

MICROWAVE ASSISTED RAPID SYNTHESIS AND ANTI-MICROBIAL ACTIVITY OF 4-OXOTHIAZOLIDINE DERIVATIVES

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ABSTRACT

A simple and novel procedure for the preparation of the titled compounds by using microwave. The synthesis of the titled compounds from phenylhydrazine with appropriate carbonyl compounds in high yield is based upon exposure to microwave irradiation. The reaction rate is enhanced tremendously under microwave irradiation as compared to conventional method with improved yield. The resulting products were characterized by IR, ¹H-NMR and Mass spectral data. The compounds were screened for their anti-bacterial and anti-fungal activity.

Keywords: Microwave, phenyl hydrazine, oxothiazolidine, anti bacterial, anti fungal.

INTRODUCTION

Heterocyclic compounds containing nitrogen, sulphur, and oxygen moieties constitute the core structure of a number of biologically interested compounds, against bacteria and fungi^{1,2}. Phenylhydrazine-4-oxothiazolidines³ and their 5-arylidenes are structural subunits of several biologically active compounds. By observing the importance of the above titled compounds we planned to synthesize such compounds in which phenyl hydrazine rearranges to schiff's base in the presence of appropriate carbonyl compounds and ultimately reacts with mercapto acetic acid to give 4-oxothiazolidine ring and it further undergoes substitution with appropriate carbonyl compounds in presence of sodium ethoxide to give 5-arylidenes. All these reactions were performed under microwave irradiation by using domestic radiator and observed that the reaction underwent faster with better yield than conventional method. All these compounds were screened for

anti-microbial activity like anti-bacterial and anti-fungal activities and observed to possess moderate to good activity.

With this intention phenyl hydrazine and benzaldehyde in ethanol and catalytic amount of glacial acetic acid was irradiated at 200 watts for 6 minutes. In conventional method^{4,5}, it requires 3 hrs for the complete process. The IR spectrum of (Ia) in KBr band at 1546(N=CH), 3434(N-H), and 3348(NH-N). ¹H NMR spectrum in CDCl₃ showed sharp singlet at δ 4.91 (N=CH) for one proton, multiplet range at δ 6.75 -7.72 for nine protons(Ar -H), and sharp singlet at δ 7.78 (NH) of single aromatic proton .

While compounds of (IIa) were synthesized with equal moles of Ia in ethanol and mercapto acetic acid with pinch of ZnCl₂ irradiated^{6,7} at 160 watts for 2 minutes. In conventional method, it requires 6 hrs for reflux. The IR spectrum of IIa in KBr showed at 1703(CO cyclic), 2963 (CH₂-S-cyclic), 3333 (Ar-H), 1548(N=CH), 3420(N-H) and 3348 (NH-N). ¹H NMR spectrum in CDCl₃ showed a sharp singlet at δ 3.14 (N-CH) for one proton, a sharp singlet at δ 3.59 (CH₂-S) for two protons, a sharp singlet at δ 7.78 (NH) and multiplet range at δ 6.8-7.7 (Ar -H) for ten protons.

In final step (IIIa) were synthesized with equal moles of IIa in ethanol and appropriate carbonyl compounds in presence of sodium ethoxide and irradiated^{8,9} at 480 watts for 3 minutes . In conventional method, the process requires over 7 hrs for reflux. The IR spectrum of IIIa in KBr showed a band at 1703 (CO cyclic), 2966(CH₂-S cyclic), 3300(Ar-H), 1543(N=CH), 3422(N-H), 3348(NH-N), and 1618 (C=CHAr). ¹H NMR spectrum in CDCl₃ showed a sharp singlet at δ 3.14 (C=CHAr) for one proton ,multiplet range at δ 6.78 – 7.71 (Ar-H) for ten protons, a sharp singlet at δ 4.0 (NH) for one proton and a sharp singlet at δ 3.57 (CH₂-S) for two protons .

The purity of compounds was monitored by TLC and melting point. The structures of all new compounds III(a -d1) were confirmed based on their spectral (IR, ¹H NMR, and Mass) data and anti-microbial activity by using standard screening methods.

