International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

MICROWAVE MEDIATED GREEN SYNTHESIS OF SOME PYRAZOLINES AND ISOXAZOLINES

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ABSTRACT

Pyrazolines and Isoxazolines have been reported to possess various activities such as analgesic, antiplatelet, antimalerial, anticancer and antiviral. Four new substituted bis benzylidiene derivative (IIIa-IIId) have been synthesized with 80-85% yield by microwave promoted condensation of ketone and aromatic aldehyde in presence of Sodium carbonate as solid phase media .A Considerable increase in the reaction rate has been observed with better yields .The newly synthesized derivatives were treated with hydrazine hydrate and hydroxylamine hydrochloride to synthesize pyrazolines(IVa-d) and isoxazolines(Va-d)with neat reaction technology .The newly synthesized derivatives were characterized by UV, IR, PMR and elemental analysis and also screened for antimicrobial activity .

Keywords:- 2,6-bis- (benzylidiene)cyclohexan-1-one , microwave effect, antimicrobial activity, Sodium carbonate.

INTRODUCTION

Pyrazolines and Isoxazolines possess a broad spectrum of biological activities Viz. antibacterial[1] antifungal[2], antitubercular[3], antitumor[4], anti depressant[5], anticonvulsant[6], insecticidal[7], antidiabetic[8], antiacetylcholinesterase[9], Molluscieidal[10] and antinociceptive,[11] pyrazolines and Isoxazolines are used extensively as useful synthons in organic synthesis [12-15]. Recently reported studies on the microwave irradiation for the synthesis of heterocyclic compounds revealed that it is safe rapid, economic and convenient, ecofriendly method for chemical synthesis. Pollution free synthesis, lesser reaction time, easy work up and minimum use of solvent are the major advantages of this technique [16-18]. It can be termed as e-chemistry because it is easy, effective, economical and eco-friendly and is believed to be a step towards green chemistry. In general the reactions are cleaner, fast and high yielding. The applications of Microwave irradiation as a non conventional energy sources for the activation of reaction has now become popular and useful technology in organic chemistry [19].

Experimental

Melting points were determined in open capillary tubes and are uncorrected. The purities of the compounds were checked by thin layer chromatography. IR spectra were recorded on SHIMADZU FT-IR spectrophotometer. NMR spectra were recorded on Bruker PR X 500 MHZ. NMR spectrophotometer using TMS as an internal standard and elemental analysis were carried out on a carlo Erba 1108 analyzer. Microwave irradiation was carried out in RG3111, 2450 MHZ Microwave synthesis system with power output of 700 watt.

General procedure for the preparation of 2,6-bis (benzylidiene) - cyclohexa1 one (IIIa - d)

A mixture of 0.01 mole of Cycloketone and 0.02 mole of substituted aromatic aldehyde were absorbed over 4gm of sodium carbonate ,. Stirred well and then irradiated under microwave for 30 sec.. Resulting product thus obtained was washed well with water and crystallized with ethanol. Similarly 2,6-bis (benzylidiene) – Cyclohexa- 1 -One (IIIa - d) were prepared. The Infra red spectra of chalcones

(IIIa-d) showed a carbonyl absorption in the region 1655 cm^{-1}which is the characteristic of the α-β unsaturated carbonyl group as well as an olefinic c=c bond in the region 1604-1611 cm^{-1}.the^{1}H NMR spectra showed the olefinic protons H-β and H-α as two doublets in the region at δ 6.57-6.72and 7.25-7.62 resp**.**

Preparation of 3- (Substituted benzylidiene)-4,5,6- trihydro-7- (Phenyl) benzopyrazolines (IVa-d) –A neat mixture of 2,6- bis- (benzylidiene)-Cyclohexa-1 One (IIIa - d) (0.01mole) and hydrazine hydrate(0.015mole) was irradiated under microwave for 2-3 minutes. The product obtained was recrystallized from ethanol to get 80-95% yeild.

Preparation of 3 -(Substituted benzylidiene)-4,5,6- trihydro-7- (Phenyl) benzoisoxazolines(Va-d) – These were prepared from 2,6- (bis)-(benzylidiene)- cyclohexa-1One (IIIa- d) with hydroxyl Amine hydrochloride. Reaction mixture was irradiated under microwave for 3 minutes. After cooling the product was decomposed in cold water. The resulting product was. Recrystallized from ethanol.

