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Microwave assisted synthesis of novel piperidone derivative comportment amino-aryl moiety and their crystal structure assessment

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Abstract: Simplistic synthesis of new phenyl bearing piperidone moieties within the main cyclic chain was synthesized through the Michael addition reaction of phenylethyl acetamide with novel chalcone. 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 compound novel chalcone were evaluated crystal structure X-ray diffraction patterns.

Keywords: Piperidone; Phenylethylacetamide; Michael addition reaction; Microwave effect.

Introduction

Heterocyclic compounds embrace a special place among pharmaceutical significance, natural products and synthetic compounds, Nitrogen heterocyclic containing a piperidinone ring is a lot found in biologically active molecules [1, 2]. Many piperidinone moieties have also been shown to possess diverse therapeutic activities such as Dipeptidyl Peptidase IV Inhibitors [3], anticancer [4], analgesic [5], anti-inflammatory [6], and local anaesthetic and antimicrobial activity [7, 8]. Anticonvulsant [9]. The piperidone moiety ring anticoagulant on the market is effective for the prevention and treatment of thromboembolic disorders [10].

However, due to the narrow therapeutic window and highly variable dose response among individuals (food interactions, drug–drug interactions, genetic polymorphisms), careful monitoring is required to provide an antithrombotic effect while minimizing the risk of severe bleeding, 2-piperidone providing a noninvasive metabolite biomarker that can be potentially used in to monitor CYP2E1 activity [11], it was envisaged that a new series of aryl Bearing piperidones and their corresponding, α,β–unsaturated carbonyl compounds would result in compounds of potent biological activities [12].

The piperidine ring is a ubiquitous structural feature of many alkaloid natural products and drug candidates [13]. Recent 10-year period there were thousands of piperidine compounds [14-17]. A stereoselective synthesis of substituted piperidines has appeared recently, the piperidones are somewhat less prominent, but often they serve a role as advanced intermediates prior to their conversion to piperidine [18]. In the last few years, greener reactions have attracted much attention in the world of chemistry, because of their convergence virtue, easy completion, mainly high yields of products, high atom economy and selectivity.

The Claisen-Schmidt condensation is one of reaction which can be used to synthesis of piperidone. This reaction is common used for carbon-carbon bonding formation because it's simple and environmental friendly [19-21]. Along with those reasons, this

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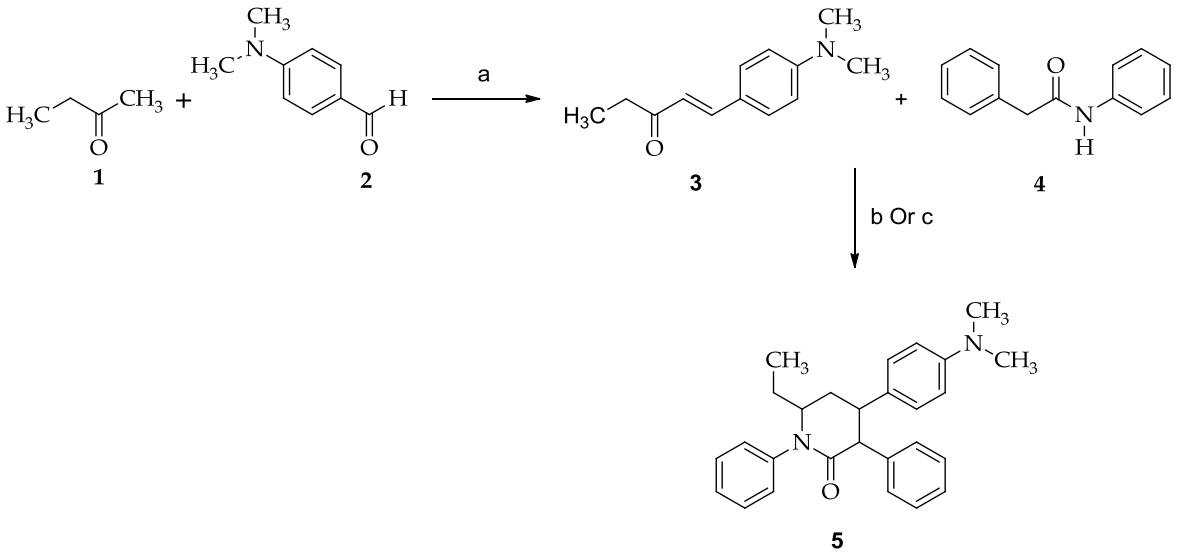
reaction is able to do combinatorial chemistry approach.

