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MICROWAVE - ASSISTED SYNTHESIS OF NOVEL PIPERIDONE DERIVATIVE BEARING AMINO-ARYL MOIETY AND THEIR ANTI-MICROBIAL ACTIVITY ASSESSMENT

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ABSTRACT

A facile synthesis of new-fangled phenyl united piperidine moieties within the main cyclic

chain was synthesized through the Michael addition reaction of phenylethyl acetamide with novel chalcone in a silica gel medium consisting of sodium hydride has been represented. It's a comparative study of synthesizing compounds by conventional as well as non-conventional microwave irradiation in a commercially modified microwave oven and conjointly confirms the attainable intervention of specific microwave effect. The structures of newly synthesized compounds were characterized by FT-IR, UV-Vis, NMR (^{13}C, ^{1}H) and GC-Mass the synthesized compounds were evaluated for their *in vitro* anti-microbial activity against a variety of microbial strains. The biological screening results indicated that some of the compounds showed significant anti-bacterial and anti-fungal activities.

KEYWORDS: Piperidone, Phenyl ethyl acetamide, Michael addition reaction, Microwave effect, Anti-microbial activity.

INTRODUCTION

Heterocyclic compounds show a broad spectrum of biological activities[i] among them nitrogen heterocycles were known to have variety of pharmacological activities like anti-arrhythmic[ii] anti-microbial and anti-tumor. Especially the Piperidinoes are reported for a wide varieties of therapeutic values such as NEP and ACE activity[iii-iv] Anesthetic[vi] Anti-arrythmetic[vii] Anti-convulsant[viii] central nervous system antidepressant drug[ix] Anti-inflammatory[x]. An attractive feature of chalcone is that they provide as starting materials for the synthesis of a different class of naturally occurring alkaloids and widely distributed heterocyclic compounds[xi].

Interest in developing environmentally benign and solvent-free reactions has exaggerated dramatically[xii]. So, operationally easy catalytic processes that circumvent the utilization of cyan genetic materials became a robust tool in constructing an organic transformation[xiii]. One of these novel synthetic methods is to carry out reactions on the

surface of solids or solid supported reagents[xiiii]. Organic reactions were found to occur with efficiency and selectively in the solid state reactions. Various methods have been reported for the preparation of Piperidinoes, including addition of an ester or amide enolate to a nitrile,tosyl imines, imidoyl halides and via addition of enamines or ketimines to activated carboxylic acid derivatives[xv-xviii]

The Michael reaction is one of the most important carbon-carbon bond-forming reactions.[xix] A variety of Michael acceptors, such as α, β - unsaturated ketones, aldehydes, esters and nitrils, can be used in this reaction, which can be readily transformed into a range of different functionalities[xx].

The traditional synthetic protocols for the above Piperidinoes intermediates and heterocyclic products suffer from some disadvantages such as low yield, lack of easy availability/ preparation of the reagent, delayed reaction time, multiple steps, need for special apparatus and harsh reaction conditions. In this construction and by knowing the advantages of microwave reactions, we felt that the synthesis of the above Piperidine compounds can also be successfully obtained by direct Michael addition of novel chalcone **3** with phenyl ethyl amide **4** under microwave irradiation.

Our interest was to study the synthesis of piperidone compounds **5** by one pot Michael addition process. The main aim of this project is to develop efficient synthetic methodology which requires lesser reaction time and reduces the number of steps involved in the synthesis of **5**. In order to achieve our aim, synthesis of **5** was carried out by a two-step reaction.

We first synthesized novel chalcone **3** for this a Claisen-Schmidt condensation reaction of dimethylaminobenazaldehyde**1** with acetophenone **2** produced the corresponding chalcones (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one **3** respectively.

EXPERIMENTAL SECTION

Material and Methods

Solvents were purified and dried by standard procedures and distilled prior to use. Commercially available reagents were purchased from Merck and Fine chemical India and Melting points were measured on an electrothermal KSB1N apparatus. IR spectra were recorded in the matrix of KBr with JASCO FT-IR-680 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a FT-NMR Bruker Avance Ultra Shield Spectrometer. The results agreed favorably with the calculated values. TLC was performed on TLC-grade silica gel-G/UV 254 nm plates.