1) 3- (benzylidiene) – 4,5,6- trihydro – 7- (Pheny) benzopyrazolines (IV A) IR (KBr Cm^{-1},) 3078 (C-H stret), 2941 (Vas CH2)1625 (>C=N Strech), 1583 (C=C stret), 1080 (C-H aromatic), ^{1}H-NMR($CDCL_3$) δ-7.8 (m ,10H,Ar-H),3.4 (br,1H,N-H) ,3.6(S,1H, C-H) 1.1-3.0(m, 8H aliphaticCH_2-CH_2.CH-CH.) Analytical **$C_{20}H_{19}N_2$** % cal.C-82, H -6.3, N-8.1 Found % C-81, H -5.8, N-8

2) 3- (4'- Bromo benzylidine) – 4,5,6- trihydro – 7-(4"- bromo phenyl) benzopyrazolines (IV B) IR(KBr Cm^{-1},) – 3047 (C-H Stre), 2941 (Vas – CH2),1625 (>C=N strech), 1562 C (C=C stre),1066 (Aryl- bromide stre), ^{1}H-NMR($CDCL_3$) δ-7.8 (m ,10H,Ar-H),3.4 (br,1H,N-H) ,3.6(S,1H, C-H) 1.1-3.0(m, 8H aliphaticCH_2-CH_2.CH-CH)Analytical – **C_{20} H_{17} N_2 Br_2**

3) 3- (2-4 dichlorobenzylidiene) – 4,5,6- trihydro – 7- (2-4" dichlorophenyl) benzopyrazolines (IV C) IR (KBr Cm^{-1},) – 3088 (C-H stre), 2935 (Vas – CH_2),1601(> C=N stre), 1428 (C = C stretch), 1685 to 1576 (= N-N stre), 771.5 (C-CL stre) ^{1}H-NMR($CDCL_3$) δ-7.8 (m ,10H,Ar-H),3.4 (br,1H,N-H) ,3.6(S,1H, C-H) 1.1-3.0(m, 8H aliphaticCH_2-CH_2.CH-CH.) Analytical - **C_{20} H_{15} N_2 CL_4**

4) 3- (4'- Chlorobenzylidiene) – 4,5,6- trihydro – 7- C (4" Chlorophenye) benzopyrazolines (IVd) IR (KBr Cm^{-1},) - 2985 (C-H strech), 2938 (Vas – CH2),1602 (> C = N stre), 1683 (C = N-Nstre) ,770 (C-Cl stre) ^{1}H-NMR($CDCL_3$) δ-7.8 (m ,10H,Ar-H),3.4 (br,1H,N-H) ,3.6(S,1H, C-H) 1.1-3.0(m, 8H aliphaticCH_2-CH_2.CH-CH)Analytical **C_{20} H_{17} N_2 Cl_2**

5) 3-(benzylidiene)-4,5,6-trihydro-7-(phenyl) benzoisoxazolines(Iva) IR (KBr Cm^{-1},) 3311 (C-H STRECH),2931 (v_{as}-CH_2),1598(C=C,C=N)ring,1012(Inplane bending C-H aromatic) 681(oop bending aromatic) ^{1}H- NMR δ 7.2-7.4(m,10H,Ar-H), 6.9(S,1H,=CH),4.6(t,2H,CH_2) 3.7(sextet,1-H,C-H$^{2a)}$,3.1(d,1-H,C7-H)1.22-1.26(M,4H,2CH2C_5C_6)

analytical- **$C_{20}H_{19}NO$**. %cal C-83,H= 6.5, N=4.8Found, %C-82,H= 6.2, N=4.6.

6)3-(4^I-Hydroxybenzylidiene)-4,5,6-trihydro-7-(4^{II}hydroxyphenyl)benzoisoxazolines(Ivb)- IR (KBr Cm^{-1},) --- 3082 (C-H stre),2868 (v_{as}-CH_2),1448 (C=N stre),1174 (Inplane bending C-H aromatic), 680(cop bending aromatic) ^{1}H- NMR δ 7.2-7.4(m,10H,Ar-H), 6.9(S,1H,=CH),4.6(t,2H,CH_2) 3.7(sextet,1-H,C-H$^{2a)}$,3.1(d,1-H,C7-H)1.22-1.26(M,4H,2CH2C_5C_6)analytical- **$C_{20}H_{19}NO_3$.**

7) **3-(4^I-Bromo benzylidiene)-4,5,6-trihydro-7-(4^{II} -bromophenyl) benzoisoxazolines(Ivc)**- IR (KBr $Cm^{-1)}$3057(C-H stre),2937(v_{as}-CH_2),1417(C=N) ,1496 (CH bending) , 700(oop bending aromatic Br stret)), ^{1}H- NMR δ 7.2-7.4(m,10H,Ar-H), 6.9(S,1H,=CH),4.6(t,2H,CH_2) 3.7(sextet,1-H,C-H$^{2a)}$,3.1(d,1-H,C7-H)1.22-1.26(M,4H,2CH2C_5C_6) 3.1(dd,2H,CH_2 analytical- **$C_{20}H_{17}NOBr_2$** .

