Int. J. Chem. Sci.: 11(2), 2013, 1086-1094
ISSN 0972-768X
www.sadgurupublications.com

MICROWAVE INDUCED SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF SOME SUBSTITUTED CHALCONES AND THEIR PYRAZOLINE AND ISOXAZOLINES DERIVATIVES

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ABSTRACT

Condensation of acetone with substituted benzaldehyde in presence of some basic alumina under microwave irradiation affords 1, 5-substituted diphenyl-1, 4-pentadiende-3-one chalcones. These chalcones undergo facile and clean cyclization with hydrazine $RNHNH_2$ (R= Ph, C_6H_4 $(NO_2)_2$, $CONH_2$, $CSNH_2$) under microwave irradiation to afford 3, 5-arylated 2-pyrazolines in quantitative yields. The cyclocondensation of chalcones prepared with hydroxylamine hydrochloride resulted in the formation of isoxazoline derivatives. The structures of all the compounds have been established on the basis of analytical and spectral data. All the compounds have screened for antibacterial and antifungal activity.

The results obtained indicate that, unlike classical heating, microwave irradiation results in higher yields, shorter reaction times and cleaner reactions.

Key words: Microwave irradiation, Chalcones, Pyrazoline, Isoxazoline, Heterocyclic synthesis.

INTRODUCTION

The chalcones were are well known synthetic intermediated in the synthesis of highly functionalized heterocyclic compounds due to the presence of enone function, Several pyrazoline and isoxazoline and their synthetic analogues have been found to exhibit broad spectrum of industrial, agriculture and biological application such as bactericidal[1], acarcidal[2], antiiflannatery[3], antidepressant[4], antipyretic[5], antibactrial[6], antifungal[7], tranquillinzing[8], muscle relaxant[9], psycho-analeptic[10], anticonvulsant[11], antihypertensive[12] activities. A literature survey reveals pyrazoline derivatives are active against many tumer cell lines. Isoxazolines

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have also been reported to possess anti-diabetic[13], diuretic[14], analgesic[15], anthelmintic[16], and hypolipidemic activity[17]. In the light of interesting biological activities exhibited by these compounds, the synthesis of pyrazoline and isoxazoline derivatives was carried out under microwave irradiation.

EXPERIMENTAL

The melting point of all the products was determined in open capillaries and is uncorrected. The IR spectra (cm^{-1}) were recorded using KBr on Shimadzu FT-IR 8201 PC spectrometer, PMR spectra ($CDCl_3$/DMSO-d_6) were recorded on Brucker-FT-WM-400 (400 MHz) using TMS as internal standard (chemical shift in δ ppm). Mass spectra were recorded on a Jeol-D-300 Spectometer. Elemental analysis was within + or -0.5% limits from their calculated values.

General procedure for microwave assisted preparation of 1, 5-substituted diphenyl-1,4-pentadiende-3-one chalcones (1, 2)

