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Microwave Assisted Synthesis of Nitrogen and Hydroxyl Containing Bioactive Compounds as Drug Motif

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Abstract: ***Organic compounds not only make up life on earth but a wide variety of classes also have healing properties like anti-bacterial, -diabetic –fungal, -HIV, -inflammatory, -tubercular etc. This therapeutic importance of carbon containing moieties especially those containing nitrogen and hydroxyl functionalities attract researchers to explore more productive and reproducible synthetic avenues like microwave-assisted approach rather to remain focused on conventional processes that are time consuming and low in purity. Moreover, due to high consumption of chemicals for prolonged time, it adversely affects environment. This key reason forces chemists to adopt microwave-assisted synthesis to achieve desired compounds. This eco-friendly technique uses microwave irradiations that speed up reactions in comparatively less time and offers high yield of products with purity. This research proposal aimed to fabricate some bio-active organic compounds (Pyrazole and alkanol derivatives) via microwave-assisted methods using interesting synthetic schemes.***

Keywords: Pyrazole, Alkanol, Microwave, Chalcone, Grignard reagents

1. Introduction

The captivating position of bioactive molecules in the field of medicines and drug discovery urges the synthetic chemists to evaluate easy and efficient routes. Microwave-assisted synthesis has become an important tool in this regard. Since its emergence in the field of organic Chemistry in 1980, this technique has captured remarkable pace in organic synthesis showing tremendous advantages over traditional ways adopted in organic synthesis. Microwave irradiation mediated synthetic routes observe fast rate of reaction thus reducing reaction time. The major summit of this technique makes it prior choice of chemists as compared to conventional synthesis. Uniform heating of reaction system by microwaves offer perfect temperature profile resulting advance reproducibility and selectivity. Superheating effect also plays an important role to attain faster reaction rates in microwave cavity [1]. In addition, reactions that proceed under these conditions yield high products with less side reactions. Microwave synthesis is eco-friendly technique yielding cleaner reactions by cutting off the usage of harmful solvents.

Increased demand of industries especially pharmaceutical industry emphasize the chemists to produce a large number of different chemical entities by cutting down the reaction time, this demand is sufficiently being fulfilled by microwave-assisted synthesis. Various classes of organic compounds possess potent biological properties e.g. anti-bacterial, -fungal, -inflammatory, -HIV, -diabetic, -tubercular etc. This therapeutic importance of Carbon containing moieties compels to explore more productive and reproducible synthetic methods i.e. “Microwave-assisted synthesis”.

Research has indicated diverse biological activity of hydroxyl group, nitrogen and aromatic ring moieties in particular [2]. Keeping this in mind, it is expected that various alkanols (alcohols) with aromatic rings and nitrogen containing ring (e.g. heterocyclic pyrazole ring) display bioactivity which facilitate their interaction with targeted molecules [3]. The present research work was aimed to devise eco-friendly and easy synthesis of bioactive nitrogen containing pyrazole (most particularly pyrazoline) and alkanol derivatives. The reaction schemes were multistep involving chalcone intermediate. The targeted molecules were achieved via “Microwave-assisted synthetic route” which was proven excellent in all respects. Synthesized pyrazoles and alkanol were expected to show anti-microbial and anti-inflammatory properties respectively.

2. Literature Survey

Antimicrobial pyrazole derivatives synthesized by fusion of pyrazole with pyrone and pyridine [4]and from cyclo addition of α-β-unsaturated carbonyl compounds with ketones [5] and using sulphur containing compounds [6] have been reported. Inhibitory action of various pyrazole containing moities has been executed against urease [7] and microorganisms [8]. Moreover antioxidant properties have also been investigated for pyrazole derivatives starting from α, β-dibromo, 4, 4’-difluorechalcones and hydrazine derivative [8]. Pharmacologically active alkylaminealkanol, esters [9] and bioactive alkanolamine synthesis [10] has been carried out and reported in literature.

Contemporary wounds can be healed by tertiary phenyl alkanol or alkylphenylalkanol and halophenylalkanol. This class of compounds shows wide range of activity as microbial scrub, anesthetic and cell regulator [11]. Some substituted alkanols of 1-{3- (heteroarylmethoxy) phenyl} have been in practice for treatment of ulcer, myocardial infection, psoriasis, asthma, arthritisand stroke [12]. Moreover a mixture of cyclolkanols is used as insect repellent [13]. 1- (p-alkanoylphenyl) alkanols have been proved good hypolipidemic and anti-diabetic agents [14].Various phenylalkanol containing thio or oxy group are

used as agrochemicals [15].Alkyl (aryl) substituted tertiary alcohols have been observed as anti-inflammatory and antimicrobial agents [16].

