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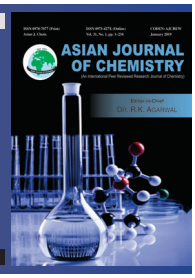

Synthesis of 3-Arylidene-4-Piperidone Derivatives as Potent Antioxidant Agents: A Solvent Free Approach

V. LALITHA[1], T. MARUTHAVANAN[2] and P. VENKATESAN[1,*]

[1]Department of Chemistry, Thiruvalluvar Government Arts College, Rasipuram-637401, India
[2]Department of Chemistry, Sona College of Technology, Salem-636005, India

*Corresponding author: E-mail : venkatesanps@yahoo.co.in

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A simple procedure using grinding method of condensation of *N*-acetyl-3-methyl-2,6-diarylpiperidin-4-one with aldehyde gave *N*-acetyl-3-arylidene-5-methyl-2,6-diarylpiperidin-4-one with good yield. The structure of the synthesized compounds was assigned on the basis of IR, ^{1}H NMR and mass spectral studies. The synthesized compounds showed remarkable *in vitro* antioxidant activity.

Keywords: Piperidin-4-one, Arylidene derivatives, Chalcone, Grinding method, Antioxidant activity.

INTRODUCTION

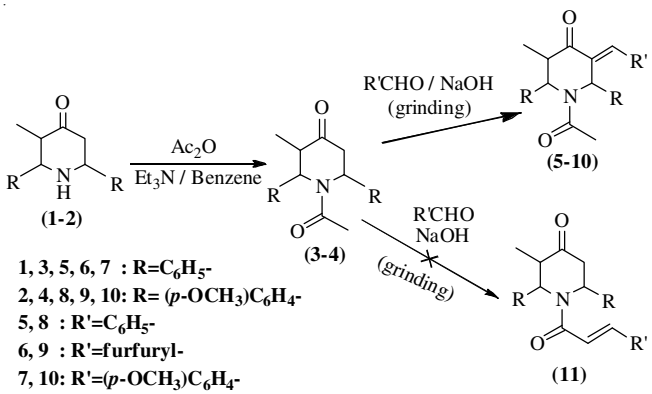
Usage of organic solvents in various synthetic processes are hazardous to the environment as well as human health. Thus, the various eco-friendly methods in Green Chemistry have drawn attention in organic synthesis. Because of simple workup procedure, time consumption, compatibility with various functional groups and good yields, the grindstone method has recently drawn attention [1] in many reactions like Reformatsky reaction [2], Grignard reaction [3], Aldol condensation [4], Knoevenagel reaction [5], Michael addition [6], Wittig reaction [7], Biginelli reaction [8], *etc*.

In addition, piperidin-4-ones moiety have been reported to show the considerable biological importance such as antipyretic, antioxidant, antimicrobial, antitumor activities [9-13]. Because of their extensive importance, we opted the grindstone method to synthesize *N*-acetyl-3-arylidene-5-methyl-2,6-diarylpiperidin-4-one. The synthesized compounds were evaluated for free radical scavenging activity.

EXPERIMENTAL

All common chemicals and solvents were purchased from Nice and Spectra Chemicals, India. IR spectrum was recorded on Perkin-Elmer 577 IR spectrometer with KBr pellets in the range of 4000 to 400 cm^{-1}. ^{1}H NMR spectrum (500 MHz) was recorded on Bruker AVANCE III 500 MHz NMR Spectrometer using $CDCl_3$ as solvent and tetramethyl silane (TMS) as the internal standard. The chemical shift of ^{1}H NMR spectrum was reported in ppm scale. Mass spectrum was carried out using Finnegan Mat 8230 mass spectrometer and fragmentations were given in *m/z* values. The elemental analysis was carried out on Vario EL-III elemental analyzer and their reports were agreed within 0.4 % of theoretical values. The progress of the reaction was monitored by thin layer chromatography on silica gel 60 F_{254} (Merck). The isolation of pure compounds was done by column chromatography with silica gel 60-120 mesh (Merck). The parent compounds (**1** and **2**) were synthesized as reported work [14].