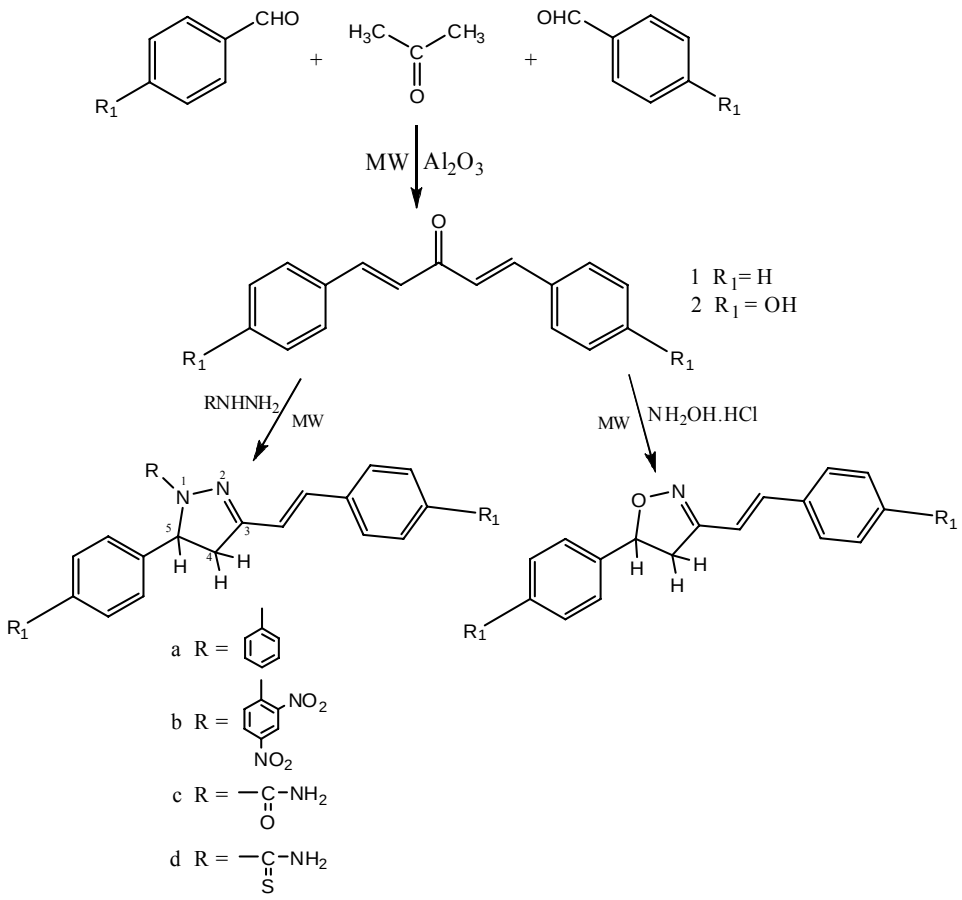
In the first step the chalcones (1, 2) were prepared by condensation of acetone (0.01 mol) and substituted benzaldehyde (0.02 mol) in the presence of basic aluminum oxide under microwave irradiation for about five minutes. The progress of the reaction was monitored with TLC. The resulting crude solid is extracted with ethanol and filtered to remove aluminum oxide. Finally, the products are recrystallized from ethanol (95%) to give the pure chalcones in 80-95% yield.

General procedure for microwave assisted preparation of 3,5-arylated-2-pyrazoline derivatives

A slurry of chalcones (0.05 mol) and hydrazine ($RNHNH_2$) (0.05 mol) was exposed to microwave irradiation in open flask for about 3-6 minutes. After completion of the reaction as indicated by TLC, the reaction mixture was cooled at room temperature and extracted with ethanol. The products were recrystallized from ethanol (95%) to give good yield (75%-90%) of pure crystals of 2-pyrazolines (**1a-1d** and **2a-2d**).

General procedure for microwave-assisted preparation of 3, 5-arylated isoxazoline derivatives

Slurry of chalcones (0.05 mol) and hydroxylamine hydrochloride (0.05 mol) in ethanol was exposed to microwave irradiation in open flask for about 3-5 minutes. After completion of the reaction as indicated by TLC, the reaction mixture was cooled at room temperature. The product was extracted and recrystallized from ethanol (95%) to give good yield (80%-90%) of pure crystals of isoxazoline derivatives (**1e** and **2e**).



Scheme 1

Table 1: Physical properties

Comp.	Molecular formula	Molecular weight	Melting point	% Yield	Found (Calculated)		
					% C	% H	N%
1	$C_{17}H_{14}O$	234	110°C	85%	87.25 (87.17)	6.05 (5.98)	
2	$C_{17}H_{14}O_3$	266	106°C	80%	76.80 (76.69)	5.25 (5.26)	
1a	$C_{23}H_{20}N_2$	324	281°C	81%	85.20 (85.18)	6.15 (6.17)	8.60 (8.64)
1b	$C_{23}H_{18}N_4O_4$	414	162°C	75%	66.61 (66.66)	4.40 (4.34)	13.50 (13.52)

Cont…

Comp.	Molecular formula	Molecular weight	Melting point	% Yield	Found (Calculated)		
					% C	% H	N%
1c	$C_{18}H_{17}N_3O$	291	302°C	75%	74.25 (74.22)	5.80 (5.84)	14.40 (14.43)
1d	$C_{18}H_{17}N_3S$	307	303°C	76%	70.30 (70.35)	5.56 (5.53)	13.65 (13.68)
1e	$C_{17}H_{15}NO$	249	177°C	78%	81.90 (81.92)	6.08 (6.02)	5.60 (5.62)
2a	$C_{23}H_{20}N_2O_2$	356	80°C	82%	77.50 (77.52)	5.65 (5.61)	7.88 (7.86)
2b	$C_{23}H_{18}N_4O_6$	446	96°C	80%	61.90 (61.88)	4.00 (4.03)	12.52 (12.55)
2c	$C_{18}H_{17}N_3O_3$	323	158°C	78%	66.85 (66.87)	5.32 (5.26)	13.05 (13.00)
2d	$C_{18}H_{17}N_3O_2S$	339	148°C	79%	63.75 (63.71)	5.02 (5.01)	12.35 (12.38)
2e	$C_{17}H_{15}NO_3$	281	140°C	76%	72.60 (72.59)	5.35 (5.33)	4.95 (4.98)