We described the first Claisen-Schmidt reaction between chalcone derived from aromatic aldehydes and an aliphatic ketone in the presence of NaOH. As an extension of our earlier work, we set out to investigate the scope and generality of this process. In this construction and by knowing the advantages of microwave reactions, we report the synthesis of piperidone compounds by one pot Michael addition process NaH catalyzed reactions of (E)-1-(4-(dimethylamino)phenyl)pent-1-en-3-one with *N*,2-diphenylacetamide that results in a highly selective method for the synthesis of aryl substituted piperidones.

Results and discussion

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



Scheme 1: (a) NaOH, EtOH, RT, 5h; (b) NaH, EtOH, 80C,6h; (c) NaH, DMF, 10min 200W in mw.

The structures of the new (chalcones) (*E*)-1-(4-(dimethylamino)phenyl)pent-1-en-3-one (**3**) were established and confirmed on the basis of their spectral data (IR, GC-MS, ^{1}H-NMR and ^{13}C-NMR). Thus, the mass spectrum of compound (**3**) as molecular formula $C_{17}H_{17}NO$ m/z (%): 205 (20) [M+1]; IR spectrum of revealed the presence of aromatic C-H stretching at 3077 cm^{-1}, methyl C-H at 2810 cm^{-1} and C=O absorption at 1677cm^{-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 6.54 and 7.52 ppm. ^{13}C-NMR spectrum showed a signal at δ 129.99 ppm and 143.09 ppm in the region of 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.

In the solvent effect on the UV-vis spectra of (*E*)-1-(4-(dimethylamino)phenyl)pent-1-en-3-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 206.80 nm, in acetonitrile λ_{max} is slightly decreased to 203.07 nm. While in highly polar protic solvent it has decreased to 202.13 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.

Effect of solvent on the IR spectrum (Fig.2 - Fig.5) of KBr pellet indicates (*E*)-1-(4-(dimethylamino)phenyl)pent-1-en-3-one (**3**) presence of carbonyl group appears at 1677 cm^{-1} and aliphatic C-H stretching appears as a 2818 cm^{-1}. In ethanol (*E*)-1-(4-(dimethylamino)phenyl)pent-1-en-3-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 3343 cm^{-1}.

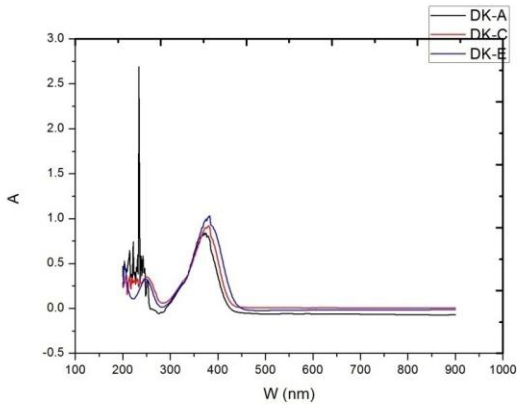


Figure 1: UV-vis spectra Comparison of (3)

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 3666 cm^{-1}. In chloroform solvent the -OH seems to be little and C=O bond appear light sharp in acetonitrile 1742 cm^{-1} chloroform seems to small peak 1648 and ethanol dilution appeared 1741, 1677 and highly diluted 80% not appeared carbonyl group in IR (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)-6-ethyl-1,3-diphenylpiperidin -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 1677 cm^{-1} and an appearance of amide stretching at 1715 cm^{1}. Furthermore the disappearance of carbonyl carbon signal at δ 201.12 ppm and appearance of signal at 180.70 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 at δ 2.99 ppm and appearance of three proton triplet at δ 0.99 for CH_3, a two proton quartet at δ 1.33 to 1.37 for ethyl CH2. A two 1.24. ppm and 1.33 ppm for CH_2 H_a, H_b proton, a quartet for one protons at δ 3.51 ppm for C_3-H, one proton doublet from δ 4.17 ppm for C_2-H and C_5-H triplet at 4.85 ppm confirmed the Michael addition reaction and the product (**5**).

Crystal structure determination:

(E)-1-(4-(dimethylamino)phenyl)pent-1-en-3-one (3):

The solubility studies in different solvents showed that the compound is insoluble in water and highly soluble in methanol and ethanol based on various experimental results, ethanol was used as solvent system to grow single crystals of title compound (**3**). A known volume of solvent was taken in a clear glass 5ml vial with plastic screw cap, which was immersed in a constant temperature bath. The mixture was heated to obtain clear solution. Vial was tightly capped and allowed to cool to room temperature. After cooling tiny particles of the original crystals are seen at the bottom of the vial and kept for another two days at room temperature. The molecular structure of (**3**) was depicted in Figure **2**.