Synthesis of *N*-acetyl-3-arylidene-5-methyl-2,6-diarylpiperidin-4-one (5-10) by grinding method: A mixture of *N*-acetyl-3-methyl-2,6-diarylpiperidin-4-one (**3**,**4**) (0.01 mol), arylaldehyde (0.01 mol) and NaOH pellets (0.5 g) were grounded well at room temperature for 25-40 min using mortar and pestle. Completion of the reaction was ascertained by TLC. Then, the reaction mixture was transferred to a beaker containing 100 mL of ice water and neutralized with acetic acid. The resulting residue is filtered, dried and subjected to column chromatogram to isolate pure compound using benzene-chloroform (3:1) eluent (**Scheme-I**).



Scheme-I: Synthetic pathway of target compounds

***N*-acetyl-3-benzylidene-5-methyl-2,6-diphenylpiperidin-4-one (5):** Pale yellow solid; m.p. 168 ºC; IR (KBr, ν_{max}, cm^{-1}): 2982 (ArCH), 1679 and 1708 (C=O *str*.), 1374 (CH_3 bend), 1880 (CH_3 overtone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85-7.74 (m, 15H, ArH), 4.51 (d, $^3J_{6a,5a}$ = 11.5 Hz, 1H, 6-H_a), 5.00 (s, 1H, 2-H_a), 3.07 (m, 1H, 5-H_a), 0.89 (d, 3H, 5-CH_3), 1.89 (s, 3H, N-$COCH_3$), 8.19 (s, 1H, 3-methylene); MS: *m/z* 395.32 (M^+). Elemental anal. calc (found) % for $C_{27}H_{25}NO_2$: C, 82.00 (81.78); H, 6.37 (6.38); N, 3.54 (3.55).

***N*-acetyl-3-(furan-2-ylmethylene)-5-methyl-2,6-diphenylpiperidin-4-one (6):** Dull white solid; m.p. 212 ºC; IR (KBr, ν_{max}, cm^{-1}): 3102 (ArCH), 1682 and 1703 (C=O *str*.), 1392 (CH_3 bend.), 1880 (CH_3 overtone). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.44-6.94 (m, 3H, furyl-H), 7.14-7.78 (m, 10H, ArH), 4.53 (d, $^3J_{6a,5a}$ = 11.5 Hz, 1H, 6-H_a), 4.98 (s, 1H, 2-H_a), 3.03-3.06 (m, 1H, 5-H_a), 0.88 (d, 3H, 5-CH_3), 1.93 (s, 3H, N-$COCH_3$), 8.14 (s, 1H, 3-methylene); MS: *m/z* 385.29 (M^+). Elemental anal. calc (found) % for $C_{25}H_{23}NO_3$: C, 77.90 (77.68); H, 6.01 (6.02); N, 3.63 (3.62).

***N*-acetyl-3-(4-methoxybenzylidene)-5-methyl-2,6-diphenylpiperidin-4-one (7):** Dull white solid; m.p. 128 ºC; IR (KBr, ν_{max}, cm^{-1}): 2996 (ArCH), 1676 and 1705 (C=O *str*.), 1388 (CH_3 bend), 1912 (CH3 overtone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84-7.92 (m, 14H, ArH), 4.49 (d, $^3J_{6a,5a}$ = 11.5 Hz, 1H, 6-H_a), 4.99 (s, 1H, 2-H_a), 3.08-3.12 (m, 1H, 5-H_a), 0.87 (d, 3H, 5-CH_3), 2.03 (s, 3H, N-$COCH_3$), 8.14 (s, 1H, 3-methylene), 3.81 (s, 3H, Ar-OCH_3); MS: *m/z* 425.41 (M^+). Elemental anal. calc (found) % for $C_{28}H_{27}NO_3$: C, 79.03 (78.91); H, 6.40 (6.38); N, 3.29 (3.30).

***N*-acetyl-3-benzylidene-5-methyl-2,6-di(4-methoxyphenyl)piperidin-4-one (8):** White solid; m.p. 172 ºC; IR (KBr, ν_{max}, cm^{-1}): 3001 (ArCH), 1674 and 1702 (C=O *str*.), 1372 (CH_3 bend.), 1896 (CH_3 overtone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.68-7.68 (m, 13H, ArH), 4.48 (d, $^3J_{6a,5a}$ = 12 Hz, 1H, 6-H_a), 4.96 (s, 1H, 2-H_a), 3.07 (m, 1H, 5-H_a), 0.84 (d, 3H, 5-CH_3), 1.88 (s, 3H, N-$COCH_3$), 8.01 (s, 1H, 3-methylene), 3.77 and 3.86 (s, 6H, Ar-OCH_3); MS: *m/z* 455.28 (M^+). Elemental anal. calc (found) % for $C_{29}H_{29}NO_4$: C, 76.46 (76.54); H, 6.42 (6.41); N, 3.07 (3.07).