Spectral data of compounds

1. IR (KBR) cm^{-1} 1668 (C=O conjugated), 3053 (=CH) ,3010 (CH- Ar), 1600 (C=C), 705, 744 (mono sub. C-H), 955 (trans CH=CH), 1450, 1500, 1580 (C=C) **NMR** ($CDCl_3$) δ 6.77-6.82 (d, 2H, H_α), 7.17-7.22 (d, 2H ,H_β), 7.42-7.66 (m, 10H, Ar-H); **Mass**: M/Z 234 (M^+), 131, 103, 91, 77, 51.

2. IR (KBR) cm^{-1} 1640 (C=O conjugated), 3400 (O-H), 3006 (CH- Ar), 3026 (=C-H), 948 (trans CH=CH), 1452,1582, 1500 (C=C), **NMR** ($CDCl_3$) δ 6.76-6.83 (d, 2H, Hα), 7.18-7.21 (d, 2H, Hβ), 7.60-7.87 (m, 8H, Ar-H), 5.30 (S, 2H, OH-P); **Mass** : M/Z 266 (M+), 267, 147, 119, 93, 51.

1a. IR (KBR) cm^{-1} 1586 (C=N), 3008 (C-H), 3032 (=C-H), 1451, 1600, 1510 (C=C), 960 (trans CH=CH), 735, 690 (mono disub. C-H), **NMR** ($CDCl_3$) δ 3.14-3.23 (dd,1H,C_4-H_A), 6.43-6.52 (d, 1H, H_α), 3.39-3.79 (dd, 1H, C_4-H_B), 5.21-5.29 (dd, 1H, C_5-H_X), 6.61-6.79 (d,

1H, H_β), 6.83-7.5 (m, 15H, Ar-H), 6.43-6.52 (d, 1H, H_α); **Mass** : M/Z 324(M^+), 247, 129, 103, 77, 91.

1b. IR (KBR) cm^{-1} 1582 (C=N), 1290 (C-N), 1580, 1500, 1465, 1610 (C=C), 1520 (NO_2 assym.), 1325 (NO_2 sym.), 3045 (=CH), 947 (trans CH=CH), 816 (C-H tri.sub.) **NMR**($CDCl_3$) δ 3.12-3.22 (dd, 1H, C_4-H_A), 3.40-3.80 (dd, 1H, C_4-H_B), 5.20-5.30 (dd, 1H,C_5-H_X), 6.44-6.52 (d, 1H, H_α), 6.60-6.80 (d, 1H, H_β), 6.82-7.55 (m, 13H, Ar-H), **Mass**: M/Z 414 (M^+), 247, 143, 129, 111, 103.

1c. IR (KBR) cm^{-1} 1580 (C=N), 1295 (C-N), 1665 (C=O amide), 3010 (C-HAr-H), 2924, 2880 (CH), 3346 (N-H, NH_2 coupled), 3165 (N-H,NH_2 sym.), 965 (trans CH=CH) **NMR** ($CDCl_3$) δ 2.80-2.88 (dd, 1H, C_4-H_A), 3.14-3.23 (dd, 1H, C_4-H_B), 5.94-6.03 (dd, 1H, C_5-H_X), 6.19-6.25 (d, 1H, H_α), 6.60-6.66 (d, 1H, H_β), 6.85 (S, 2H, NH_2), 7.18-7.52 (m, 10H, Ar-H), **Mass**: M/Z 291(M^+), 247, 214, 162, 148, 129, 77.

1d. IR (KBR) cm^{-1} 1585 (C=N), 1160 (C=S weak band), 3360 (N-H, NH_2 coupled), 3150 (N-H,NH_2 sym.), 1590, 1600, 1455, 1515 (C=C Ar), 1425 (C-N), 712, 736 (mono sub. C-H bend), 955 (trans CH=CH); **NMR**($CDCl_3$) δ 2.80-2.87 (dd,1H,C_4-H_A), 3.15-3.5223 (dd, 1H, 5.C_4-H_B), 5.95-6.02 (dd, 1H, C_5-H_X), 6.20-6.24 (d, 1H, H_α), 6.61-6.66 (d, 1H, H_β), 6.84 (S, 2H, NH_2), 7.19-7.50 (m, 10H, Ar-H), **Mass**: M/Z 307(M^+), 230, 204, 178, 154, 143, 129, 103.

