Heterocyclic Letters
Vol. 14| No.2|243-248|Feb-April|2024
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

MICROWAVE ASSISTED SYNTHESIS AND STUDY OF ANTI-MICROBIAL ACTIVITY OF SOME 3,5- DIARYLATED 2-PYRAZOLINES

S.L. Kumbhare[a], Y.K. Meshram[b]

[a]*Department of Chemistry, Shri Shivaji Science & Arts College, Chikhli, Dist.- Buldana (M.S.), 443201, India*
[b]*Department of Chemistry, G.S. College, Khamgaon, Dist.- Buldana (M.S.),444303, India*
Email- infoslkumbhare@yahoo.com

ABSTRACT
In the present study,2-Acetyl thiophene on condensation with various aromatic aldehydes in ethanolic NaOH solution yielded chalcone (1a-1g). These chalcones were reacted with hydrazine hydrate to give pyrazolines (2a-2g). All these compounds were characterized by means of their IR, 1HNMR spectral data. These compounds were evaluated for antimicrobial activities and were found to possess significant activity as compared to Standard drugs.

KEY WORDS – Pyrazolines, Chalcones, Antimicrobial, Microwave, Spectral Analysis, Antifungal

INTRODUCTION
Various substituted pyrazolines and their derivatives are important biological agents and a significant amount of research activity has been focused on the synthesis of 2-Pyrazoline.In particular, they are used as antitumor [i], antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular and insecticidal agents [ii-x]. Some of these compounds have also anti-inflammatory, anti-diabetic, anesthetic and analgesic properties. [xi-xx]

The synthesis of thiophene, furan, pyrazoline derivatives has engrossed substantial attention from organic and medicinal chemist for many years as they belong to a class of compounds with more utility in medicinal chemistry. Thiophene derivatives are known to be associated with multiple biological activities. Therefore , both the pyrazoline and thiophene possess worthy and imperative bioactivities which render them useful substance in drug research. Pyrazolines are the most frequently studied compounds and various methods have been worked out for their synthesis. A classical synthesis of these compounds involves the base catalyzed Aldol condensation reaction of aromatic ketones and aldehydes to give α, β unsaturated ketones (chalcones), which undergo a subsequent cyclization reaction with hydrazine affording 2-pyrazolines. This method is generally used simple and convenient procedure for synthesis of pyrazolines but this method require heating about 3-5 hours and gives less yield. In view of these observations, to overcome the disadvantages of classical method for preparation of pyrazoline derivatives, we have synthesized these derivatives using

microwave irradiation. This method reported a synthesis of 3, 5- diarylated 2-pyrazoline derivatives [xv]. The structures of various synthesized compounds were assigned on the basis of IR, ^{1}HNMR and mass spectral data. These compounds were also screened for their antimicrobial and antioxidant activity.

EXPERIMENTAL :

GENERAL PROCEDURE :

All the chemicals used in synthesis were obtained from standard commercial sources. The melting points were determined in open capillaries using Thiel's tube and are uncorrected. IR spectra were recorded on Schimadzu IR-4350-04 instrument using potassium bromide pellets. The 1HNMR spectra of the compounds were recorded on 400 MHz NMR spectrophotometer using TMS as an internal standard and DMSO as solvent.3,5 diarylatedPyrazoline derivatives were prepared as per following Scheme.

General Procedure for preparation of 3(2-thionyl), 5- Aryl, 2-Pyrazolinederivatives