3. Material and Methods

Melting points were determined using Gallenkamp melting apparatus. UV spectra were recorded within the range 200-600 nm on Hitachi U-2800 spectrophotometer. FTIR spectra were recorded within the range 400-4000 cm^{-1} as KBr pellets on a Midac M-200 spectrometer (USA) while mass data were recorded on GC-MS Schimadzo QP- 210 spectrometer (Japan). For microwave-assisted synthesis, microwave oven DW-180, 2450 MHz, 950W was used.

3.1 Synthesis of pyrazole derivatives [17]

Starting from acetophenone, three derivatives of pyrazole were prepared in two steps as shown in figure 1.

- The first step involved the synthesis of chalcones which served as intermediate.
- The chalcone was reacted with isonicotinic acid hydrazide to form pyrazole derivatives

3.1.1 STEP 1

A reaction mixture containing acetophenone (1.2 mL), solution of p-substituted benzaldehyde (1.1g) in NaOH (9.09 mL) and ethanol (2.8 mL) was treated under microwave irradiation. The crude product was refrigerated overnight. It was filtered, washed with cold water until the basic product became neutral then washed with cold ethanol successively. Precipitate thus obtained were dried and recrystallized with ethanol.

3.1.2 STEP 2

The chalcone (10 mmol) solution prepared in ethanol was treated with isonicotinic acid hydrazide (10 mmol) in presence of glacial acetic acid in microwave oven. Crushed ice was added to the mixture and it was kept at room temp. Overnight. The resulting product was filtered off and washed with water. The yellow precipitates were dried and recrystallized by using ethanol. Needle like crystals were obtained.

3.2 Synthesis of substituted alkanols [16]

The synthesis was accomplished in three steps as shown by figure 2.

3.2.1 Synthesis of substituted chalcones

Four chalcones were prepared by utilizing substituted benzaldehyde and acetophenones. A mixture of benzaldehyde and its derivative (1.1g), NaOH (9.09 mL) and ethanol (2.8mL) was reacted with acetophenone/substituted acetophenone (1.2mL) under microwave irradiation and subsequent work up was carried out as mentioned in previous section.

3.2.2 Synthesis of Grignard reagents

Four types of Grignard reagents were prepared by irradiating alkyl halide (1.3 g) with magnesium ribbon (0.25g) in presence of THF using silica bath.

3.2.3 Synthesis of substituted alkanols

Chalcone (1.2 g) was added to freshly prepared solution of alkyl magnesium halide in ether. The reaction mixture was subjected to microwave irradiations. The resulting compound was filtered and recrystallized with ethanol. The final product was obtained in crystalline form.