1e. IR (KBR) cm^{-1} 1576 (C=N), 3012 (C-H Ar-H str.), 865 (N-O), 1459, 1512, 1609 (C=C), 718, 766 (mono sub. C-H bend), 968 (trans CH=CH) **NMR**($CDCl_3$) δ 2.71-2.80 (dd, 1H, C_4-H_A), 3.35-3.43 (dd, 1H, C_4-H_B), 5.51-5.63 (dd, 1H, C_5-H_X), 6.11-6.18 (d, 1H, H_α), 6.50-6.55 (d, 1H, H_β), 7.51-7.88 (m, 10H, Ar-H), **Mass**: M/Z 249 (M^+), 172, 168, 143, 107, 129.

2a. IR (KBR) cm^{-1} 1580 (C=N), 3380 (O-H), 1460, 1500, 1600 (C=C str.), 3016 (Ar-CH), 3048 (=CH), 814 (C-H tri. Sub.), 960 (Trans CH=CH); **NMR** ($CDCl_3$) δ 2.50-2.64 (dd, 1H, C_4-H_A), 3.30-3.42 (dd, 1H, C_4-H_B), 5.83-5.90 (dd, 1H,C_5-H_X), 5.32 (S, 2H, OH), 6.20-6.28 (d, 1H, H_β), 6.95-7.9 (m, 10H, Ar-H); **Mass** : M/Z 356 (M^+), 279, 263, 237, 159, 119.

2b. IR (KBR) cm^{-1} 1340 (NO_2 sym.), 1550 (NO_2 assym.), 3400 (OH), 965 (trans CH=CH), 3017 (CH Ar-H), 3041 (=CH), 814 (C-H bend tri sub.), 1584 (C=N str.); **NMR** ($CDCl_3$) δ 2.53-2.65 (dd, 1H, C_4-H_A), 3.31-3.43 (dd, 1H, C_4-H_B), 5.82-5.90 (dd, 1H, C_5-H_X), 5.31 (S, 2H, OH), 6.19-6.27 (d,1H, H_α), 6.70-6.72 (d,1H, H_β), 6.93-7.81 (m, 11H, Ar-H), **Mass**: M/Z 446(M^+), 279, 336, 167, 159, 119.

2c. IR (KBR) cm^{-1} 3355 (N-H str. of NH_2), 3170 (N-H str.sym.), 1650 (C=O conjugated), 1300 (C-N), 1580 (C=N), 3012 (C-H), 958 (trans CH=CH), 822 (p-disub. C-H bend); **NMR** ($CDCl_3$) δ 2.55-2.65 (dd, 1H, C_4-H_A), 3.28-3.40 (dd, 1H, C_4-H_B), 5.82-5.91 (dd, 1H, C_4-H_X), 5.30 (S, 2H, OH), 6.18-6.27 (d, 1H, H_α), 6.70-6.73 (d, 1H, H_β), 6.93-7.81 (m, 8H, Ar-H), 5.62 (S, 2H, NH_2); **Mass**: M/z 323(M^+), 279, 204,177,137,119, 106, 93.

2d. IR (KBR) cm^{-1} 3150 (N-H str. of NH_2 sym.), 3345 (N-H str. of NH_2 coupled), 1585 (C=N), 1422 (C-N), 1165 (C=S weak band), 3045 (=CH), 3016 (-CH Ar-H), 961 (CH=CH trans), 830 (p-disub. C-H); **NMR** ($CDCl_3$) δ 2.50-2.65 (dd, 1H, C_4-H_A), 3.30-3.40 (dd, 1H, C_4-H_B), 5.81-5.90 (dd, 1H, C_4-H_X), 5.30 (S, 2H, OH), 6.25-6.28 (d, 1H, H_α), 6.95-7.80 (m, 8H, Ar-H), 5.60 (S, 2H, NH_2); **Mass:** M/z 339(M^+), 246, 279, 220, 193, 145, 137.

2e. IR (KBR) cm^{-1} 1578 (C=N), 3390 (O-H), 3044 (=CH), 1599, 1575, 1505, 1457 (C=C benzene), 962 (trans CH=CH), 830 (p-disub. C-H), 3014 (C-H Ar-H,) 860 (N-O) **NMR** ($CDCl_3$) δ 2.51-2.63 (dd, 1H, C_4-H_A), 3.32-3.42 (dd, 1H, C_4-H_B), 5.82-5.91 (dd, 1H, C_4-H_X), 5.31 (S, 2H, OH), 6.22-6.28 (d, 1H, H_α), 6.67-6.73 (d, 1H, H_β), 6.94-7.78 (m, 8H, Ar-H), **Mass**: M/z 281 (M^+), 188, 162, 137, 119, 93.

