Synthesis of some derivatives of pyrimidine, oxadiazole and indole in combination by conventional and microwave method

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Abstract

In this work, an efficient synthesis for the preparation of some derivatives of pyrimidine, oxadiazole and indole in combination compounds by 4 steps by using both conventional (4a-i) and microwave methods (Ma_4-Mi_4). The resulting derivatives were characterized by IR, NMR, ^{13}CNMR and mass spectral analysis.

Key words : Pyrimidine, oxadiazole and indole in combination derivatives, IR, NMR, Mass spectroscopy.

Introduction

Pyrimidine derivatives are highly effective in antitumour agent [1], antibacterial activity[2,3], anti lukemic activity[4], HIV induced cytopathic effect[5]. Oxadiazole derivatives are useful in antibacterial activity [6,7,8], anti inflammatory activity[9,10], antitubercular activity [11], anticonvulsant activity [12], anti fungal activity [13,14], analgesic activity [15], insecticidal activity [16,17], anti cancer activity [18], anti HIV [19], plant growth regulating activity [20].Indole derivatives are effective in antibacterial activity [21], anti fungal activity [22,23],antitumour[2][24,25], antiviral [26,27], antioxidant [28], antimicrobial [29], progesterone antagonist [30], anti mitotic potency[31]. On the basis of our observation the present research work was carried out to evaluate the derivatives of pyrimidine, oxadiazole and indole in combination for antimicrobial and anti oxidant activity.

Results and discussion

Pyrimidine, oxadiazole and indole in combination derivative compounds were synthesized and characterized by spectral analysis. The melting point of the synthesized compounds were found out by open capillary tube method. The structure of the synthesized compounds were characterized by its IR,H_{NMR} spectral analysis in which it complies with the normal values.

In the present work 9 derivatives of 5-(4-aryl, 6-methyl –pyrimidin-2-one), 2-imino indolino 1,3,4-oxadiazole (4a-4i) w synthesized by conventional and microwave method.

Scheme

The scheme ends up with four steps. Starting with the synthesis of aryl pyrimidinone in the first step it precedes through the formation of oxadiazole ring, which further condense with isatin to give imino indolinone derivative.

Step I

This step involves the synthesis of 4- aryl-5-carboethoxy 6- methyl 2-pyrimidinone (1a-1i), from urea, ethyl acetoacetate and an aldehyde, which provides the substituted aryl group in the first step to form the derivatives in the later steps, in the presence of an alcohol. The first step products were also synthesized by 20% power in 90 secs by Micro Wave method (Ma_1-Mi_1)

Step II

The esters so produced in the first step are converted to hydrazide (2a-2i), (4-aryl-5-carbonyl hydrazido 6- methyl 2-pyrimidinone) by hydrazine hydrate in this step so that they can undergo ring cyclisation to provide oxadiazole derivativesin the later step. The hydrazides were also prepared by Micro Wave method in 60 secs with 40% power (Ma_2-Mi_2)

Step III

In this step the hydrazides produced in the second step reacts with cyanogens bromide to give amino oxadiazolyl pyrimidinone by the elimination of hydrogen bromide. Formation of the products (3a-3i), 4-aryl 5- (5’ (1’, 3’, 4’, oxadiazolyl 2’ amino) 6 methyl 2- pyrimidinones, takes 36 hours under stirring condition.

Step IV

In the final step compounds (3a-3i), reacts with isatin to form schiff’s base imino indilinones by the elimination of water. All the derivatives of the final step, (5-(4-aryl, 6-methyl –pyrimidin-2-one)- 2-imino indolino -1,3,4-oxadiazole were also synthesized by microwave method (Ma_2-Mi_2) by 40% power in 30 seconds

Materials and methods:

All the chemicals are analytical grade and were purified by the established methods. Melting points and were determined by open capillary tubes method purity and homogeneity of the compounds was routinely determined by thin layer chromatography on glass plates using silica gel G as absorbent and solvent system. Benzene: Ethylacetate: Methanol (8.5:1.4:0.1). Spots were visualized by iodine vapor by irradiation with UV light.^{1}HNMRspectra was recorded on Bruker Ultra shield (300MHZ) spectrometer using DMSO (TMS as internal standard).