8) **3-(4^I-nitro benzylidiene) -4,5,6- trihydro -7-(4^{II}-nitrophenyl) benzoisoxazolines (Ivd) -)**- IR (KBr $Cm^{-1)}$2987 (C-H stre), 2937(v_{as}-CH_2), 1602(>C=N),1685 (>C=O) , 700(oop bending),. ^{1}H-NMR δ 7.2-7.4,(m,10H,Ar-H), 6.9(S,1H,=CH), ,4.6(t,2H,CH_2) 3.7(sextet,1-H,C-H$^{2a)}$,3.1(d,1-H,C7-H),1.22-1.26(M,4H,2CH2C_5C_6) Analytical **$C_{20}H_{17}N_3O_5$**

Antimicrobial activity: The cultures of plant pathogens namely Viz: *E.coli, K. pneumoniae, S.aureus, B. subtilis* were treated with the taste compound. The punch discs of 6.25 m.m. diameter of Whatman filter paper No. 1 were prepared and dispensed in the batches of 100 each in screw capped bottles. These were sterilized by dry heat at 140^0c for 60 minutes. The solutions of 0.01 mol dilution of test compounds were prepared in dioxane solvent separately. The discs were soaked, assuming that each disc will contain approximately 0.01 ml of test solution.

RESULTS AND DISCUSSION

2,6-bis (benzylidiene) - cyclohexa1 one (IIIa - d)have been prepared by the cyclohexanone and substituted aldehydes in presence of sodium carbonate as solid substrate**.** PMR signal reveals a very highly symmetrical molecule. Quintet at (δ 1.18 , 2-H, 4-CH2) for C^4 Confirms CH2-CH2-CH2 fragment in

the molecule. Triplet at(δ 2.93 , 4H, 2CH2) for C^3 to C^5 CH_2 groups equivalent to four hydrogen just double to quintet but in quite deshielded region due to inductive effete of >C=0 at C^1 and =CHPh groups at C^2 and C^6 carbon atoms. Singlet at (δ7.8 2H,, = CH) Confirms two symmetrical benzylidiene protons, Desheilded due to >C=0 and aromatic ring. Similarly multiplets in aromatic region (δ 7.26 – 7.47) equivalent to 10 Protons Confirms the presence of two phenyl groups. IR frequency at 1600 Cm^{-1} Corrosponds to Conjugated carbonyl group which decreases the carbonyl frequency and carbonyl overtone at 3320cm^{-1}, 3022Cm^1, 2862Cm^{-1} for C-H stretching aromatic. 2933Cm^1, 2862 Cm^{-1} for v(asymmetric) CH_2 and V_5 – CH_2 C-H stretch. Band of Monosubstituted benzyl and other frequencies at 1606 Cm^1, 1575 Cm^{-1}, 1560Cm^1 1435 Cm^{-1}, 771 Cm^{-1}, 684 Cm^{-1} Corresponding to Aromatic and bending Vibrations.bis(benzilidiene) cyclohexa1 one(IIIa-d)treated with hydrazine hydrate under microwave for 1 minute without solvent to afford(Iva-d)following analytes support the neat reaction technology . PMR Signal of Comp. (Iva) reveals that there is multiplet at δ 7.0 – 8.0 it is due to ten aromatic hydrogen atom.

