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Synthesis of 3,5-Diaryl Azoline and [1,4] Diazepine Derivatives via Microwave Irradiation

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Abstract. An efficient microwave irradiation synthesis of 2-isoxazoline (4), 2-isothiazoline derivatives (5), 2-pyrazoline derivatives and pyrimido [4,5-b] [1,4] diazepine derivatives (10). The effect of microwave irradiation was compared by classical method. The results show that microwave irradiation shortens the reaction times while affording comparable yields. Some of the synthesized compounds were tested for their biological activity.

Introduction

Microwave (MW)-accelerated solvent-free organic synthesis are of great interest and important in view of their simplicity, high and tunable selectivities, easy work-up and time- and energy-saving protocols. Recyclability of the solid supports employed and the diminished amount of solvent usage also renders this technique an environmental friendly procedure[1-3].

The chemistry of α,β-unsaturated ketone has recently received considerable interest[4]. These compounds are important intermediate in organic synthesis. Chalcones, 3,5-diaryl azoles and [1,4] diazepine are well known for their significant biological activities[5-8]. We wish to report here condensation reaction of chalcone, with hydroxylamine hydrochloride, hydrazine hydrate and 4,5-diaminopyrimidine. The effect of microwave irradiation on condensation reactions was compared with "classical" conditions.

Experimental

All melting points were determined on Gallen Kamp apparatus. The ^{1}HNMR spectra were recorded in $CDCl_3$-d_1 on a Junmex-400 FT NMR AM 400 spectrophotometer using TMS as internal reference. IR spectra were recorded in KBr on Perkin-Elmer 380 Spectrometer. The elemental analyses were performed on a Heraus C,H,N analyzer. Mass spectra were recorded on micromass 7070 spectrophotometer operating at 70 eV. Microwave irradiation was carried out with commercial microwave oven [2450 MHz].

General procedure for synthesis of chalcones (1a-e): These were synthesized according to a previously published literature methods[9,10]. General procedure for synthesis 3,5-diaryl azoline (classic method) have been prepared according to the method reported earlier[11,12].

3,5-Diaryl-2-isoxazolines [4a-e]

A mixture of chalcones (3a-e,1.0mmol), hydroxylamine hydrochloride (1.2 mmol), and potassium carbonate (3.0 g) in (3 ml) acetic acid was stirred at room temperature for 5 min. The mixture was irradiated for 10 min at 375 W (reaction progress monitored by TLC). The mixture was cooled and product was extracted with CH_2Cl_2 (20 ml). The product was collected by evaporating the solvent under pressure and recrystallized from the proper solvent to give 4a-e (Table 1).

3,5-Diaryl-2-isothiazolines [5a-e]

A solution of 3,5-diaryl-2-isoxazolines ([3a-e,1.0 mmol) and phosphorus pentasulphide (1.0 mmol) in pyridine 10 ml. The reaction mixture was mixed and stirred for 10 min. The mixture was heated under microwave irradiation (375 W) for 4-5 min. The mixture was cooled and product was extracted into CH_2Cl_2 (30 ml). The product was collected by evaporating the solvent under pressure and recrystallised from the proper solvent to give 5a-e (Table 1).

3,5-Diaryl-2-Pyrazolines [8a,b]

To a solution of chalcones (1a-e, 1.0 mmol) and hydrazinehydrate (1.2 mmol) in (10 ml) ethanol. After stirring for 5 min the reaction mixture was irradiated in microwave for 6-8 min at 375W. The product was collected and recrystallized from appropriate solvent to give 8 a,b (Table 1).

Table 1. Analytical and physical data of compounds 4-10.