Antibacterial activity

The *in vitro* antibacterial activities of the synthesized compounds were evaluated by Kirby-Bayer method, using standard literature protocol. In this method the microorganisms of interests is swabbed uniformly across an autoclaved culture dish having nutrient medium in muller hilten agar base. This culture dish is sealed and incubated. When a layer of microbial growth takes place, a filter paper disk, impregnated of the compound to be tested, is placed on the surface of the agar and incubated at 40^0C for 18-20 hours. The compound diffuses out from the filter paper into the agar. If the compound is effective against bacteria/fungal at a certain concentration, no colonies will grow wherever the concentration in agar is greater or equal to that effective concentration. This region called Zone of inhibition is a measure of the compound's effectiveness. DMSO was used as a solvent to prepare solution of the test compounds. Standard drugs used were ciprofloxacin and amphotericin.

RESULTS AND DISCUSSION

In the present work, the microwave assisted condensation reactions between acetone and substituted benzaldehydes in the presence of basic alumina resulted in the intermediate chalcones 1 and 2, which undergo a rapid cyclization with hydrazine (**a-d)** and

hydroxylamine hydrochloride (**e)** under microwave irradiation to yield 2-pyrazolines **1a-d, 2a-d** and isoxazolines **1e, 2e** respectively in 3-7 minutes (**Scheme 1**). The products were characterized on the basis of their IR, ^{1}H-NMR, MS spectral and elemental analysis.

Table 2: Biological evaluation

Compd.	Antibacterial activity		Antifungal activity	
	B. cereus	***E. Coli***	***C. albicans***	***A. fumigatus***
1	17 (0.85)	16 (1.06)	13 (0.72)	10 (0.83)
2	16 (0.80)	10 (0.66)	15 (0.83)	9 (0.75)
1a	5 (0.25)	13 (0.86)	6 (0.33)	4 (0.33)
1b	17 (0.85)	8 (0.53)	12 (0.66)	6 (0.50)
1c	18 (0.90)	14 (0.93)	16 (0.88)	8 (0.66)
1d	14 (0.70)	0 (0)	5 (0.27)	11 (0.91)
1e	5 (0.25)	9 (0.60)	10 (0.55)	10 (0.83)
2a	11 (0.55)	11 (0.73)	16 (0.88)	8 (0.66)
2b	10 (0.50)	4 (0.26)	14 (0.77)	0 (0)
2c	12 (0.60)	11 (0.73)	15 (0.83)	13 (1.08)
2d	10 (0.50)	9 (0.60)	24 (1.33)	12 (1.0)
2e	14 (0.70)	13 (0.86)	0 (0)	8 (0.66)
Standard	20	15	18	12

Standard : Ciproflaxacin (Antibacterial), Amphotericin (Antifungal)

All the 12 compounds were screened for antibacterial activity, and except compound **1d** rest compounds were found active against both the types of bacteria. Compounds **1**, **2**, **1b** and **1c** have shown good activity against *B. cereus*. Compound **1** has shown excellent activity against *E. coli* and compounds **1a**, **1c** and **2e** have shown good activity against *E. coli*.

All the 12 compounds were also screened for antifungal activity. Compound **2d** has shown excellent activity and compounds **2**, **1c**, **2a** and **2c** have shown good activity against *C. Albican*. Compounds **2c** and **2d** have shown excellent activity and compounds **1**,**1d** and **1e** have shown good activity against *A. Fumigatus*.

CONCLUSION

On summing up, this work demonstrates a rapid, efficient and environmentally friendly method for the synthesis of compounds (chalcones, pyrazolines and isoxazolines) under microwave irradiation. The results obtained confirm that the microwave assisted synthesis is a dry media reaction condition that leads to considerable saving in reaction time and energetically profitable over the conventional method.

ACKNOWLEDGEMENT

The authors are thankful to UGC (Bhopal) for providing financial support. Authors are also grateful to Principal and Head, Department of Chemistry, S. G. G. Government College, Banswara (Raj.) for providing laboratory facilities. Thanks are due to Director, CDRI, Lucknow for elemental and spectral analysis. Thanks are also due to Dr. Sushil Sahu, R. N. T. Medical College, Udaipur (Raj.) for biological analysis of the compounds.

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Accepted : 04.04.2013