Procedure for synthesis of (E)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one **3**

A mixture of dimethylaminobenzaldehyde (1.49g, 0.01 mole) and acetophenone (1.25mL, 0.01 mole) in dry ethanol (25 ml) was refluxed with added NaOH (1.0 g), monitoring the progress of reaction by TLC. The reaction was stopped at the appropriate point 6 h, the reaction mixture was worked up and subjected to column chromatography over silica gel (60-120 mesh) using 02:98% ethyl acetate in petroleum ether as eluent. Orange crystal, m.p. 180-185°C; 82% yield; IR (KBr, ν_{max}, cm^{-1}): 3257, 3051, 2908, 2111, 1644, 1597, 1556, 1525, 1222; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, 2H, *J* =7.00 Hz, phenyl-C_2,C_5-H), 7.806 (d, 1H, *J* =15 Hz, benzylic-H), 7.55-7.46 (m, 5H, phenyl-H), 7.34 (d, 1H, *J* = 15.5, benzylic-H), 6.70 (d, 2H, *J* = 9, aminophenyl-C_3,C_4-H), 3.04 (s, 6H, N-CH_3); ^{13}C NMR (120 MHz, $CDCl_3$): δ 190.75, 152.07, 145.88, 139.12, 130.42, 128.46, 128.33,117.00, 111.85, 40.14; GC-MS: m/z [M+1] 252.

Procedure for Synthesis of substituted 4- (4-(dimethylamino) phenyl)-1,3,6-triphenylpiperidin-2-one **5**

Conventional method (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one (3) (2.51g, 0.01 mole) in dry toluene, sodium hydride (0.1 molar equiv) and *N*,2-diphenylacetamide (4) (2.12g. 0.01 mole) were added. The resultant mixture was stirred at

90-100°C for 5h, cooled and then the reaction mixture was added to a large amount of water. The crude product was purified by recrystallization from ethanol.

Microwave method (2.51g, 0.01 mole) of (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one **3** and N,2-diphenylacetamide (2.21g, 0.01mole) (4) are dissolved in small amount of DMF and a catalytic amount of sodium hydride is added. Then the reaction mixture is heated for 3 minutes at 140°C in 250 watts. A yellow colour solid is obtained; it is cooled to room temperature then poured into 1000 mL cold water, neutralized with dilute HCl, filtered, dried and washed with 200 mL of ethyl acetate. It was recrystallized from ethanol; a pure yellow crystalline powder is obtained with good yield. The physical data obtained exactly matched with the product formed in the conventional method. **Conventional**: Yield 75%; **Microwave**: Yield 90%; m.p. 130-135 °C; 82% yield; IR (KBr, ν_{max}, cm^{-1}): 3373, 3058, 2888, 2789, 2050, 1672, 1598, 1511, 1258; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10-7.18 (m, 19H, 4-phenyl ring), 5.10 (t, 1H, *J* =7 Hz, piperidone-C_6-H), 4.14 (d, 1H, *J* = 7.5 Hz, piperidone-C_3- H), 3.65 (t, 1H, piperidone- C_4-H, benzylic-H), 3.03 (s, 6H, $N(CH_3)_2$), 2.47 and 1.80 (d, and t, 2H, piperidone-C_4- H); ^{13}C NMR (120 MHz, $CDCl_3$): δ 173.70, 149.22, 138.18, 136.68, 134.65, 131.26, 131.13, 128.97, 128.31, 128.14, 126.47, 112.50, 66.33, 50.88, 43.73, 40.39, 34.96; GC-MS: m/z [M^+] 446.

BIOLOGICAL ACTIVITY

Anti-bacterial activity: Anti-bacterial activity of the newly synthesized compounds **3-5** were determined *in vitro* for anti-bacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus pyogenes* by paper disc diffusion method with DMF as solvent control nutrient agar was employed as culture media. After 24h hot incubation at 37°C the zone of inhibition were measured in mm[xxi].