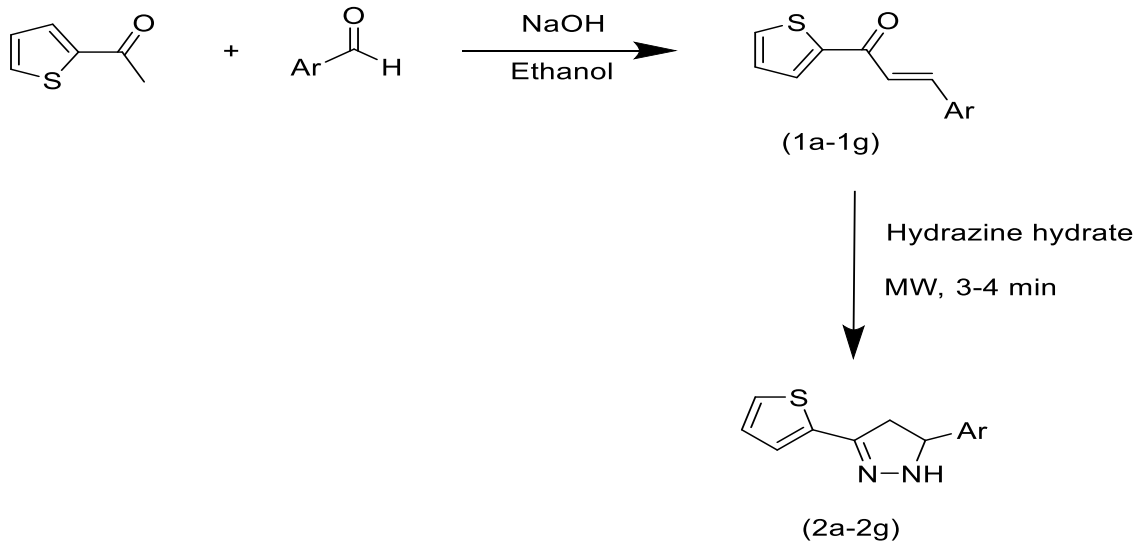
It consist of two steps -

1) Preparation of 3-Aryl-1-(thiophene-2-yl) prop-2-en-1-ones (1a-1g) -

Firstly chalcones 1a-1g were prepared by the reaction between 2-acetylthiophene (0.01mol) and substituted benzaldehydes (0.01mol). During the preparation a mixture 2-acetylthiophene (0.01mol) and appropriate aldehydes(0.01mol)was dissolved in minimum quantity of alcohol (20ml). The reaction mixture was heated at about 60^0C and then added 40% NaOH(10ml) slowly with constant stirring about 45 minutes. The reaction mixture then allowed to cool and acidified with dil. HCl. The solid chalcones obtained separated by filtration and recrystallized the chalcones with ethanol and determine its melting point.

2) Preparation of 3(2-thionyl)-5-(aryl)-2-Pyrazoline (2a-2g) –

In the second step, the solutions of synthesized chalcones (0.01mol) in ethanol (30ml) and hydrazine hydrate (0.02mol) was irradiated under microwave oven at 600watt for 3-4 minutes. The reaction mixture then poured in to cold water. The solid pyrazoline obtained separated by filtration. The progress of reaction monitored by TLC and product recrystallized by ethanol.



ANALYTICAL DISCUSSION :

The analytical data of synthesized compounds were summarized in Table 1.

Table 1. Microwave synthesis of 3,5-arylated 2-pyrazolines (2a-2g) (power = 600 W)

Compound	Ar	Mol. Formula	M.P.	% Yield
2a	4-Chlorophenyl	$C_{13}H_{11}N_2SCl$	130^0C	85
2b	4-Hydroxyphenyl	$C_{13}H_{12}N_2SO$	160^0C	80
2c	4-Bromophenyl	$C_{13}H_{11}N_2SBr$	128^0C	83
2d	4-Fluorophenyl	$C_{13}H_{11}N_2SF$	135^0C	84
2e	4-Methoxyphenyl	$C_{14}H_{14}N_2SO$	100^0C	82
2f	4-Ethoxyphenyl	$C_{15}H_{16}N_2SO$	98^0C	87
2g	4-NItrophenyl	$C_{13}H_{11}N_3SO_2$	210^0C	80

Synthesized 3,5 diarylated Pyrazolines were analyzed by IR and NMR spectra.

Table 2. IR, ^{1}H-NMR and MS (EI) spectral data of the 2-pyrazoline products

Compound	IR Spectral data	^{1}HNMR Spectral data
2a	3300 (Pyrazoline N-H), 1590(ring C=N),1563(ring C=C), 1480(ring N-N), 1122(C-N), 1065(C-S-C), 863(C-Cl)	3.29 (dd,1H,CH2(Pyraz)), 5.17 (dd,1H, CHPyraz), 6.44(d,1H, CH_{furyl}) , 7.45-8.00 (dd,4H, Ar-H), 10,2(s,1H,N-H)
2b	3310 (Pyrazoline N-H), 3500(O-H), 1580(ring C=N),1565(ring C=C), 1485(ring N-N), 1120(C-N), 1067(C-S-C), 1120(C-O)	3.27 (dd,1H,CH2(Pyraz)), 5.18 (dd,1H, CHPyraz), 6.43(d,1H, CH_{furyl}) , 7.30-8.00 (dd,4H, Ar-H), 10.1(s,1H,N-H)
2c	3320 (Pyrazoline N-H),1593(ring C=N),1564(ring C=C), 1483(ring N-N), 1126(C-N), 1063(C-S-C), 803(C-Br)	3.28 (dd,1H,CH2(Pyraz)), 5.16 (dd,1H, CHPyraz), 6.43(d,1H, CH_{furyl}) , 7.40-8.00 (dd,4H, Ar-H), 10.3(s,1H,N-H)
2d	3307 (Pyrazoline N-H),) 1590(ring C=N),1563(ring C=C), 1480(ring N-N), 1122(C-N), 1065(C-S-C), 1110(C-F)	3.23 (dd,1H,CH2(Pyraz)), 5.15 (dd,1H, CHPyraz), 6.37(d,1H, CH_{furyl}) , 7.45-8.00 (dd,4H, Ar-H), 10,2(s,1H,N-H)
2e	3315 (Pyrazoline N-H), 1595(ring C=N),1566(ring C=C), 1487(ring N-N), 1125(C-N), 1067(C-S-C), 1158(C-O)	3.29 (dd,1H,CH2(Pyraz)), 3.75(s,3H, OCH_3) 5.17 (dd,1H, CHPyraz), 6.30(d,1H, CH_{furyl}) , 7.45-8.00 (dd,4H, Ar-H), 10,2(s,1H,N-H),
2f	3312 (Pyrazoline N-H), 1594(ring C=N),1543(ring C=C), 1480(ring N-N), 1122(C-N), 1065(C-S-C), 1150(C-O)	3.29 (dd,1H,CH2(Pyraz)), 3.75(s,3H, OCH_3) 5.18 (dd,1H, CHPyraz),