Conventional method: Scheme

Step 1: *preparation of ethyl 6-methyl-2-oxo-4-aryl-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxylate (1)*

Urea (0.5 moles), ethylacetoacetate (0.75 moles) and aromatic aldehyde (0.75 moles) were mixed in ethanol (25 ml). Catalytic amount of conc. HCl was added to the mixture which was then refluxed for 3 hours. The contents were kept in refrigerator overnight. The solid separated out was filtered off. The filtrate was further refluxed on a water bath for 1.5 hour. On cooling a solid separated out was filtered and recrystallized from ethanol M.P.210°C

Step 2:*Preparation of 6-methyl-2-oxo-4-aryl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide (2)*

To 0.1 mole of (1) in ethanol (20 ml), hydrazine hydrate (0.1 mole) was added followed by the addition of a catalytic amount of conc. H_2SO_4 (3 drops).The mixture was refluxed for two hours. Excess solvent was removed and on cooling a solid was formed. The solid was crystallized from ethanol. MP = 196°C

Step 3: *Preparation of 5-(5-amino-1, 3, 4-oxadiazol-2-yl)-6-methyl-4-aryl-3, 4-dihydropyrimidin-2 (1H)-one (3) .*

To 0.01 mole of (2) in absolute ethanol (25 ml) an aqueous solution of sodium bi carbonate (2 gm in 5 ml water) was added and stirred for a few minutes at room temperature. 0.01 Mol of cyanogen bromide (1.05 gm) was then added and stirring was continued for 36 hours. Concentration of reaction mixture to ¼ of its volume left a residue which was poured over crushed ice. The solid separated was filtered, dried and crystallized from ethanol.

Step 4: *Preparation of 3-{[5-(6-methyl-2-oxo-4-aryl- 1, 2, 3, 4-tetrahydro- pyrimidin-5-yl)-1, 3, 4-oxadiazol-2-yl]imino}-1, 3-dihydro-2H-indol-2-one(4)*

0.01 Mole of (3) and 0.01 mole of isatin were refluxed in methanol in presence of catalytic amount of glacial acetic acid for 30 minutes and cooled. The solid separated was filtered.

The compounds 4(a-i) were prepared in the same fashion and their characterization data are given in table 1.

Micro wave procedure

All the compounds (4a- 4i) were synthesized by microwave method and their yield and melting points were compared with the conventional products.

***Step I*:**

All the esters in the first step (1a-1i), were synthesized by microwave with 20% power and varying time of 90-130 seconds and their characterization was done.

Microwave method for first step was followed under both the influence and absence of catalyst. Among them only the products synthesized under the influence of catalyst (Conc. HCl) was taken to proceed to further steps due to their better correlation with the conventional products.

***Step II*:**

The esters from both conventional and micro wave method ,(1a-1i) & (Ma_1-Mi_1) were subjected to MW synthesis towards second step with 40 % power and varying time of 60-90 seconds. The reaction was carried out both with and without catalyst.