Compound no.	Solvent for crystallization MP ºC	Molecular formula / Molecular weight	Elemental analysis (%) : Calcd. / found		
			C	H	N
3a	EtOH 285-288	$C_{23}H_{17}NO$ 323	85.64 85.31	5.26 5.20	4.33 9.5
3b	EtOH 116-120	$C_{24}H_{19}NO$ 337	85.45 85.8	5.63 5.44	4.15 4.11
3c	EtOH 198-200	$C_{23}H_{16}ClNO$ 375.5	77.20 77.20	4.47 4.90	3.91 3.85
3d	MeOH 158-160	$C_{23}H_{16}BrNO$ 401.9	68.67 68.55	3.98 3.95	3.48 3.48
3e	EtOH-H_2O 100-103	$C_{29}H_{21}NO$ 399	87.21 87.30	5.26 5.23	3.50 3.40
5a	MeOH 143	$C_{23}H_{17}NS$ 339	81.40 81.40	5.01 5.04	4.12 4.4
5b	EtOH 100	$C_{24}H_{19}NS$ 353	81.58 81.02	5.38 5.40	3.96 3.55
5c	EtOH 140	$C_{23}H_{16}CNS$ 373.5	73.89 73.56	4.28 4.00	3.74 3.69
8a	ACOH 194	$C_{23}H_{18}N_2$ 322	85.71 85.77	5.59 5.60	8.69 8.33
8b	EtOH 150	$C_{23}H_{17}ClN_2$ 356.5	77.41 77.45	4.76 4.66	7.85 7.50
10a	ACOH 118-120	$C_{27}H_{20}N_4$ 324	81.00 81.13	5.00 5.30	14.00 14.11
10b	EtOH 120-	$C_{28}H_{22}N_4$ 414	81.15 81.30	5.31 5.4	13.52 13.60
10c	ACOH 138	$C_{27}H_{19}N_4Cl$ 434.5	74.56 74.50	4.37 4.37	12.88 12.90
10d	ACOH 121-123	$C_{27}H_{19}N_4Br$ 478.9	67.65 67.66	3.96 3.98	11.69 11.70

2,3-Dihydro-2,4-diaryl-1H-pyrimido [4,5-b] [1,4] diazepine [10a-d]

Method A

A solution of chalcones (1a-e,1.0 mmol) and 4,5-diaminopyrimidine (1.2 mmol) in dry ethanol (15 ml) and acetic acid (2 ml) was refluxed for 4 hours. The reaction mixture was cooled and stored overnight at 0ºC filtered off and recrystallized from the the proper solvent to give 10a-d (Table 1).

Method B

Basic alumina (20 g) was added to a solution of chalcones (1_{3a-d}) (1.0mmol) and 4,5-diaminopyrimidine (1.2 mmol) in Ethanol (15 ml). The reaction mixture was mixed and the adsorbed material was dried. The reaction mixture was irradiated in microwave oven for 12-14 min at 375 W. Then cooled and the product was extracted by CH_2Cl_2 (20ml), evaporating the solvent and recrystallized from the proper solvent to give 10a-d.

Results and Discussion

It is known that 1,3-diaryl-2-propen-1-ones (chalcones) (1a-e) were classically condensed with hydroxylamine hydrochloride in ethanol solution to give 2-isoxazoline derivatives[9]. In the present work, we study this reaction under microwave irradiation in the present of catalytic amounts of K_2CO_3 Scheme 1. The reaction time has been brought down. From hours to minutes with good yield as compared to conventional heating for all reaction. The effect of irradiation time on the reaction were also studied and the results are summarized in Table 2. It was found that the high yield compounds can be obtained in 375 for 10 min.