		6.40(d,1H, CH_{furyl}) , 7.45-8.00 (dd,4H, Ar-H), 10,2(s,1H,N-H),
2g	3307 (Pyrazoline N-H), 1589(ring C=N),1567(ring C=C), 1548(N=O), 1485(ring N-N), 1114(C-N), 1060(C-S-C), 1158(C-O)	3.27 (dd,1H,CH2(Pyraz)), 5.19 (dd,1H, CHPyraz), 6.43(d,1H, CH_{furyl}) , 7.45-8.00 (dd,4H, Ar-H), 10,2(s,1H,N-H)

RESULT AND DISCUSSION :

Different substituted 3,5 diarylated pyrazolines were prepared by reacting substituted chalcones (1a-1g) with hydrazine hydrate under the microwave irradiation at 600 watt for 3-4 minutes.. All prepared compounds were analyzed by different spectroscopic technique and tested their antimicrobial activity.

Antimicrobial activity

Cup plate method using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of **(2a-g)** against *Staphylococcus aureus, Staphylococcus faecalis, E.coli* and *Pseudomonas fluorescens.* The agar medium was purchased from Hi-media Laboratories Ltd. Mumbai, India. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound (5 mg) was dissolved in 5 mL of dimethyl sulfoxide. Ofloxacin was employed as reference standard (1000 μg/mL) to compare the results. The pH of the all the test solutions and control was maintained at 2-3 by using conc. HCl, because the compounds were not diffused through agar medium at pH below 3. All the compounds were tested at a concentration of 0.05 mL (50 μg) and 0.1 mL (100 μg) level. DMSO as control did not show any inhibition.Same cup plate method using PDA (Potato-Dextrose-Agar) medium was employedto study the preliminary antifungal activity of **(2a-2g)** against *Trichophyton rubrum and Candida albicans.* The PDA medium was purchased from Hi-media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium and PDA medium was done as per the standard procedure. Each test compound (5 mg) was dissolved in 5 mL of dimethyl sulfoxide. Ofloxacin was employed as reference standard (1000 μg/mL) to compare the results. The pH of the all the test solutions and control was maintained at 2-3 by using conc. HCl, because the compounds were not diffused through agar medium at pH below 3.

All the compounds were tested at a concentration of 0.05 mL (50 μg) and 0.1 mL (100 μg)level. DMSO as control did not show any inhibition. The cups each of 7 mm diameter were made by scooping out medium with a sterilized cork borer in a petri dish, which was streaked with the organisms. The solutions of each test compound, control and reference standards (0.05 and 0.1 mL) were added separately in the cups and petri dishes were subsequently incubated at 37 ± 1oC for 24 h for antibacterial activity and kept aside at room temperature for 48 h for antifungal activity. Zone of inhibition produced by each compound was measured in mm and the results arepresented in Table 3 for antibacterial activity and in Table 4 for antifungal activity.