EXPERIMENTAL

All the melting points were determined on a DBK precision melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer RX-1 series FT- IR Spectrophotometer. ¹H NMR Spectra on a Varian Gemini 200 MHz Spectrometer using TMS as internal standard and mass spectra on a HITACHI RMU GL at 70ev. Purity of all the compounds was checked by TLC on silica gel-G plates. Microwave irradiations were carried out on LG MS-192 W domestic microwave oven.

2,2'-disubstituted Phenyl hydrazone (Ia): Phenyl hydrazine (0.1 mole) and benzaldehyde (0.1 mole) in ethanol (30ml) and catalytic amount of glacial

acetic acid was irradiated in a domestic microwave oven (200 W) for the specified time. After completion of the reaction, filtered, dried and recrystallized by using ethanol as solvent. m.p 140⁰C, yield 72%, IR, KBr, cm⁻¹: 1546 (N=CH), 3424 (N-H), 3348 (NH-N).

¹H NMR, (CDCl₃), (δ, ppm): 4.91 (s, 1H, N=CH), 6.75-7.72 (m, 9H, Ar), 7.80 (s, 1H, NH).

2,2'-disubstituted-3-anilino-4-oxo thiazolidine^{10,11} (IIa): A mixture of compound Ia (0.1 mole) in ethanol (50 ml) and mercapto acetic acid (0.1 mole) with a pinch of ZnCl₂ was irradiated in a domestic microwave oven (160 W) for specified time. The separated solid was filtered, dried and recrystallized from ethanol to give compound. m.p 165⁰C, yield 76%, IR, KBr, cm⁻¹: 1703 (CO cyclic), 2963 (CH₂-S cyclic), 3333 (Ar-H), 1548 (N=CH), 3420 (N-H), 3348 (NH-N).

¹H-NMR, (CDCl₃), (δ, ppm):

3.14 (s, 1H, N-CH), 3.59 (s, 2H, CH₂-S), 7.78 (s, 1H, NH), 6.80-7.70 (m, 10H, Ar-H).

2,2'-disubstituted-5,5'-arylidine disubstituted-3-anilino-4-oxothiazolidine^{12,13} (IIIa): Equimolar solution of IIa (0.02 mole) and benzaldehyde (0.02 mole) in dioxane (30 ml) in the presence of sodium ethoxide was irradiated at (180 W) for specified time and solvent was removed in vacuum. The resulting solid was filtered, dried and recrystallized from ethanol to give compounds. m.p 183⁰C, yield 88%, IR, KBr, cm⁻¹: 1703 (CO cyclic), 2966 (CH₂-S cyclic), 3300 (Ar-H), 1543 (N=CH), 3422 (N-H), 3348 (NH-N), 1618 (C=CHAr).

¹H NMR, (CDCl₃), (δ, ppm): 3.14 (s, 1H, N-CH), 3.59 (s, 2H, CH₂-S), 4.0 (s, 1H, NH), 6.80-7.70 (m, 10H, Ar-H).

¹³C NMR, (CDCl₃), (δ, ppm): 63.4 (s, 1C, CH-thiazolidine), 164.5 (C=O), 129.3 (Ar-C=C), 125.2 (C=CHAr), 113.2-151.0 (Ar), 127.2-141.7 (Ar), 126.8-131.2 (Cl-Ar).

PHARMACOLOGICAL EVALUATION ANTIMICROBIAL ACTIVITY¹¹⁻¹³

All the synthesized compounds were screened for their antibacterial and antifungal activities. For preliminary screening, the antimicrobial tests were carried out by the disc-diffusion method. Using Mueller-Hinton agar (MHA) medium and Sabouraud's dextrose agar (SDA) medium, for bacteria and fungi respectively. The discs (6 mm in diameter), impregnated with the test compounds (25 μg/ml/disc for bacteria and 1000 μg/ml/disc for fungi). Negative controls were prepared using the same solvent (DMSO) employed to dissolve the test compounds. Ofloxacin (25 μg/ml/disc) and Clotrimazole (1000 μg/disc) were used as positive reference standards to determine the sensitivity of each microbial species tested. The inoculated plates were incubated at 37⁰ C for 24 h and 27⁰ C for 72 h for bacterial and fungal strains respectively. Antimicrobial activity was evaluated by measuring the diameter of zone of inhibition against test organisms.