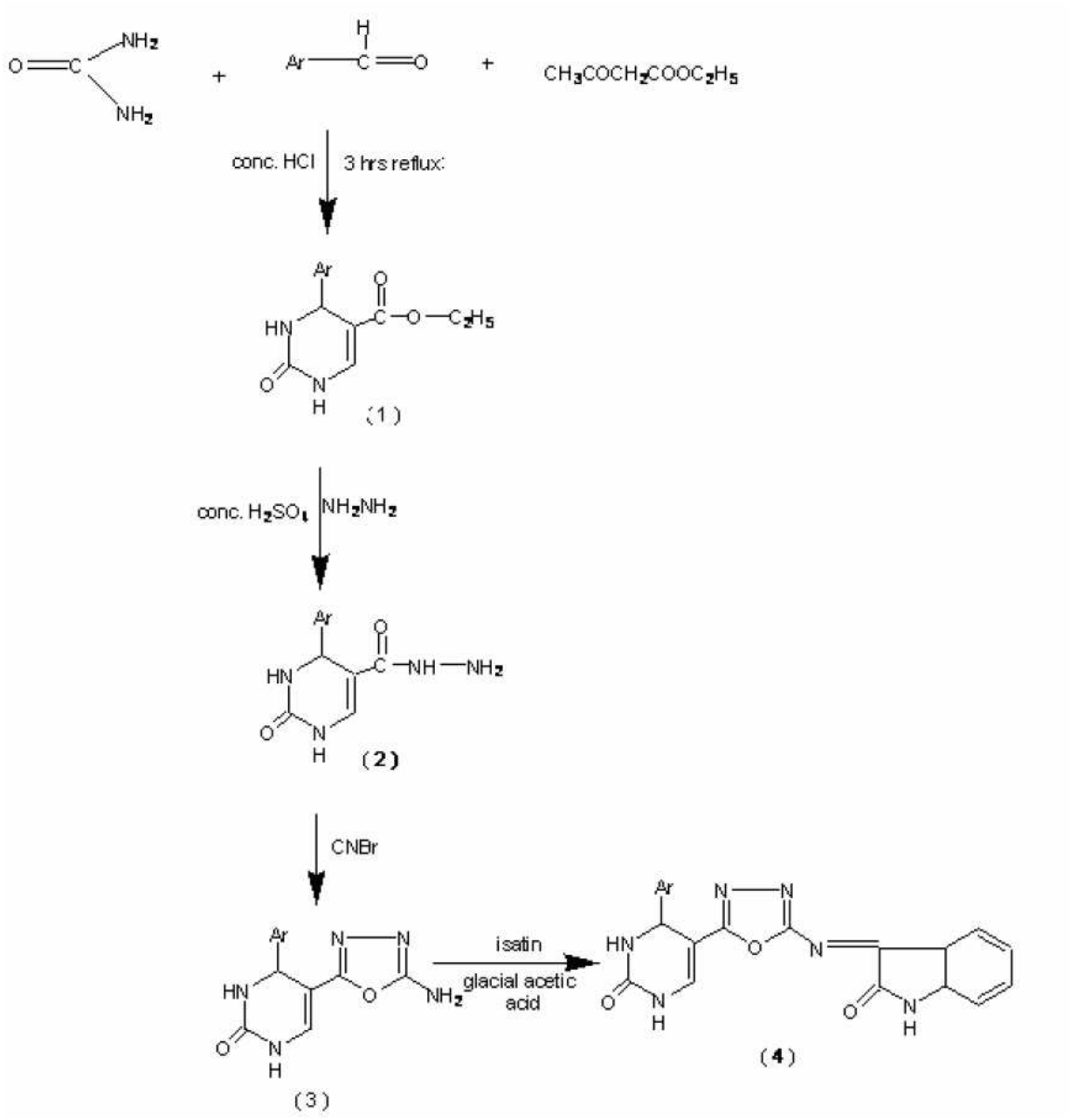
Among them the products synthesized under influence of catalyst (Conc. H_2SO_4) showed better correlation with the conventional products and were taken to proceed further. MW products of second step (Ma_2-Mi_2) prepared from both conventional and MW esters (1a-1i) & (Ma_1-Mi_1) showed good correlation in melting points.

***Step III*:**
Products from MW second step (both the conventional and MW series) [(2a-2i) & (Ma_2-Mi_2)] were subjected to MW synthesis towards third step with varying time and % power. But none of them showed good correlation with the conventional products prepared solely by conventional method.

And thus this step was continued conventionally with both the products of MW and conventional series to get third step products (3a-3i)

***Step IV*:**
Products of third step (both the conventional and MW series) were subjected to MW synthesis toward final step with 40 % power and varying time of 30-60 seconds.
All the products (Ma_4-Mi_4) showed good correlation with the products prepared solely by conventional method.

