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MICROWAVE INDUCED SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF SOME N^1- MORPHOLINO ETHANOYL-3, 5-DIARYL-2-PYRAZOLINE DERIVATIVES

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ABSTRACT

Some new N^1-substituted diaryl pyrazoline derivatives have been prepared by condensation of 3, 5-diaryl-2-pyrazolines (2) with chloroacetyl chloride followed by the reaction with morpholine under .non conventional MWI reaction condition. The synthesized compounds have been screened for their anti- bacterial activity in vitro. Some of the compounds were found to possess good activity.

Keywords: 3, 5-diaryl-2-pyrazolines, morpholine, microwave.

INTRODUCTION

Pyrazoline function is quite stable and has inspired the chemists to utilize this stable fragment on bioactive moieties to synthesize new compounds containing biological activities. A large number of variously substituted 2-pyrazolines and their N-substituted derivatives have been synthesized and evaluated for their biological activities [1,2] . Significant biological activities such as anti inflammatory, anti fertility, anti tubercular, and anti tumor activities are associated with pyrazoline nucleus[3-10.] . In the recent years a new approach for the synthesis of N-keto substituted pyrazolines were developed due to considerable medicinal value of such compounds. Recently some 1-N –substituted thiocarbamoyl -3, 5-diaryl-2-pyrazoline derivatives have been reported to be better anti amoebic agents against HMI:IMSS strain of Entamoeba histolytica.

Microwave induced (MWI) protocol is now a days a well established procedure for the synthesis of heterocyclic compounds due to several advantages over conventional heating methods [11-13] . It can be termed as e-chemistry because it is easy, economic, efficient and eco-friendly and is believed to be a step ahead towards green chemistry. Keeping in view the advantages of MWI protocol and significance of pyrazolines as potent biodynamic moiety in the present investigation some new N^1-substituted -3,5-diaryl-2-pyrazolines have been synthesized using eco friendly MWI method and evaluated for their anti microbial activities. 2-Hydroxy chalcones (1) were treated with hydrazine hydrate under solvent free MWI condition to get corresponding 3,5-diaryl-2-pyrazolines (2) . These pyrazolines were reacted with freshly prepared chloro acetyl chloride at room temperature to afford N^1-chloroacetyl-3, 5-diaryl-2-pyrazolines (3). The reaction of (3) with morpholine under MWI was carried out to get the title compounds (4) in 80-90 % yields.

EXPERIMENTAL

The required 3, 5-diaryl-2-pyrazolines were prepared by the interaction of 2-hydroxy chalcones with hydrazine hydrate under MWI condition[14].

(A) Synthesis of 1N-chloroacetyl-3, 5-diaryl-2-pyrazolines (3a-g):
To a solution of 3,5-diaryl-2-pyrazolines(0.01mole) in chloroform(20ml) was added freshly prepared chloroacetyl chloride (0.01 mole) with continuous stirring. A vigorous reaction takes place. After complete addition the reaction mixture was further stirred for 30 minutes at room temperature. The separated solid was filtered off and crystallized from ethanol to afford the analytical sample.

(B) Synthesis of N^1-morpholino-ethanoyl-3, 5-diaryl-2-pyrazolines (4a-g):
Compounds 3a-g (0.01mole) and morpholine (0.01mole) were mixed thoroughly to form an intimate mixture. This mixture was subjected to MWI at 300 watt power for 3-5 minutes with occasional disruption for 30 sec. After completion of the reaction the residue was cooled to room temperature and extracted with ethanol. On standing at room temperature the solid separated was filtered and crystallized from benzene- petroleum ether to get the analytical sample of 4a-g.

RESULTS AND DISCUSSION

Condensation of 3,5-diaryl-2-pyrazolines (1) with chloroacetyl chloride and morpholine afforded the title compounds , characterized as N^1-morpholino ethanoyl-3,5-diaryl-2-pyrazolines (4). The structure of newly synthesized compounds was established on the basis of their analytical data and spectral analysis. The IR spectra (KBr,ν cm^{-1}) of compounds (3) exhibited a broad band at 3430-3200 (-OH), 2950-2930 (-CH stret.), 1680-1660 (>C=O of $COCH_2Cl$), and a high intensity broad band at 1590-1570 (C=N and N-N combined vibrations). The IR spectra of compounds (4) showed broad band at 34350-3400 (-OH), 2960-2850 (-CH stret.), and a high intensity peak at 1660-1650 (>C=O). The ^1H – NMR spectra ($CDCl_3$, δ ppm) of compounds (4) gave signals at δ 3.20-3-37 (dd, C_4-H_a), δ 3.86-3.92 (dd, C_4-H_b), δ 5.52-5.58(C_5-Hx) confirming the presence of typical ABX pattern of the pyrazoline ring. The aromatic protons gave a multiplet at δ 6.91-7.41, whereas the proton of -OH group gave a singlet at δ 10.2. The methylene protons resulting from CH_2-O-CH_2 and CH_2-N-CH_2 grouping of morpholine nucleus appeared as singlet at δ 2.52-2.60 respectively. The mass spectra (FAB) of all the synthesized compounds gave molecular ion peaks corresponding to their molecular masses.

Antibacterial activity
The synthesized pyrazoline derivatives were screened for their antibacterial activity in-vitro against S.aureus, S.albus, E.coli, K.pneumonae, and P.vulgaris at a concentration 250µg/ml. The results were compared with standard drug amoxyclove. N^1-chloroacetyl derivatives were found to possess good to moderate activity against K.pneunomae. Compound 3c and 3f were found to have excellent activity against S.aureus. Substitution of 3, 5-dimethoxy phenyl, 4-dimethylamino phenyl and furanyl rings at 5-position tends to increase the biological activity. Compounds 4a-g were found to have moderate activity against all strains of pathogens. Replacement of phenyl ring by furanyl ring has been shown to decrease the biological activity.