RESULTS AND DISCUSSION

The data given in Table 1, 2 and 3 represent the data for Physical, Spectral and Antimicrobial activity. It has shown that all prepared compounds have

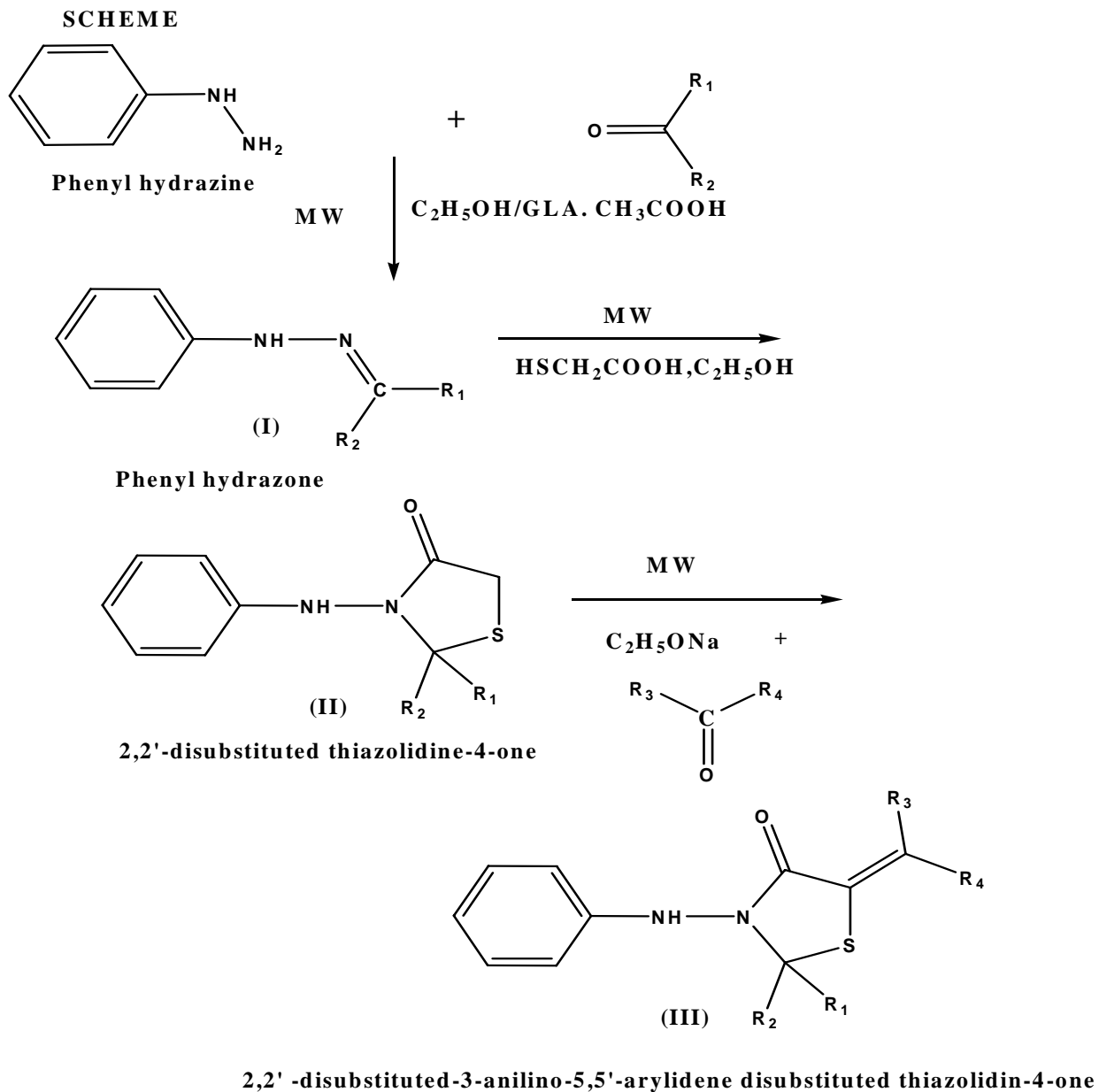


TABLE :1 PHYSICAL DATA

III	R ₁	R ₂	R ₃	R ₄	M.F	MW	IR	T(S)
a	H	C ₆ H ₅	H	2-Cl C ₆ H ₄	C ₂₂ H ₁₇ ClN ₂ OS	392	480	3
b	H	2-Cl C ₆ H ₄	H	2-Cl C ₆ H ₄	C ₂₂ H ₁₆ Cl ₂ N ₂ OS	427	480	2
c	H	2-OH C ₆ H ₄	H	2-Cl C ₆ H ₄	C ₂₂ H ₁₇ ClN ₂ O ₂ S	408	400	2
d	H	2-NO ₂ C ₆ H ₄	H	2-Cl C ₆ H ₄	C ₂₂ H ₁₆ ClN ₃ O ₃ S	437	400	3
e	H	2-Br C ₆ H ₄	H	2-Cl C ₆ H ₄	C ₂₂ H ₁₆ BrClN ₂ OS	471	480	3
f	H	2-OH, 5-OCH ₃ C ₆ H ₃	H	2-Cl C ₆ H ₄	C ₂₃ H ₁₉ ClN ₂ O ₃ S	438	390	2
g	H	(CH ₃) ₂ N-C ₆ H ₄	H	2-Cl C ₆ H ₄	C ₂₄ H ₂₂ ClN ₃ OS	435	420	1
h	CH ₃	C ₆ H ₅	H	2-Cl C ₆ H ₄	C ₂₃ H ₁₉ ClN ₂ OS	406	440	2
i	CH ₃	C ₂ H ₅	H	2-Cl C ₆ H ₄	C ₁₉ H ₁₉ ClN ₂ OS	358	360	2
j	C ₆ H ₅	C ₆ H ₅	H	2-Cl C ₆ H ₄	C ₂₈ H ₂₁ ClN ₂ OS	469	420	2
k	H	C ₆ H ₅	H	2-OH C ₆ H ₄	C ₂₂ H ₁₈ N ₂ O ₂ S	374	480	2
l	H	2-Cl C ₆ H ₄	H	2-OH C ₆ H ₄	C ₂₂ H ₁₇ ClN ₂ O ₂ S	408	460	3
m	H	2-OH C ₆ H ₄	H	2-OH C ₆ H ₄	C ₂₂ H ₁₈ N ₂ O ₃ S	390	430	3
n	H	2-NO ₂ C ₆ H ₄	H	2-OH C ₆ H ₄	C ₂₂ H ₁₇ N ₃ O ₄ S	419	420	3
o	H	2-Br C ₆ H ₄	H	2-OH C ₆ H ₄	C ₂₂ H ₁₇ BrN ₂ O ₂ S	453	480	4