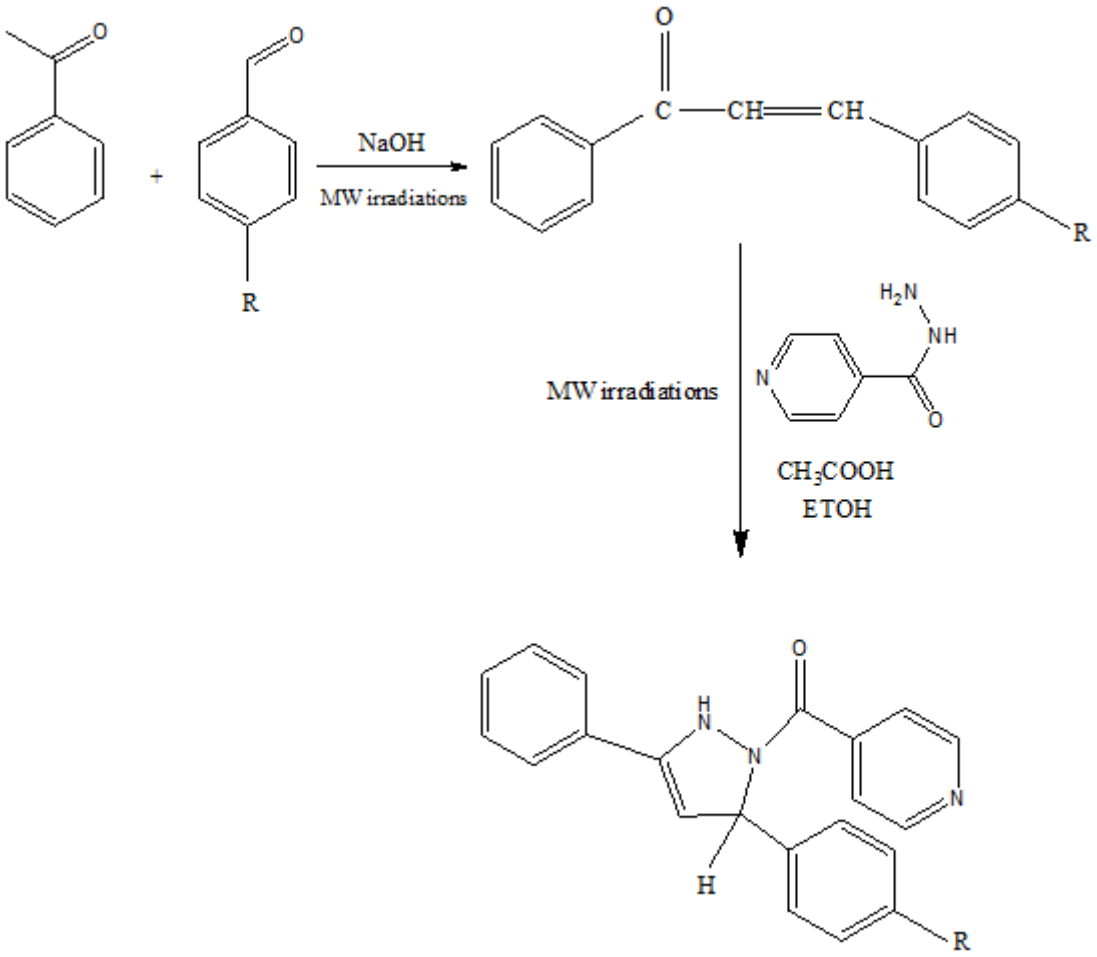

Figure 1: Showing synthesis of pyrazole derivatives

Where 1.R=Br 2. R=Cl3. R=H

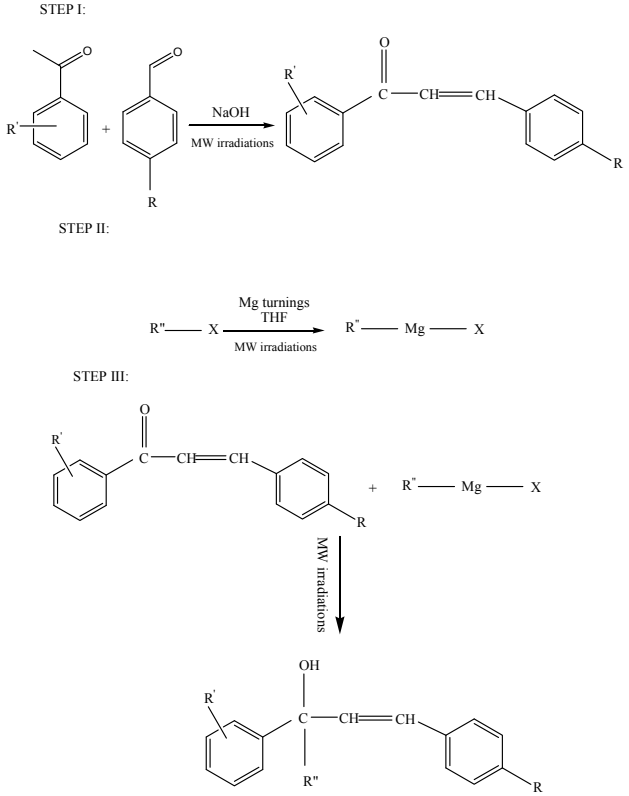

Figure 2: Systematic scheme showing the synthesis substituted alkanols

Where

	R	‘R	“R	
4.	H	H	C2H5	
5.	2-OH	H	C6H5	
6.	2-OH	4-Cl	C6H5CO	
7.	2-OH	4-F	CH2=CH-CH2-	
8.	2-OH	3-OH	--	
9.	3-OH	4-Cl	--	

4. Results and Discussion

Three pyrazole derivatives (1-3) were obtained in good to excellent yields asgiven in T-1 and shown by figure 1.

Table 1: Synthesis of pyrazole showing time and yield

Compound	*Time (sec)*	*Yield (%)*
1	80	82
2	60	79
3	100	140

Irradiation time for chalcones synthesis was 60, 60 and 130 seconds for compounds 1, 2, 3 respectively.

Four alkanol derivatives were prepared as:

STEP 1: Different chalcones were prepared by this method as shown by fig.2. Table-2 shows the time required for the synthesis of chalcones which act as an intermediate in both cases i.e. pyrazole and alkanols synthesis.
STEP 2: Different Grignard reagents were successively prepared under microwave within seconds as shown in T-3
STEP 3: Synthesis of substituted alkanols by the reaction of chalcones with Grignard reagents

Table 2: MW Synthesis of different chalcones showing physical appearance and time in seconds

Sr. No	*Chalcones*	*Physical Appearance*	*Time Sec.*
1	Benzalacetophenone	Yellow ppt	100
2	3`-hydroxy-4-chlorochalcone	-	300
		Brown ppt	50
3	2`-hydroxychalcone	Yellow ppt	65
	2`-hydroxy-4-	Yellow ppt	90
4	chlorochalcone	-	250
5	2`-hydroxy-4-fluorochalcone		
6	2`-hydroxy-3-hydroxychalcone		