Antifungal activity
Newly prepared pyrazoline derivatives were tested for their antifungal activity against A.niger and M.phascolina at a concentration 250µg/ml. Moderate activity was displayed by the compounds 3(a-g), whereas compounds 4(a-g) were found to possess low activity.
A comparison of the biological activities of compounds 3a-g and 4a-g indicates that transformation of chloroacetyl derivatives to corresponding morpholino derivatives has no marked effect on the biological activities.

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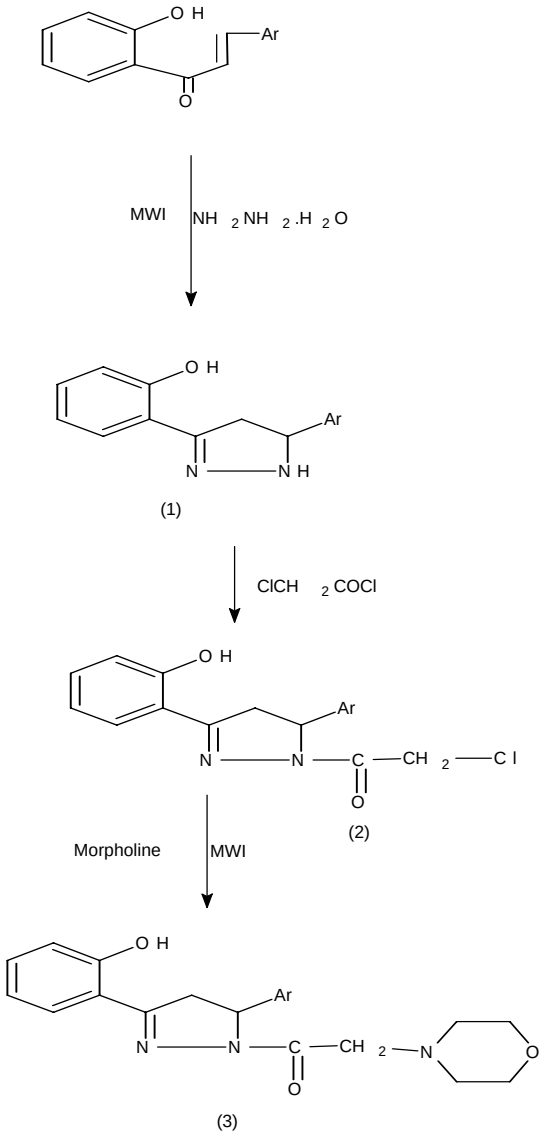

Scheme-1

Table-1: Physical data of compounds 3a-g and 4a-g.

Compd	Ar	Mol. Formula (M.wt.)	M.P (^oC)	Yield (%)	Rxntime (min.)	% N	
						cal	found
3a	phenyl	$C_{17}H_{15}N_2O_2Cl$ (314.5)	164	83	-	8.90	8.94
3b	4-oMe phenyl	$C_{18}H_{17}N_2O_3Cl$ (344.5)	183	85	-	8.12	8.01
3c	3,4-dioMe phenyl	$C_{19}H_{19}N_2O_4Cl$ (374.5)	148	85	-	7.47	7.24
3d	3,4,5-trioMephenyl	$C_{20}H_{21}N_2O_5Cl$ (404.5)	204	86	-	6.92	6.01
3e	4-Cl phenyl	$C_{17}H_{14}N_2O_2Cl_2$ (349)	192	87	-	8.02	7.88
3f	4-NMe_2 phenyl	$C_{19}H_{20}N_3O_2Cl$ (357.5)	184	83	-	11.74	12.01
3g	2-furanyl	$C_{15}H_{13}N_2O_3Cl$. (304.5)	140	80	-	9.19	9.31

4a	phenyl	$C_{21}H_{23}N_3O_3$ (365)	146	85	3.5	11.50	11.32
4b	4-oMe phenyl	$C_{22}H_{25}N_3O_4$ (395)	155	87	4.0	10.63	10.51
4c	3,4-dioMe phenyl	$C_{23}H_{27}N_3O_5$ (425)	156	94	4.0	9.88	10.01
4d	3,4,5-trioMe phenyl	$C_{24}H_{29}N_3O_6$ (455)	148	89	3.0	9.23	9.11
4e	4-Cl phenyl	$C_{21}H_{22}N_3O_3Cl$ (399.5)	180	90	4.0	10.51	10.15
4f	4-NMe_2phenyl	$C_{23}H_{28}N_4O_3$ (408)	160	85	5.0	13.72	13.59
4g	2-furanyl	$C_{19}H_{21}N_2O_4$(355)	152	82	5.5	11.83	11.69

Table -2 : Biological activity result of compounds 3a-g and 4a-g
(Zone of inhibition in mm.)

	Antibacterial Activity					Antifungal Activity	
Compd.	E.coli	P.vulgaris	K.pneumonae	S.aureus	S.albus	A.niger	M.phascolina
3a	11	-	13	-	-	14.66	-
3b	-	-	14	-	-	13.50	-
3c	-	-	16	13	-	51.56	-
3d	9	-	12	-	-	29.09	-
3e	-	-	14	-	-	59.0	-
3f	17	-	12	16	14	42.16	-
3g	-	-	-	11	-	53.33	-
4a	-	-	17	9	-	19.0	-
4b	-	-	12	-	-	12.66	-
4c	-	-	13	-	-	56.0	-
4d	13	-	14	-	-	5.0	-
4e	-	-	16	9	9	46.66	-
4f	-	-	13	-	-	10	-
4g	-	-	-	9	-	12.33	-
Amoxyclove (std. drug)	15	12	16	15	23		

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