A clear light green Rectangular-like specimen of $C_{13}H_{17}NO$, A good quality single crystal of approximate dimensions 0.190 mm x 0.220 mm x 0.250 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

A total of 724 frames were collected. The total exposure time was 2.01 hours. The frames were integrated with the Bruker SAINT [22] Software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 8992 reflections to a maximum θ angle of 24.99° (0.84 Å resolution), of which 2057 were independent (average redundancy 4.371, completeness = 100.0%, R_{int} = 2.56%, R_{sig} = 2.13%) and 1512 (73.51%) were greater than $2\sigma(F^2)$. The final cell constants of a = 12.6351(10) Å, b = 15.1318(12) Å, c = 6.2172(4) Å, β = 100.193(3)°, volume = 1169.92(15) $Å^3$, are based upon the refinement of the XYZ-centroids of 3353 reflections above 20 σ(I) with 5.384° < 2θ < 50.94°. Data were corrected for absorption effects using the multi-scan method (SADABS) [23]. The ratio of minimum to maximum apparent transmission was 0.950. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9820 and 0.9860.

The final anisotropic full-matrix least-squares refinement on F^2 with 140 variables converged at R1 = 4.44%, for the observed data and wR2 = 12.68% for all data. The goodness-of-fit was 1.042. The largest peak in the final difference electron density synthesis was 0.191 $e^-/Å^3$ and the largest hole was -0.119 $e^-/Å^3$ with an RMS deviation of 0.029 $e^-/Å^3$. On the basis of the

final model, the calculated density was 1.154 g/cm^3 and F(000), 440 e$^-$.

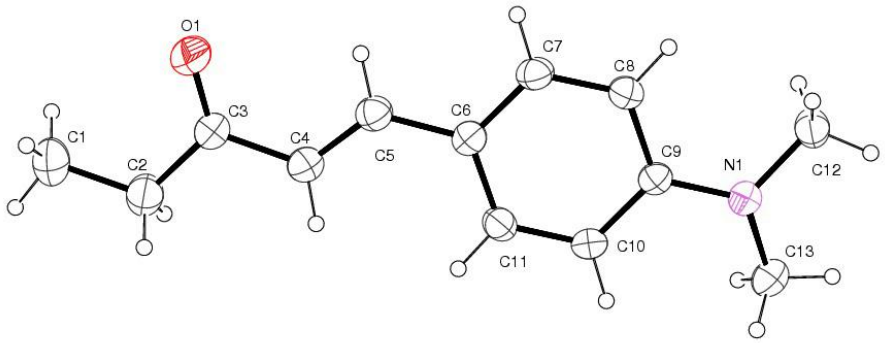


Figure 2: ORTEP view of the molecule *(E)-1-(4-(dimethylamino)phenyl)pent-1-en-3-one*.

Table 1: Crystal data for (3) parameters for $C_{13}H_{17}NO$.

Chemical formula	$C_{13}H_{17}NO$	
Formula weight	203.27 g/mol	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal size	0.190 x 0.220 x 0.250 mm	
Crystal habit	clear light green Rectangular	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 12.6351(10) Å	α = 90°
	b = 15.1318(12) Å	β = 100.193(3)°
	c = 6.2172(4) Å	γ = 90°
Volume	1169.92(15) Å^3	
Z	4	
Density (calculated)	1.154 g/cm^3	
Absorption coefficient	0.073 mm^{-1}	
F(000)	440	

Table 2: Data collection and structure refinement for (3).

Theta range for data collection	1.64 to 24.99°	
Index ranges	-14<=h<=15, -17<=k<=16, -7<=l<=6	
Reflections collected	8992	
Independent reflections	2057 [R(int) = 0.0256]	
Coverage of independent reflections	100.0%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9860 and 0.9820	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	2057 / 0 / 140	
Goodness-of-fit on F^2	1.042	
Δ/σ_{max}	0.001	
Final R indices	1512 data; I>2σ(I)	R1 = 0.0444, wR2 = 0.1103
	all data	R1 = 0.0630, wR2 = 0.1268
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0501P)^2+0.3792P]$ where $P=(F_o^2+2F_c^2)/3$	
Extinction coefficient	0.0090(20)	
Largest diff. peak and hole	0.191 and -0.119 eÅ^{-3}	
R.M.S. deviation from mean	0.029 eÅ^{-3}	

The molecular structure **(3)** shown in Figure **2** (ORTEP) [24]**.** It comprises of chalcone derivative with *N, N*- Dimethylamine. The chalcone moiety bears one aromatic substituent on *N, N* Dimethylamine and Ethyl group atom. The structural parameters, including bond distances and bond angles (Table **3**) show normal geometry.

Table 3: Bond lengths (Å) and Bond angel for (3).