Table 3: Antibacterial activity of 2-pyrazolines (2a-2g)

Compound	**Zone of Inhibition (in MM)**			
	Staphylococcus aureus	*Staphylococcus faecalis*	*E.coli*	*Pseudomonas fluorescens*
2a	**18**	**10**	**15**	**12**
2b	**12**	**05**	**10**	**10**
2c	**16**	**09**	**13**	**14**
2d	**17**	**08**	**14**	**15**
2e	**18**	**17**	**11**	**16**
2f	**20**	**20**	**10**	**18**
2g	**14**	**13**	**12**	**11**
Ofloxacin	**20MM**	**10 MM**	**10 MM**	**12 MM**

Table 4 : Antifungal activity of 2-pyrazolines (2a-2g)

Compound	**Zone of Inhibition (in MM)**	
	Trichophyton rubrum	*Candida albicans*
2a	**18**	**15**
2b	**20**	**10**
2c	**17**	**16**
2d	**16**	**17**
2e	**14**	**15**
2f	**20**	**20**
2g	**14**	**10**
Ofloxacin	**14**	**14**

CONCLUSION

In summary, this work demonstrates a rapid, efficient and environmentally friendly method of synthesis of 3,5-diarylated pyrazolines under microwave method, and study of antimicrobial activity. The results obtained confirm the superiority of the microwave irradiation method over classical heating one and good antimicrobial activity with the reference standard drug.

ACKNOWLEDGEMENT :

The authors are thankful to Director, SAIF, Punjab University, Chandigarh, India for providing IR, ^{1}HNMR spectral data.

REFERENCES

i Turgut Z;YolacanC;AydoganF;BagdatliE;Ocal N. Synthesisof new pyrazolothiazole derivatives from 4-thiazolidinones; Molecules;2007,12,2151.

ii. Sharma PC; Sharma SV; Badami S; Sharma A; Suresh B.Microwave-assisted efficient synthesis and anti fungalevaluationof some N-phenyl-3-(substituted phenyl) propenamides ;Indian JPharm Educ Res ;2007,41,140.

iii Bakr F; Abdel-Wahab; Hatem A; Abdel Aziz; Essam MA.Synthesis and antimicrobial evaluation of 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3-

(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles;Eur J Med Chem.; 2009,44,2632.

iv. Ozdemir A; Turan-Zitouni G;KaplancZA;Revial G; Guven K.Synthesis and antimicrobial activity of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives;Eur J Med Chem.;2007,42,403.

v. Andrea SD; Zheng ZB; DenBleyker K; Fung-Tomc JC; Yang H; Clark J. Synthesis and antibacterial activity of dihydro-1,2-oxazineand 2-pyrazoline oxazolidinones: novel analogs of linezolid;Bioorg Med Chem Lett;2005,15,2834.

vi. Turan-Zitouni G; Ozdemir A; Guven K; Synthesis of Some 1-[(N,N-Disubstitutedthiocarbamoylthio)acetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives and investigation of their antibacterial andantifungal activities; Arch Pharm.;2005,338,96.

vii Mamolo MG, Zampieri D, Falagiani V, Vio L, Banfi E. Synthesis and antifungal activity of(±)-1-(5-aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanone derivatives. Farmaco.;2003,58,315.

viii Kreutzberger A; Kolter K; Antiviral agents. XXVII: amino methynylation of 5-oxo-2pyrazoline-3-carboxylic acid derivatives; ArchPharm;1986,319,18.

ix Kucukguzel;Rollas S; Synthesis, characterization of novel coupling products and 4-Arylhydrazono-2-pyrazoline-5-ones as potential antimycobacterial agents. Farmaco.;2002,57,583.

x. Shaharyar M; Siddiqui AA; Ali MM, Sriram D;YogeeswariP.Synthesis and in vitroantimycobacterial activity of N1-nicotinoyl-3-(40-hydroxy-30-methyl phenyl)-5-[(sub)phenyl]-2-pyrazolines.Bioorg Med Chem Lett.;2006,16,3947.

xi. PalaskaE;AytemirM;Uzbay T; Erol D; Synthesis and antidepressant activities of some 3,5-diphenyl-2-pyrazolines;Eur J MedChem.;2001,36,539.

xii. Palaska E; Erol D;Demirdamar R; Synthesis and antidepressant activities of some 1,3,5-triphenyl-2-pyrazolines;Eur J Med Chem.;1996,31,43.

xiii. Abid M; Azam A; 1-N-Substituted Thiocarbamoyl-3-Phenyl-2-pyrazolines: synthesis and in vitro antiamoebic activities;EurJMed Chem.,2005,40:935.

xiv. Abid M; Azam A; Synthesis, characterization and antiamoebic activity of 1-(thiazolo[4,5-b]quinoxaline-2-yl)-3-phenyl-2-pyrazolinederivatives. Bio org Med Chem Lett.,16,2812 (2006).

xv. Flora F; Hosni HH; Girgis AS; Novel bis(1-acyl-2-pyrazolines) of potential anti-inflammatory and molluscicidal properties; Bio org Med Chem.;2006,14:3929.

Received on January 24, 2024.