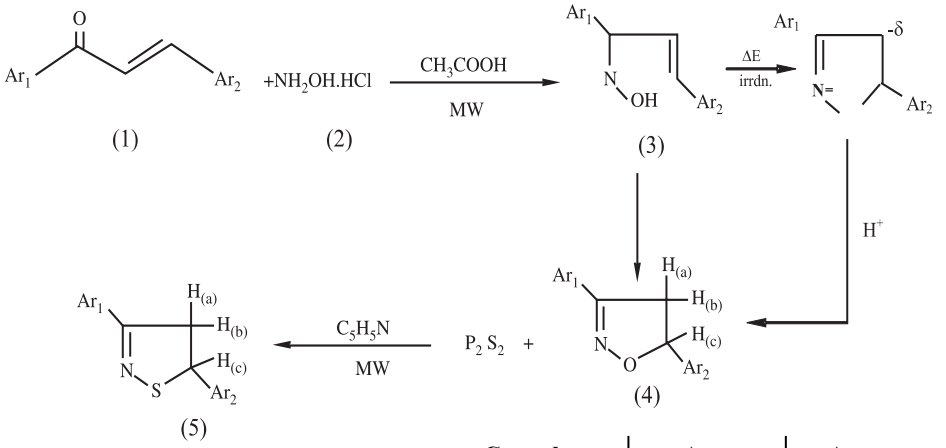
Structure of all the synthesized compounds were established on the basis of their spectroscopic data were IR spectra of condensed products **3** display disappearance of band at 1650-1660 cm^{-1} due to C = O of chalcone and appearance of a band at 1590-1620 cm^{-1} due to C = N formed. The 'H NMR spectra show an ABX pattern in which each of H_a, H_b and H_c protons is represented by a pair of doublet. The structure of $\mathbf{4_a}$ was also confirmed by mass spectrum which showed a molecular ion peak at m/2 = 323 calculated for $C_{23}H_{17}NO$ with a base peak at m/z = 133.

It was found that the reaction of phosphorus pentasulphide in pyridine at MW in 4-5 min at 375 led to replacement of ring oxygen by sulphur atom (Scheme 1).

The IR spectrum of compounds **5** showed absorption band at 1200-1100 and 830-850 cm^{-1} due to C-S group. The structure of compounds **5** were further supported by their 'H NMR spectra (Table 4).

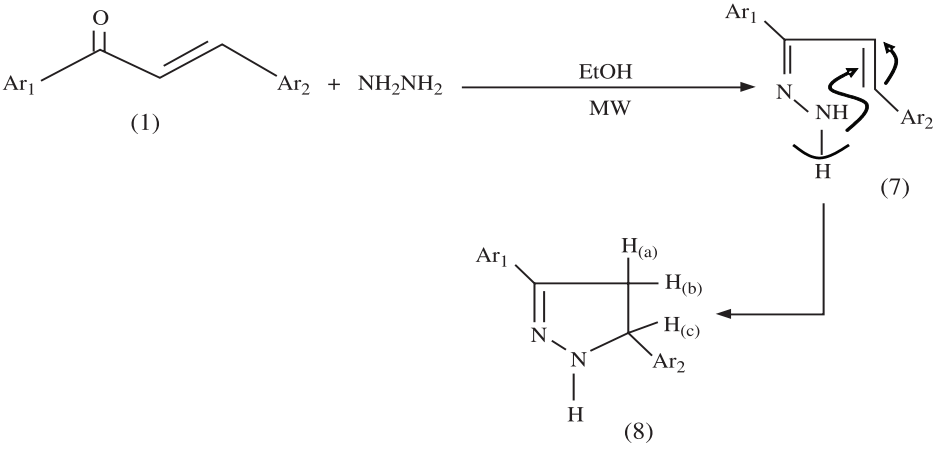
Similarly, condensation of **1** with hydrazine hydrate in abs. ethanol under microwave irradiation (8-10 min) afforded the addition product 7 which followed by ring closure reactions led to the formation of 3,4-diaryl-2-pyrozoline derivatives 8 a,b (Scheme 2).