p	H	2-OH, 5-OCH ₃ C ₆ H ₃	H	2-OH C ₆ H ₄	C ₂₃ H ₂₀ N ₂ O ₄ S	420	380	4
q	H	(CH ₃) ₂ N-C ₆ H ₄	H	2-OH C ₆ H ₄	C ₂₄ H ₂₃ N ₃ O ₂ S	417	420	3
r	CH ₃	C ₆ H ₅	H	2-OH C ₆ H ₄	C ₂₃ H ₂₀ N ₂ O ₂ S	388	440	2
s	CH ₃	C ₂ H ₅	H	2-OH C ₆ H ₄	C ₁₉ H ₂₀ N ₂ O ₂ S	340	460	2
t	C ₆ H ₅	C ₆ H ₅	H	2-OH C ₆ H ₄	C ₂₈ H ₂₂ N ₂ O ₂ S	450	440	3
u	H	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	C ₂₈ H ₂₂ N ₂ OS	434	410	2
v	H	2-Cl C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	C ₂₈ H ₂₁ ClN ₂ OS	468	460	2
w	H	2-OH C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	C ₂₈ H ₂₂ N ₂ O ₂ S	450	450	2
x	H	2-NO ₂ C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	C ₂₈ H ₂₁ N ₃ O ₃ S	479	480	2
y	H	2-Br C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	C ₂₈ H ₂₁ BrN ₂ OS	512	380	1
z	H	2-OH, 5-OCH ₃ C ₆ H ₃	C ₆ H ₅	C ₆ H ₅	C ₂₉ H ₂₄ N ₂ O ₃ S	480	420	2
a1	H	(CH ₃) ₂ N-C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	C ₃₀ H ₂₇ N ₃ OS	477	390	2
b1	CH ₃	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	C ₂₉ H ₂₄ N ₂ OS	448	480	3
c1	CH ₃	C ₂ H ₅	C ₆ H ₅	C ₆ H ₅	C ₂₅ H ₂₄ N ₂ OS	400	480	2
d1	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	C ₃₄ H ₂₆ N ₂ OS	510	400	3
		NOTE : W-WARTZ			T-TIME(seconds)			