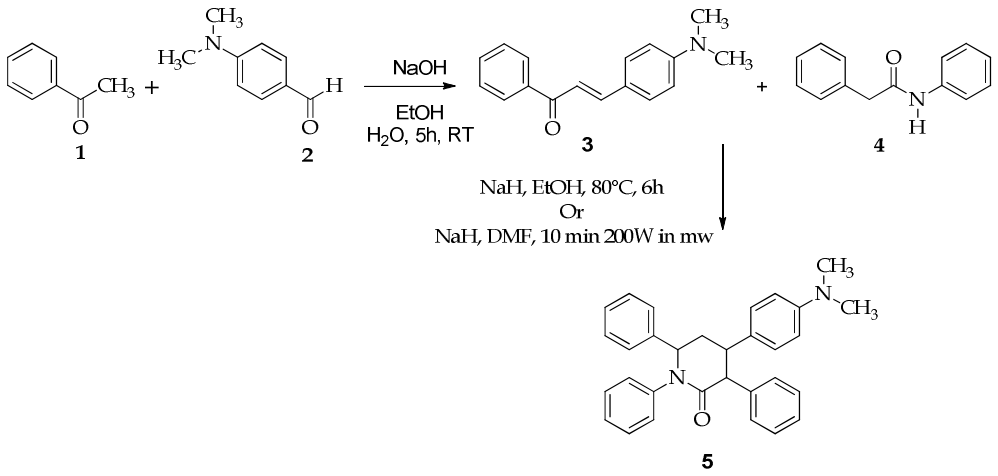
Anti-fungal activity: The compounds **3-5** were screened for their anti-fungal activity against *Aspergillus niger*, *Pencilium chrogenum*, *Fusarium oxysporum*, *Trigoderma veride* by paper

disc diffusion methods at concentration of 2 and 5 mg/mL with DMF as solvent control and nutrient agar was employed as culture media. After 48h incubation at 25°C the zone of inhibition were measured in mm[xxii].

RESULTS AND DISCUSSION

We first synthesized novel chalcone **3** for this a Claisen-Schmidt condensation reaction of Dimethylaminobenazaldehyde **1** with acetophenone **2** produced the corresponding chalcones (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one **3** respectively.

Scheme 1



The structures of the new chalcones **3** were established and confirmed on the basis of their spectral data (IR, GC-MS, ^{1}H NMR and ^{13} C NMR)[xxiii]. Thus, the mass spectrum of compound **3** as molecular formula $C_{17}H_{17}NO$ m/z (%): 252 (60) [M+1]; IR spectrum of revealed the presence of aromatic C-H stretching at 3051 cm^{-1}, methyl C-H at 2908 cm^{-1} and C=O absorption at 1644 cm^{-1}; the ^{1}H-NMR spectrum showed six protons of two CH_3 as a singlet at δ 3.04 ppm and α, β - unsaturated benzylic proton appear at 7.78 and 7.99 ppm. ^{13}C-NMR spectrum showed a signal at δ 40.14 ppm and 40.67 ppm in the region of secondary carbon atom for C-H and disappearance of a signal at the olefinic carbon region confirmed

the structure **3**, The compound **3** was evaluated for effect of solvent on the IR and UV spectra of Claisen-Scmidt condensation reaction.

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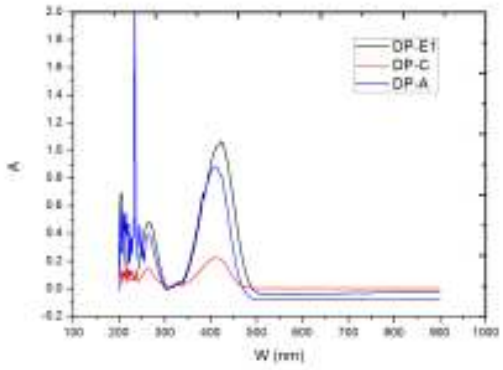
In the solvent effect on the UV-vis spectra of (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one **3,** $\pi \longrightarrow \pi^*$ transition were observed in all the solvent in the range of 205 nm. In $CHCl_3$ it is observed at 204 nm, in acetonitrile λ_{max} is slightly increased to 207.45 nm. While in highly polar protic solvent it has decreased to 204.13 nm. These absorptions may be attributed to $\pi \longrightarrow \pi^*$ transition. The solvent effect in the intensity of λ_{max} of n to π^* transition is higher than that of π to π^* transition.