Scheme-I

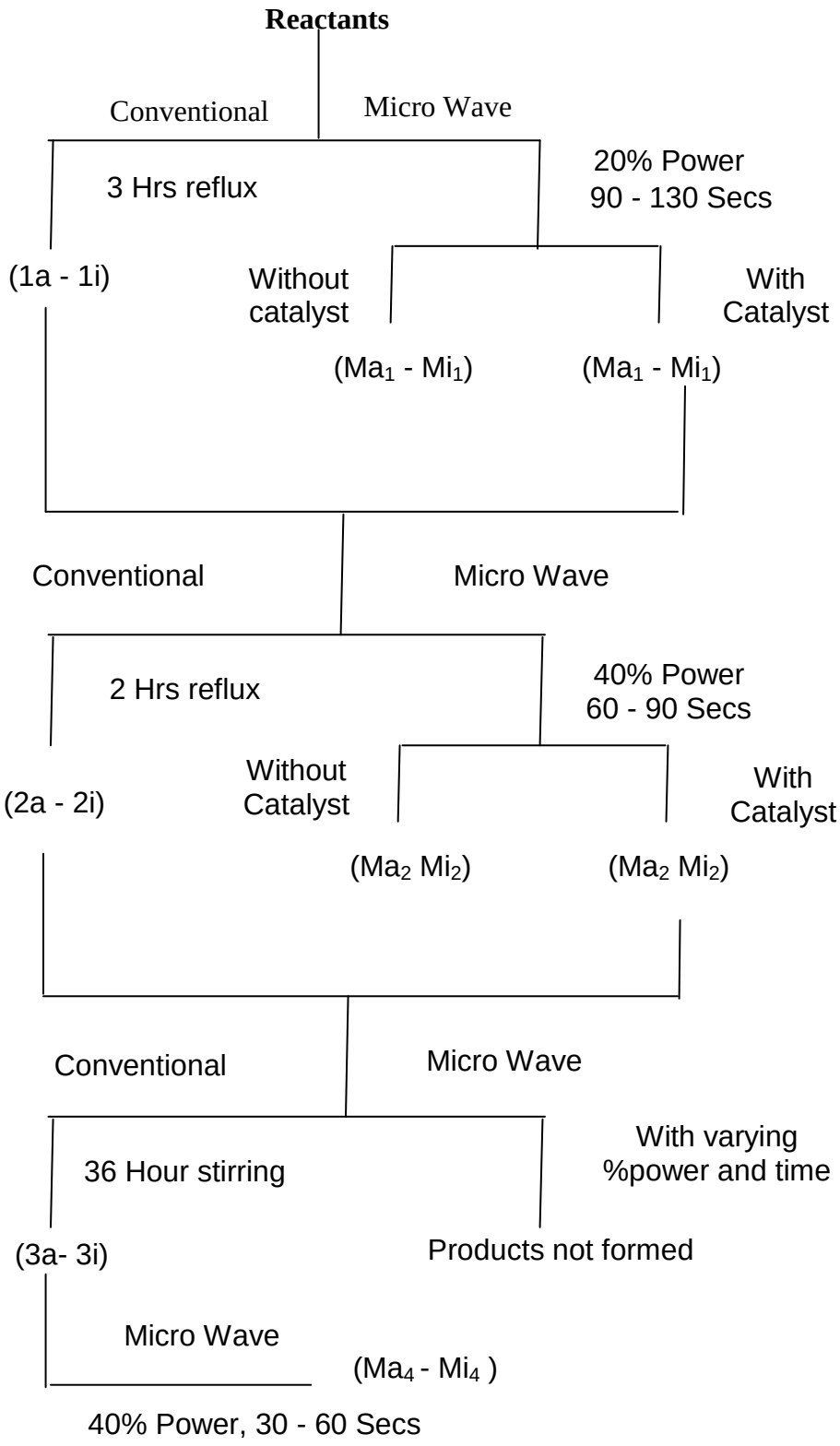


Ar- Benzaldehyde, O-Chloro Benzaldehyde, 4 di chloro Benzaldehyde, 4,5 tri methoxy Benzaldehyde, Cuminaldehyde, m- nitro Benzaldehyde, p- fluro Benzaldehyde,Vanilline, p-dimethyl Benzaldehyde.

Table 1: Melting points of the compounds in different steps of synthesis

Sl. No	Substituents and their products	Ester (°C)	Hydrazide (°C)	Oxadiazole (°C)	Indolinone (°C)
1	Benzaldehyde	207	194	342	184
2	O-Cl Benzaldehyde	215	237	301	240
3	2,4-Dicloro Benzaldehyde	240	216	298	200
4	3,4,5-trimethoxy Benzaldehyde	152	191	231	196
5	4-isopropyl benzaldehyde	151	190	217	248
6	m- Nitro Benzaldehyde	208	230	299	221
7	p-Fluoro Benzaldehyde	170	180	290	208
8	p-Dimethyl amino-Benzaldehyde	252	222	308	297
9	3-Hydroxy,4-methoxy Benzaldehyde	240	225	302	198

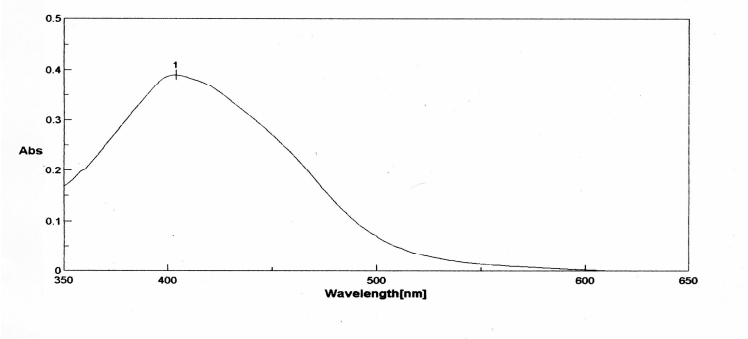
Scheme : Flow chart for microwave synthesis