TABLE :2 SPECTRAL DATA

III	Mass, Bass peak	IR cm ⁻¹	¹ H-NMR (δ)	¹³ C-NMR (δ)
a	392	1703, 1543, 3300,780	6.75-7.72,3.12,3.57,4,	63.4,164.5,127.2-141.7
b	427	1720, 1550, 3320,789	6.67-7.20,7.60,4.4,5.9	54.4,164.3,127.8-133.1
c	408	1700, 1543, 3400,790	7.08-7.22,7.59,4,5.01	53.3,164.0,115-154.9
d	437	1710, 1580, 3300,810	7.32-8.07,7.60,4.1,5.9	54.9,164.6,113.2-151.0
e	471	1722, 3310,790,590	6.69-7.31,7.6,4.1,5.9	55.7,163.9,122.7-144.3
f	438	1723, 1550, 3480,782	6.40-6.50,3.73,4,5.0	53.3,160.5,55.9,120-155.9
g	435	1703, 1543, 3308,1300	6.06-7.19,7.61,4,2.85	63.5,148,40.3,114.3-148.0
h	406	1710, 1550, 3320,1480	6.6-7.24,7.06-7.14,2.03	69.2,164.5,127.2-146.2
i	358	1712, 1542, 3420, 737	6.60-7.20,2.05,2.18,0.96	66.3,164.0,23.4,27.5,55.5
j	469	1710, 1550, 3100,785	6.66-7.18,7.65,4,5.92	77.8,126-147.7,128.3-147
k	374	1700, 1544, 3422,764	6.66-7.18,7.65,4,5.92	63.5,131.2,127.8-141.9
l	408	1720, 1550, 3440,785	7.00-7.20,7.60,4.4,5.9	54.4,133.2,158.7,115-158
m	390	1702, 1540, 3489,785	7.08-7.22,7.59,4,5.01	53.3,158,154.9,113.2-150
n	419	1709, 1585, 3445,812	7.32-8.07,7.60,4.1,5.9	54.9,147.8,158,113-151.7
o	453	1722, 3480,795,592	6.69-7.31,7.6,4.1,5.9	55.9,164.5.1,159,127-141
p	420	1723, 1551, 3480,780	6.40-6.50,3.73,4,5.0	53.4,164.1,55.1,120.2-142
q	417	1710, 1540, 3488,1302	6.06-7.19,7.61,4,2.85	63.7,164.149,41,112-148.7
r	388	1710, 1550, 3480,1480	6.6-7.24,7.06-7.14,2.03	69.4,164.5,127.2-146.7
s	340	1710, 1540, 3429, 738	6.60-7.20,2.05,2.18,0.96	66.3,164.1,23.3,27.5,55.9
t	450	1703, 1543, 3480,780	6.66-7.18,7.65,4,5.92	77.7,126-147.7,128.2-147
u	434	1710, 1550, 3100,2980	6.66-7.18,7.65,4,5.91	63.3,130.9,127.7-141.9
v	468	1712, 1543, 3100,2900	6.67-7.20,7.60,4.4,5.9	54.9,133.2,157.7,115-128
w	450	1706, 1544, 3488,3100	7.08-7.22,7.59,4,5.01	53.6,155.9,115.9-155.9
x	479	1708, 1543, 3200,820	7.32-8.07,7.60,4.1,5.9	55.1,164.3,,121-147.8
y	512	1720, 3310,792,598	6.69-7.31,7.6,4.1,5.89	56.0,164.0,122.2-144.7
z	480	1722, 1552, 3120,780	6.40-6.50,3.73,4,5.0	53.7,160.7,55.7,114-160.5
a1	477	1720, 1554, 3108,1303	6.06-7.19,7.61,4,2.85	63.7,164.5,40.4,114.3-148
b1	448	1715, 1545, 3123,1487	6.6-7.24,7.05-7.154,2.03	69.2,164.3,127.2-141.7
c1	400	1710, 1541, 3125, 738	6.60-7.20,2.05,2.18,0.96	68.9,164.0,127.2-141.9
d1	510	1722, 1543, 3100,2982	6.66-7.18,7.65,4,5.9	78.2,113-151,126-141