Structures of these compounds were deduced from their elemental analysis and compatible spectral data. IR spectrum of compound **8** showed absorption band at region 3320-3360 cm^{-1} due to presence NH group. The ^1H NMR spectra led to further support to the structure of these compounds **8**. They show sig-



Compd. no.	Ar_1	Ar_2
4,5a	C_6H_5	9-C_4H_9
4,5b	4-$CH_3C_6H_4$	9-$C_{14}H_9$
4,5c	4-ClC_6H_4	9-$C_{14}H_9$
4d	4-BrC_6H_4	9-$C_{14}H_9$
4e	4-PhC_6H_4	9-$C_{14}H_9$

Scheme 1



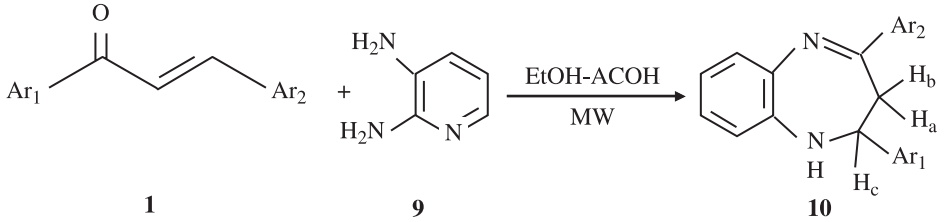
Compd. no.	Ar_1	Ar_2
8a	C_6H_5	9-$C_{14}H_9$
8b	4-Cl_6CH_4	9-$C_{14}H_9$

Scheme 2

nals corresponding to proton at C4 and C5 of 2-pyrazoline ring. The three protons are represented by typical (ABX) system. Each of the Ha, Hb and Hc is represented by a double doublet.

The mass spectrum of **8a** showed a molecular ion at m/z = 322 calculated for $C_{23}H_{18}N_2$. The mechanism of the formation of the above 3,5-diaryl isoxazoline and pyrazoline derivative may proceed via polarization of carbonyl group followed by addition of nuclephilic which cyclize through a stereoselective enamine-imine tautomerism step.

On the other hand, preparation of [1,4] diazepine derivatives **10** via treating under classic reaction conditions also was studied. Chalcones **1** with 4,5-diaminopyrimidine in ethanol-acetic acid gave the desired product **10** after 2 hours refluxing. Using of microwave irradiation products **10** were prepared from the same component but react time was shortened to 7-8 minutes (Scheme 3) (Table 1).



1 **9** **10**

Compd. no.	Ar_1	Ar_2
10a	C_6H_5	9-$C_{14}H_9$
10b	4-$CH_3C_6H_4$	9-$C_{14}H_9$
10c	4-ClC_6H_4	9-$C_{14}H_9$
10d	4-BrC_6H_4	9-$C_{14}H_9$

Scheme 3

The structure of compounds **10a-d** were established by elemental analysis and spectral data (Tables 1 & 4).

IR spectra of compounds **10a-d** show bands in the regions 3230-3310 cm^{-1} due to NH. The 'H NMR spectra gave further support to the structure of these compounds. 'H NMR spectrum of compound **10a** in $CDCl_3$ showed a signals at 2.3 (S, 1H, CH_3); 3.9 (S, 1H, NH), δ4.12 (d, 1H, H-a), δ 4.6 (d, 1H, H-b); 6.9 (dd, 1H, H-c); δ 7.2-8.6 (m, 14H, ArH's) (Table 4).

From the above study we can conclude that using MWI in synthesis of 3,5-diarylazoline and [1,4] diazepine derivatives is a rapid economic methodology and simplification of classical procedure. The result shown in Tables 2 & 3, demonstrates the versatility of the process as considerable

reaction rate enhancement, which has been observed by bringing down the reaction time from hours to minutes with comparable yield as compared to conventional heating.

Table 2. Comparisons between classical and microwave procedures for preparation of compounds 4-10.

Compd. no.	Classical conditions		MW reaction	
	Reaction time (h)	Yield %	Reaction time (min)	Yield %
4a	3	81	10	79
4b	3	79	12	75
4c	3	88	12	79
4d	3	88	10	80
4e	3	86	12	79
5a	4	80	5	78
5b	2	88	5	80
5c	3	83	4	81
8a	4	89	6	80
8b	4	87	8	81
10a	4	50	12	45
10b	4	45	14	42
10c	4	51	12	45
10d	4	43	12	39

Table 3. The effect of microwave irradiation time on the yield of 4-10.