Comparative table of conventional and microwave method

Compound code		Ar	Molecular formula	Molecular weight	Reaction time		%yield		Melting point		R_f value	
Con	**MW**				**Con (min)**	**MW (sec)**	**Con**	**MW**	**Con**	**MW**	**Con**	**MW**
4a	Ma_4	C_6H_5	$C_{21}H_{16}N_6O_3$	400	30	30	60	85	184	186	0.76	0.76
4b	Mb_4	C_6H_4Cl	$C_{21}H_{15}N_60_3Cl$	434	30	35	70	83	240	237	0.75	0.75
4c	Mc_4	$C_6H_3Cl_2$	$C_{21}H_{14}N_60_3Cl_2$	469	30	40	58	79	200	198	0.72	0.73
4d	Md_4	$C_6H_2(OCH_3)_2$	$C_{24}H_{22}N_6O_6$	490	30	33	56	68	196	195	0.81	0.81
4e	Me_4	$C_6H_4(C_3H_7)$	$C_{24}H_{22}N_60_3$	442	30	55	67	81	248	247	0.4	0.84
4f	Mf_4	$C_6H_4NO_2$	$C_{21}H_{15}N_7O_5$	445	30	60	62	79	222	220	0.70	0.71
4g	Mg_4	4-FC_6H_4	$C_{21}H_{15}N_6O_3F$	418	30	45	58	86	208	205	0.6	0.68
4h	Mh_4	4-$N(CH_3)_2C_6H_4$	$C_{23}H_{21}N_7O_3$	443	30	30	65	87	297	298	0.79	0.79
4i	Mi_4	4-OCH_3, 3-OHC_6H_4	$C_{22}H_{18}N_60_5$	446	30	50	66	78	198	196	0.77	0.77

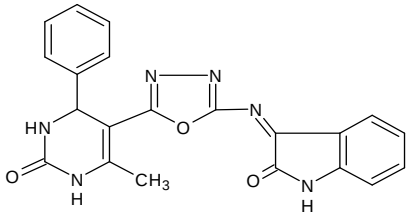
UV/Visible spectrum 4a



λ max 404

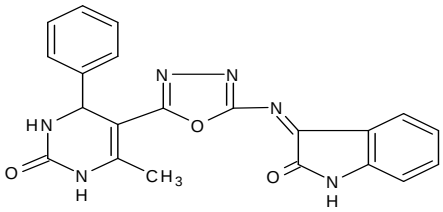
Solvent used Methanol

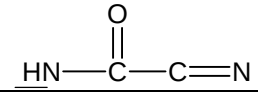
IR Spectrum of the compound 4a



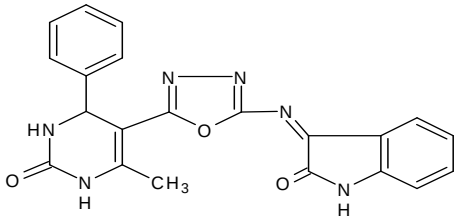
Sl.No	Type of Vibration	Peak No	Frequency in cm^{-1}
1	C=O Aromatic stretching	14	1734.66
2	C-O Aromatic stretching	20	1222.65
3	C-N stretching	19	1347.03
4	N-H stretching	6	3478.95
5	C=C Aromatic stretching	16	1608.34
6	C=N stretching	17	1571.7
7	C-H Aliphatic stretching	11	2927.41

PMR spectral data for compound 4a

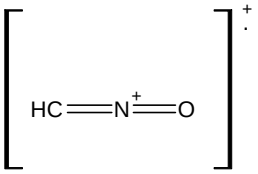


SL. No	Chemical Shift (δ values)	Type of Protons	Number of Protons (integrated height)
1	7.3-7.9	Aromatic-H (multiplet)	8
2	1.26	CH_3 (singlet)	3
3	5.4	$H_5C_6—C—NH—C=O$	1
4	9.3		1
5	5.1	$H_3C—C—NH$	1
6	6.9	CH Attached to aromatic ring	1

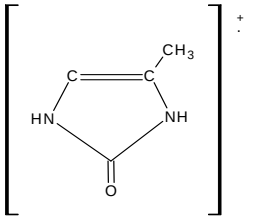
Mass Spectral data for compound 4a.



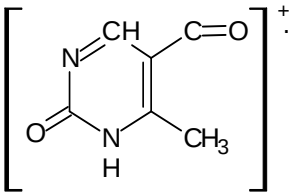
1. Mass peak at 43 corresponds to the fragment ion with the following structure



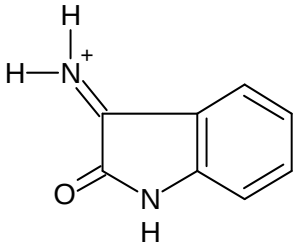
2. Mass peak at 97 corresponds to the fragment ion with the following structure



3. Mass peak at 137 corresponds to the fragment ion with the following structure



4. Mass peak at 147 corresponds to the fragment ion with the following structure



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