TABLE 3: ANTI MICROBIAL ACTIVITY

S.No.	III	EC	PA	PE	AN
1	a	12	15	68	70
2	b	14	16	67	77
3	c	10	14	70	67
4	d	11	15	60	71
5	e	10	13	60	79
6	f	9	19	68	70
7	g	12	16	59	63
8	h	10	13	68	77
9	i	11	14	69	70
10	j	12	17	59	70
11	k	12	15	68	70
12	l	14	16	67	77
13	m	10	14	70	67
14	n	11	15	60	71
15	o	11	13	67	76
16	p	9	19	68	70
17	q	12	16	59	63
18	r	10	13	68	77
19	s	11	14	79	77
20	t	13	17	59	70
21	u	12	15	68	70
22	v	9	16	69	70
23	w	10	14	70	67
24	x	11	15	60	71
25	y	10	13	60	79
26	z	9	19	68	70
27	a1	12	16	59	63
28	b1	8	15	68	77
29	c1	11	14	59	70
30	d1	11	17	60	70
	STD	14	20	80	83

Note: *Escherichia coli*,e (EC), *Pseudomonas aeruginosa*(PA)
Penicillium expansum(PE), *Aspergillus niger* (AN).

STD :Ofloxacin (25 μ mg/ml/disc) for bacteria

Clotrimazole(1000 μ g/disc) for fungi

significant inhibition effect, in particular III b,l,and t against *Escherichia colie* (EC) , III b, f, g, j, k, p, q, t, and z against *Pseudomonas aeruginosa* (PA). The compounds exhibited good antifungal activity, in particular III s,w,m,and c against penicillium expansum(PE),and III e, b, h, l, o, r, s, y, and b1 against *Aspergillus niger* (AN).

All the oxathiazole derivatives are prepared by standard procedures and confirmed by spectral analysis. In step 1, phenyl hydrazine and benzaldehyde in ethanol and catalytic amount of glacial acetic acid was irradiated at 200 watts for 6 minutes. The structures were confirmed as follows, the IR spectrum of (Ia) in KBr band at 1546, 3434, and 3348. ^1H NMR spectrum in CDCl_3 showed sharp peak at δ 4.91, 6.75 - 7.72, 7.78. While compounds of (IIa) were synthesized with equal moles of Ia in ethanol and mercapto acetic acid with pinch of ZnCl_2 irradiated at 160 watts for 2 minutes. The structures were confirmed as follows, IR spectrum of IIa in KBr showed at 1703, 2963, 3333, 1548 3420 and 3348. ^1H NMR spectrum in CDCl_3 showed a sharp peak at δ 3.14, 3.59, 7.78, 6.8-7.7. In final step (Ixia) were synthesized with equal moles of IIa in ethanol and appropriate carbonyl compounds in presence of sodium ethoxide and irradiated at 480 watts for 3 minutes. In conventional method, the process requires over 7 hrs for reflux. The structures were confirmed as follows, IR spectrum of Ixix in KBr showed a band at 1703, 2966, 3300, 1543, 3422, 3348, and 1618. ^1H NMR spectrum in CDCl_3 showed at δ 3.14, 6.78 - 7.71, 4.0 (NH), 3.57. ^{13}C NMR, 63.4, 164.5, 129.3, 125.2, 113.2-151.0, 127.2-141.7, and 126.8-131.2.

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