C1-C2	1.493(3)	C1-H1A	0.96
C1-H1B	0.96	C1-H1C	0.96
C2-C3	1.479(3)	C2-H2A	0.97
C2-H2B	0.97	C3-O1	1.207(2)
C3-C4	1.479(3)	C4-C5	1.315(2)
C4-H4	0.93	C5-C6	1.459(2)
C5-H5	0.93	C6-C7	1.391(2)
C6-C11	1.397(2)	C7-C8	1.376(2)
C7-H7	0.93	C8-C9	1.400(2)
C8-H8	0.93	C9-N1	1.377(2)
C9-C10	1.404(2)	C10-C11	1.377(2)
C10-H10	0.93	C11-H11	0.93
C12-N1	1.448(2)	C12-H12A	0.96
C12-H12B	0.96	C12-H12C	0.96
C13-N1	1.445(2)	C13-H13A	0.96
C13-H13B	0.96	C13-H13C	0.96

Table 4: Selected torsion angles (3).

C1-C2-C3-O1	1.6(3)	C1-C2-C3-C4	-179.12(19)
O1-C3-C4-C5	-4.1(3)	C2-C3-C4-C5	176.61(19)
C3-C4-C5-C6	-179.69(17)	C4-C5-C6-C7	178.01(18)
C4-C5-C6-C11	-0.6(3)	C11-C6-C7-C8	1.7(2)
C5-C6-C7-C8	-176.98(16)	C6-C7-C8-C9	0.7(3)
C7-C8-C9-N1	178.78(15)	C7-C8-C9-C10	-2.5(2)
N1-C9-C10-C11	-179.40(15)	C8-C9-C10-C11	1.8(2)
C9-C10-C11-C6	0.6(3)	C7-C6-C11-C10	-2.3(2)
C5-C6-C11-C10	176.30(16)	C8-C9-N1-C13	-166.56(16)
C10-C9-N1-C13	14.7(2)	C8-C9-N1-C12	-4.9(2)
C10-C9-N1-C12	176.36(15)		

Experimental

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:

(E)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one (3):

A mixture of Dimethylaminobenzaldehyde **(2)** (14.9g, 0.1 mole) and butan-2-one (**1**) (7.2.mL, 0.1 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. The Single crystal suitable for X-ray diffraction study was grown by slow evaporation method and was dimerized during crystallization. Orange crystal, m.p. 180-181°C; 82% yield; IR (KBr, ν_{max}, cm^{-1}): 3343, 2977, 2900, 2818, 1677, 1578, 1519, 1229, 1000; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, 1H, *J* =16 Hz, benzylic-H), 7.45 (d, 1H, phenyl-C_2) 6.58 (d, 1H, *J* = 16, benzylic-H), 6.67 (d, 2H, *J* = 9, phenyl-C_3-C_5), 2.66 (q, 2H, CH_2), 1.14 (t, 3H, CH_3) 3.08 (s, 6H, N-CH_3); ^{13}C NMR (120 MHz, $CDCl_3$): δ 201.12, 151.89, 143.09, 129.99, 122.22, 121.25, 111.88,111.01, 40.12, 33.59, 8.65; GC-MS: m/z [M+1] 204 (16%).

4- (4-(dimethylamino) phenyl)-1,3,6-triphenyl piperidin-2-one (5):

Conventional method:

(E)-1-(4-(dimethylamino)phenyl)pent-1-en-3-one **(3)** (2.04g, 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 precipitate formed was collected by filtration and purified by re-crystallization from ethanol. The crude product was purified by re-crystallization from ethanol.

Microwave method:

(2.04g, 0.01 mole) of *(E)*-1-(4-(dimethylamino)phenyl)pent-1-en-3-one **(3)** and N,2-diphenylacetamide **(4)** (2.21g, 0.01mole) 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. 130-131 °C; 82% yield; IR (KBr, ν_{max}, cm^{-1}): 3398, 3252, 3135, 3059, 2920, 2852, 1654, 1596, 1548, 1162, 751; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10-7.37 (m, 14H, 3-phenyl ring), 4.87 (d, 1H, *J* =7 Hz, piperidone-C_3-H), 4.19-4.15 (m, 1H, piperidone-C_5-

H), 3.52 (q, 1H, *J* = 6.5, piperidone- C_4-H), 2.99 (s, 6H, $N(CH_3)_2$), 1.37 and 1.30 (t, and d, 2H, piperidone-C_4- H), 1.12 (q, 2H, $-CH_2-$), 0.99 (t, 3H, $-CH_3$); ^{13}C NMR (120 MHz, $CDCl_3$): δ 180.70, 148.12, 137.98, 135.20, 134.65, 128.98, 128.60, 128.36, 128.29, 128.14, 126.77, 112.59, 66.33, 50.11, 43.45, 43.91, 25.96, 10.34 ; GC-MS: m/z [M^+] 398 (29 %).

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