Table 3: Synthesis of Grignard reagents under MW showing time in seconds

Sr. No	*Grignard reagent*	*Time (sec)*
1	Ethyl magnesium iodide	70
2	Phenyl magnesium bromide	170
3	Benzoyl magnesium chloride	120
4	Allyl magnesium bromide	160

Table 4: Melting point and λ_{max} of synthesized compounds

Compd. No.	*Melting point in ^0C*	λ_{max} *(nm)*
1	190	318
2	320	316
3	232	300
4	57	290
5	135	386
6	105	382
7	184	288

The value of λ_{max} indicates n π^* electronic transitions. It indicates presence of C=C, C=O, R- NH in pyrazole derivatives, also gives evidence of O-H and C=C group in alkanol compounds. Aromatic character is also evident from this data.

FTIR analysis was carried out using Midac M-2000 FTIR spectrophotometer. Information obtained from FTIR spectra are reported below.

Compound 1:
3458, 1599 (N-H), 3097 (Arst), 684 (Ar bend), 1524 (C=C), 1657 (C=O), 3050 (C-H), 605 (C-Br), 1322 (C-N) cm^{-1}

Compound 2:
3405, 1636 (N-H), 3050 (Arst), 823 (Ar bend), 1560 (C=C), 1684 (C=O), 3000 (C-H), 775 (C-X), 1211 (C-N) cm^{-1}

Compound 3:
3500, 844 (N-H), 3055 (Arst), 690 (Ar bend), 1592 (C=C), 1657 (C=O), 3007 (C-H), 1211 (C-N) cm^{-1}Values of N-H stretching and C=C is much clear in spectrum and corresponds to reported values in literature. Presence of halide group in 1 and 2 is indicated by IR bands in expected region.

Compound 4:
3621 (O-H), 1662 (C=C), 3092 (Ar), 1300 (C-O), 2933 (C-H) cm^{-1}

Compound 5:
3378 (O-H), 1640 (C=C), 2990 (Ar), 1104 (C-O), 3000 (C-H) cm^{-1}

Compound 6:
3298 (O-H), 1631 (C=C), 2998 (Ar), 1216 (C-O), 3023 (C-H), 748 (C-Cl) cm^{-1}

Compound 7:
3382 (O-H), 1625 (C=C), 3087 (Ar), 1710 (C=O), 1211 (C-O), 2997 (C-H), 1387 (C-F) cm^{-1}

In compound 4 absorption frequency 3621 cm^{-1} shows free O-H group of alkanol.While in samples 5, 6, 7 values ranging from 3298-3382cm^{-1} is indication of hydrogen bonded O-H group. C=C stretching values are also accurate.

C-O value is indicative of the alcoholic C-O group in all samples.

GC-MS Schimadzo QP-2010 spectrometer (Japan) was used to attain mass fragmentation pattern of compounds. Injection temperature was 210^0C which remained stable for two minutes and raised upto 280^0C. The mass spectra of synthesized compounds showing base and molecular peek is given in table 5.

Table 5: Mass spectra of synthesized compounds showing base peak

Compound	*Base peak*
1	45.05
2	45.05
3	45.05
4	45
5	45

6	45
7	45

5. Conclusion

From the results of experiments and investigation it was concluded that microwave-assisted synthesis give the clean reaction, high yield of products, shorter reaction time, ease of workup and use of various substrates which make it useful and attractive strategy for the synthesis of important bioactive compounds under safe and environment friendly conditions.

Mass spectra of pyrazole compounds give base peak at 45 .This value corresponds to the fragment that is produced by cleavage of pyrazole ring from double bond. m/z 69 gives information about fragment C_3H_3. Peak at 44 is produced due to $C_2H_4NH_2$ fragment ion. Value of m/z at 73 shows substituted amine. Loss of halide from aromatic ring gives a signal at m/z 51.

Alkanol compounds produced base peak at m/z 45 which arises due to the fragment produced by cleavage of aliphatic chain from double bond and from all aromatic groups $RCH{=}OH^+$. Molecular ion peak was in accordance with the fragmentation pattern. Loss of water and loss of alkene is also shown by peaks in mass spectra.

6. Future Scope

The reported research proposal has offered an avenue for coming researchers in the field of medicine. Microwave-assisted synthesis of pyrazole and alkanol derivatives specifically and nitrogen/hydroxyl containing moieties in general can be utilized for commercial use. Reduced reaction time, improved purity of products and versatility of reactions that can be accomplished through this technique is the key for the success of this eco friendly technique. This can be utilized to cut down the expense for the synthesis of drugs that is especially important for research in the developing countries.

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