Compd. no.	Irradiation time min / Yield %			
	3	5	8	10
3a	15	35		79
3b	16	39		69
3c	10	30		66
3d	15	33		77
5a	35	78		
5b	30	80		
8a	25	55	–	
8b	23	58	81	
10a	12	20		36
10b	12	25		36
10c	10	18		25

The Antimicrobial Activity

The obtained compounds have been evaluated towards the following organisms:

1. *Strep. pyog*
2. *Pseudomonas aeruginosa*
3. *Escherichia coli*
4. *Proteus mirabilis*
5. *Salmonella*
6. *Candida albican*

The biological activity was evaluated according to the cup-plate method adopted with some modifications [13]. Whatman No. 2 filter paper disk (6.5 cm) were impregnated with 200 mg of the compound. The disk was placed on the surface of the cold solid medium petridishes, inoculated with the considered organisms, and then incubated at 5ºC for one hour, to permit good diffusion and then transferred to an incubator at 28ºC for 24 h and determine the effective diameter. A summary of the biological activity results is shown in Table (4).

Relation between structure-activity showed that the highly active compounds 10d (*Salmonella*), 8b (*Paeruginosa*), 5b (*Candida albican*) and 5a (*P. mirabilis*) are due to the presence of halogen atoms in the structure. Also, the moderate active compounds 10c (*Salmonella*), 5a (*C. albican*), 4b (*Salmonella*) and 4a (*P. aeruginosa*); (*E. coli*). While the lethal active compounds towards (*S. pyog*), (*P. aeruginosa*) and (*E. coli*).

Table 4. IR and ^{1}H-NMR spectral data of compounds 3,5.

Compd. no	IR υ (cm^{-1})	^{1}H-NMR- (δ ppm in $CDCl_3$)
4a	1600, 1640 (C=N, C=C)	3.2 (dd, 1H, H-a); 3.8 (dd, 1H, H-b); 5.8 (dd, 1H, H-c); 6.9-8.1 (m, 14H, ArH's)
4b	1600, 1610 (C=N δ C=C)	2.4 (s, 3H, CH_3); 3.3 (dd, 1H, H-a); 3.7 (dd, 1H, H-b); 5.8 (dd, 1H, H-c); 7.1-8.3 (m, 13H, ArH's)
4c	1590, 1610 (C=N, C=C)	3.2 (dd, 1H, H-a); 3.8 (dd, 1H, H-b); 5.8 (dd, 1H, H-c); 7.2-8.9 (m, 13H, ArH's)
4d	1590, 1610 (C=N, C=C)	3.2 (dd, 1H, H-a); 3.7 (dd, 1H, H-b); 5.9 (dd, 1H, H-c); 7.2-8.8 (m, 13H, ArH's)
4e	1620, 1615 (C=N, C=C)	3.3 (dd, 1H, H-a); 4.0 (dd, 1H, H-b); 5.9 (dd, 1H, H-c); 7.2-8.9 (m, 18H, ArH's)
5a	1610, 1540 (C=N δ C=C); 830 (C-S); 920 (S-N)	3.2 (dd, 1H, H-a); 3.6 (dd, 1H, H-b); 5.7 (dd, 1H, H-c); 6.9-7.9 (m, 14H, ArH's)
5b	1610, 1540 (C=N δ C=C); 820 (C-S); 915 (S-N)	2.4 (s, 3H, CH_3); 3.3 (dd, 1H, H-a); 3.7 (dd, 1H, H-b); 5.8 (dd, 1H, H-c); 7.1-8.8 (m, 13H, ArH's)

Table 4. Contd.

