012,2 (1),115-125,
3. Verma R.S. and R. Dahiya,Tetrahedron,Lett, 1997,38,2039,
4. Gupta R. Gupta A.K. Paul S., P.L, Indian them 1995, 34,B61,
5. Rathod A.K./ Int.J.PharmTech Res.2012,4 (2),852-859
6. Kidwai M.,Goel Y. Kumar R., Indian J. them 1998, ,37B, 174
7. Gillavd, A.Fabis F., Jolivwd Fouchet S. Rault S Telrahedron Letl 1997, 2271,38 (C13),
8. A.A.Ben –Alloum Bakkas's soofiaoui M; Telrabedoom let 1997, ,88 , (36) ,6395
9. Kidwmigh M.,Dave R Venkatraman Indian chem. 2002, 41B,2414,
10. AnneM., Dominique M., Andre G.,and Jean-PaulP., *Tetrahedron Asymm.,* 1995,*6,*853.
11. Cyrille,L., David,D. Alain R.,and Jean C.M., *Synthesis,* 2002,403
12. Bernath,O, Szakonyi,Z., Fulop F.,and Sohar.P.,Ac M*Pham* Hung.,* 1994,64,153
13. Peter W.,and Hgregory,B.H., *Tetrahedron,* 1998,54,698
14. Raghuvanshi P.B.and Doshi,B.G., *Asian J. Chem.,* 1994,5,291
15. Laldhar Y.S., Sangeetha S.,and Anjum,V., *J. Agri. FmdChem.,* 1992,40,1214
16. Koketsu. M., Kohsuke. T.T., Yuichi, T., Cecil D.K., Hideharu, *Eur. J. Pharm. Sci., IS,* 2002. 307
17. Bhople, K.K.,Tripathi N.,and Sai G.S.T., *Indian /. Chem.,* 1981,20B, 471
18. Shehata, L.A.,ElSubbagh,H.I.,Abdelal, A,M., Eherbeny and Aaobaid,A.A., *Mtd. Chem. Res.,* 1996,148.
19. Harris,M.,Price,R.N., Robinson,R., MayI.E., and Wadayama N.,*Chem.Abstr*.1987,106,133753b
20. Guiyu, J.,C., Chunyang,L., Linato, Jun R.,and Guofengj,Z., *Pesticide ScL,* 1999,1,15
21. Sladowska,H.,Malikand A.B,Zawisza,T.,*Farma o Ed. Sci.,* 1986,41,964.
22. Bozsing,D., Sonar, P.GiglerG.,and Kovacs, G.,*Eu* J. Med. Chem.,* 1996,31,663