Fig. 1



Effect of solvent on the IR spectrum of KBr pellet indicates (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one **3** the presence of carbonyl group appears at 1644 cm^{-1} and aromatic C-H stretching appears as a 3051 cm^{-1}. In ethanol (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one **3** prefers to exhibit keto-enol tautomerism as it was observed from weakening of the intensity of carbonyl absorption and in high dilution it disappears and appearance of -OH stretching frequency at 3608 cm^{-1}.

In less aprotic solvent like acetonitrile and chloroform the enol form exist as shown by the weak carbonyl absorption and comparatively strong -OH absorption at 3664cm^{-1}. In chloroform solvent the -OH seems to be little and C=O bond appear light sharp.

(Scheme 1) The second step Michael addition reaction of chalcones **3** with *N*,2-diphenylacetamide **4** and sodium hydride in microwave oven conditions 200W in 5 min gave the compound 4-(4-(dimethylamino)phenyl)-1,3,6-triphenylpiperidin-2-one **5.** The reaction was completed in 30 min as evident from TLC (petroleum ether: ethyl acetate (85: 15, v/v)). After the completion of reaction as evident from TLC showed the appearance of a new spots. Then the reaction mixture was poured into an ice-cold water; the yellow precipitate was filtered, dried and purified through column chromatography; the yield was 80% and m.p is 130-135°C. The identity of **5** was established by analysis via FT-IR: disappearance of the characteristic stretching of C=O at 1664 cm^{-1} and an appearance of amide stretching at 1715 cm^{-1}. Furthermore the disappearance of carbonyl carbon signal at 190.15 ppm and

appearance of signal at 179.23 ppm from the ^{13}C-NMR spectrum confirmed the functional group modification.

On comparing the ^{1}H-NMR spectrum of **5** with **3**, it was observed that amine methyl proton signal was unchanged at 3.04 ppm and appearance of a two proton triplet at 2.30 ppm and 2.80 ppm for CH_2 H_a, H_b proton, a quartet for one protons at 3.68 ppm for C_3-H, one proton doublet from 4.31 ppm for C_2-H and C_5-H triplet at 4.8 ppm confirmed the Michael addition reaction and the product **5**.

Anti-bacterial activity: The resulted (3-5) compounds were screened for anti-bacterial activity at a concentration of 10 mg/mL using DMF as control, Ciprofloxacin 100 mg/disc used as standard. The compound 3 showed moderate activity against *Escherichia coli* and *Staphylococcus aureus*, the compound 5 exhibited high activity against *Bacillus subtilis* and moderate activity against *Staphylococcus aureus*. The compounds 3, 4 and 5 possess weak activity *Pseudomonas aeruginosa* and *Staphylococcus pyogenes.***Table -1**

Anti-fungal activity: All the three compounds were also screened for anti-fungal activity. However compounds 3 showed marked activity against *Pencilium chrogenum* and *Trigoderma veride* (Fig. 7). The compounds 5 showed good activity against *Fusarium oxysporum* and week activity *Aspergillus niger*, *Pencilium chrogenum* and *Trigoderma veride.***Table -1**

Table -1:Biological Activity Data

Compounds	**Anti-bacterial activity**					**Anti-fungal activity**		
	E. coli	*S. ureus*	*B. subtilis*	*P. aeruginosa*	*S. pyogenes*	*F. oxysporum*	*A. niger*	*P. chrogenum*
3	++	+	-	-	-	+	+	+

4	-	-	-	-	-	+	-	+
5	+	++	+	-	-	++	+	+

Inhibition zone diameter in nm: (-) <11 mm, (+) 11-14 mm, (++) 15-18mm, standard (+++) 22-26 mm.

CONCLUSIONS

In summary, new piperidone derivatives containing amino-aryl moiety have been synthesized through the microwave irradiation method. This synthetic strategy allows the construction of piperidine ring system, by Michael addition protocol; Microwave reduced the reaction time from 6 hours to 3 minutes and enhanced the yield considerably. It can be determined from anti-microbial screening against a panel of human pathogens that many of the above synthesized derivatives are found to be highly active, compared to standard drugs against *Staphylococcus aureus* and *Fusarium oxysporum* bacterial pathogens, influences the activity. The present study throws light on the identification of this new structural class as anti-microbials which can be of interest for further detailed preclinical investigations.

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