Compd. no	IR υ (cm^{-1})	^{1}H-NMR- (δ ppm in $CDCl_3$)
5c	1600, 1540 (C=N δ C=C); 820 (C-S); 915 (S-N)	3.2 (dd, 1H, H-a); 3.6 (dd, 1H, H-b); 5.6 (dd, 1H, H-c); 6.8-8.8 (m, 13H, ArH's)
8a	3400 (NH), 1590, 1600 (C=N δ C=C)	3.09 (dd, 1H, H-a); 3.8 (dd, 1H, H-b); 6.4 (dd, 1H, H-c); 7.2-8.4 (m, 14H, ArH's); 8.6 (s, 1H, NH)
8b	3450 (br.NH), 1580, 1610 (C=N, C=C)	3.3 (dd, 1H, H-a); 3.8 (dd, 1H, H-b); 6.4 (dd,1H, H-c); 7.4-8.6 (m, 13H, ArH's); 8.4 (br.s, 1H, NH)
10a	3310 (Str, NH); 1620, 1800 (C=N, C=C)	3.9 (br.S, 1H, NH); 4.22 (dd, 1H, Ha); 4.5 (dd,1H, Hb); 6.7 (dd, 1H, Hc); 7.1-8.6 (m, 16H, ArH's and δ H_6, H_8-pyrimidine protons).
10b	3230 (Str, NH); 1630, 1610 (C=N, C=C)4.2 (dd,	2.3 (S, 3H, CH_3); 3.90 (brS, 1H, NH); 1H, Ha); 4.5 (dd, 1H, Hb); 6.3 (dd, 1H, Hc); 7.0-8.6 (m, 13H, ArH's and δ H_6, H_8-pyrimidine protons).
10c	3240 (Str, NH); 1620, 1610 (C=N, C=C)	3.9 (brS, 1H, NH); 4.2 (dd, 1H, Ha); 4.5 (dd, 1H, Hb); 6.9 (dd, 1H, Hc); 7.3-8.6 (m, 15H, ArH's and δ H_6, H_8-pyrimidine protons).
10d	3250 (Str, NH); 1620, 1610 (C=N, C=C)	3.9 (brS, 1H, NH); 4.2 (dd, 1H, Ha); 4.6 (dd,1H, Hb); 6.9 (dd, 1H, Hc); 7.2-8.6 (m, 15H, ArH's and δ H_6, H_8-pyrimidine protons).

Table 5. Antimicrobial activity of selected compounds.

Test organism	3a	3b	3c	5d	5b	5c	5d
Strep. pyog	–	+	–	–	+	+	+
P. aeruginosa	++	–	+	–	+	–	–
Escherichia coli	++	–	–	+	–	–	–
Proteus mirabilis	–	+	++	–	+++	–	–
Salmonella	+	++	–	–	–	++	+++
Candida albican	+	–	++	+	+	–	+

The sensitivity of microorganisms to the compound is identified in the following manner:
+++ = highly sensitive (inhibition zone 1.2 – 1.5 mm)
++ = fairly sensitive (inhibition zone 1.2 – 0.9 mm)
+ = slightly sensitive (inhibition zone 0.9 – 0.6 mm)
– = not sensitive

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تحضير مشتقات ٣، ٥-ثنائي أريل أزولين و [١، ٤] ثنائي أزابين باستخدام أشعة المايكروويف

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المستخلص. تم تحضير مشتقات ٢- أيزواكسازولين ٤ و٢- أيزوثيازولين (٥) و٢- بيرازولين ومشتقات بيرميدو [٤، ٥ ب] [١، ٤] ثنائي أزابين (١٠) باستخدام تقنية المايكروويف، وأظهرت هذه الطريقة، مقارنة مع الطريقة الكلاسيكية لتحضير هذه المركبات ، أن استخدام تقنية المايكروويف اختزل زمن التفاعل من ساعات إلى دقائق، وأعطى مردوداً ناتجيًا جيداً ومقارباً من المركبات الناتجة عن الطريقة الكلاسيكية. كذلك تمت دراسة التأثير الحيوي لبعض المركبات المحضرة .