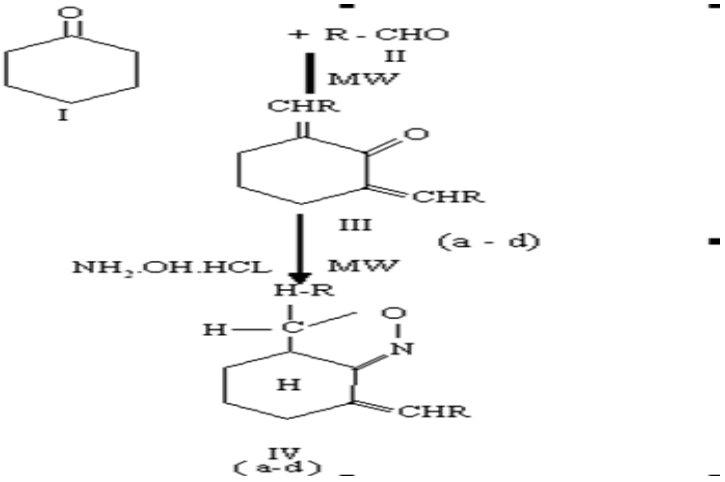
Whereas there is δ 3.0 which is due to N-H bending. Compound also shows singlet at δ - 3.6 due to C – H and δ 1.1 to 3 which is multiplet envelope due 8 aliphatic hydrogen atom. IR frequency at 3078 cm^{-1} which is due to C – H strech where as 1625 cm^{-1} shows the >C = N, 1080 cm^{-1}, are due to the aromatic and bending Vibration. similarly compound (IIIa - d) reacts with hydroxylamine hydrochloride under microwave t afford compound(Va-d). In PMR spectra of compound Va, there are various signals in aliphatic range from 1.22 to 4.6 & show that the compound is highly asymmetric, due to different environment of -CH2 aliphatic protons at C4,C5, C6 positions. A multiple at 1.22- 1.26 & , 4H, 2CH2, C2 and C6 in a packet at upfield and characteristic doublet at 3.1 &, 1H, C-H (isoxazoline). A multiplet (sextet) at 3.7 &, IH, C-4 Slightly downfield due to paramagnetic resonance. 4.6 & a triplet, 2H, CH2 also deshielded, 6.9 & (s, 1H, =CH benzylidine protons), 7.2 to 7.4 & (m, 10 H aromatic protons). Its synthon I shown only two signals for -CH2-CH2-CH2- protons a highly symmetrical compound . In IR absorption spectra absence of > C=O. st. frequency also confirms the attack of the reagent result in heterocyclisation to get target molecule. Other absorptions at 3310, 3082, 3052 for -C-H aro st., 2931,2868 Vas- CH2, Vs- CH2, C-H st., 1598, 1448, C=C and C=N ring structure, 1498 C-H bending (CH2). 1012, 1157, 681, 700 inplane and out of plane bending frequencies confirm the structure of newly synthesized compound as 3-benzylidiene- 4,5,6-trihydro-7- (phenyl) benzoisoxazoline (va). An assay of newly synthesized heterocycles revels that, almost all the compounds were active against all the test pathogens. The compounds IVc and Vd were most dominant amongst all the test compounds

CONCLUSION

we demonstrated new and neat reaction technology for the synthesis of **3- (**Substituted benzylidiene)-4,5,6- trihydro-7- (Phenyl) benzopyrazolines (IVa- d) ,3 -(Substituted benzylidiene)- 4,5,6- trihydro-7-(Phenyl) benzoisoxazolines(Va-d)

ACKNOWLEDGEMENT

The authors are thankful to the Principal, Vidyabharati Mahavidyalaya, Amravati, Dr. F.C.Raghuwanshi and Director, Garware research lab, pune for providing spectral data of the compounds.



Scheme .1

Table1 – Physical and Analytical characterization data of newly synthesized compounds

Com-pounds	Molecular Formula	Mol. Wt.	Yield(%)	M.P.(^{o}C)	MW irradiation time(minutes)
IV A	$C_{20}H_{19}N_2$	299	90	124	3
IV B	$C_{20}H_{17}N_2Br_2$	457	86	63	1.30
IV C	$C_{20}H_{15}N_2Cl_4$	445	98	82	1
IV D	$C_{20}H_{17}N_2C_{l2}$	368	93	113	4
VA	$C_{20}H_{19}NO$	289	88	182	3
VB	$C_{20}H_{19}NO_3$	321	80	120	2.40
VC	$C_{20}H_{17}NOBr_2$	445	90	110	3
VD	$C_{20}H_{17}N_3O_5$	379	85	119	2.45

Table2 : Anti microbial data of synthesized compounds

S. No.	Test Compounds	Zone of inhibition (mm)			
		E.coli,	*K.pneumoniae*	*S.aures*	*B.subtilis*
IVA	**3- (benzilidiene) – 4,5,6 – trihydro – 7- (Phenyl) benzopyrazolines**	12	15	13	17
IVB	**3- (4'- Bromo benzilidine) – 4,5,6-trihydro – 7- (4"- bromo phenyl) benzopyrazolines**	16	18	21	19
IVC	**3- (2-4 dichlorobenzilidiene) – 4,5,6- trihydro – 7- (2-4" dichlorophenyl) benzopyrazolines**	29	28	24	25
IVD	**3- (4'- Chlorobenzilidiene) – 4,5,6-trihydro – 7- C (4" Chlorophenyl) benzopyrazolines**	17	20	23	25
VA	**3-(benzylidiene)-4,5,6-trihydro-7-(phenyl)benzoisoxazolines**	13	17	15	14
VB	**3-(4^{I}-Hydroxy benzylidiene)-4,5,6-trihydro-7-(4^{II}hydroxyl phenyl)benzoisoxazolines**	17	16	16	15
VC	**3-(4^{I}-Bromo benzylidiene)-4,5,6-trihydro-7-(4^{II} -bromophenyl)benzoisoxazolines**	16	17	22	22
VD	**3-(4^{I}-nitro benzylidiene)-4,5,6-trihydro-7-(4^{II-} nitrophenyl)benzoisoxazolines**	29	27	28	28

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