***N*-acetyl-3-(furan-2-ylmethylene)-5-methyl-2,6-di(4-methoxyphenyl)piperidin-4-one (9):** Dull white solid; m.p. 68 ºC; IR (KBr, ν_{max}, cm^{-1}): 3112 (ArCH), 1680 and 1707 (C=O *str*.), 1392 (CH_3 bend.), 1899 (CH_3 overtone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.31-6.78 (m, 3H, furyl-H), 6.86-7.84 (m, 8H, ArH), 4.47 (d, $^3J_{6a,5a}$ = 11 Hz, 1H, 6-Ha), 4.95 (s, 1H, 2-H_a), 3.04 (m, 1H, 5-H_a), 0.87 (d, 3H, 5-CH_3), 1.92 (s, 3H, N-$COCH_3$), 7.91 (s, 1H, 3-methylene), 3.77 and 3.85 (s, 6H, Ar-OCH_3); MS: *m/z* 445.26 (M^+). Elemental anal. calc (found) % for $C_{27}H_{27}NO_5$: C, 72.79 (72.86); H, 6.11 (6.08); N, 3.14 (3.13).

***N*-acetyl-3-(4-methoxybenzylidene)-5-methyl-2,6-di(4-methoxyphenyl)piperidin-4-one (10):** Pale yellow solid; m.p. 164 ºC; IR (KBr, ν_{max}, cm^{-1}): 3012 (ArCH), 1677 and 1704 (C=O *str*.), 1380 (CH_3 bend.), 1902 (CH_3 overtone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62-7.68 (m, 12H, ArH), 4.43 (d, $^3J_{6a,5a}$ = 11 Hz, 1H, 6-H_a), 4.97 (s, 1H, 2-H_a), 3.05-3.09 (m, 1H, 5-H_a), 0.87 (d, 3H, 5-CH_3), 1.90 (s, 3H, N-$COCH_3$), 7.96 (s, 1H, 3-methylene), 3.78, 3.80 and 3.89 (s, 9H, Ar-OCH_3); MS: *m/z* 485.08 (M^+). Elemental anal. calc (found) % for $C_{30}H_{31}NO_5$: C, 74.21 (74.14); H, 6.43 (6.41); N, 2.88 (2.89).

Synthesis of *N*-acetyl-3-arylidene-5-methyl-2,6-diarylpiperidin-4-one (5-10) by conventional method [15]**:** The appropriate *N*-acetyl-3-methyl-2,6-diarylpiperidin-4-one (**3**, **4**) (0.01 mol) and appropriate arylaldehyde (0.01 mol) was added to 100 mL ethanol. To the reaction mixture, 0.002 mol of NaOH was added and refluxed till completion of the reaction. Then, it was transferred into a beaker containing 100 mL of ice water. The resulting residue is filtered, dried and subjected to column chromatogram to isolate pure compound using chloroform-benzene (1:3) eluent.

RESULTS AND DISCUSSION

An attempt was made to synthesize 3-methyl-2,6-diaryl-1-(2-arylacetyl)-piperidin-4-one (**11**) by condensation of *N*-acetyl-3-methyl-2,6-diarylpiperidin-4-one (**3**, **4**) and aryl aldehyde as given in **Scheme-I**. The reaction mixture was taken in pestle and ground well using a mortar with catalytic amount of NaOH. We observed that the reaction mixture was in semi-liquid state while grinding and gradually solidified. The progress of reaction was monitored by TLC and the resulted products were separated by column chromatography with benzene-chloroform eluent to get pure compounds. On careful investigation based on spectral data, it was found that a formation of new series of compounds, *N*-acetyl-3-arylidene-5-methyl-2,6-diphenylpiperidin-4-one (**5-10**) instead of an expected compound, 3-methyl-2,6-diaryl-1-(2-arylacetyl)-piperidin-4-one (**11**).

The IR spectrum of *N*-acetyl-3-benzylidene-5-methyl-2,6-diphenylpiperidin-4-one (**5**) showed the stretching absorption for -C=O at 1679 cm^{-1} and 1708 cm^{-1} due to carbonyl group at C-4 position and acetyl group, respectively. The ^{1}H NMR spectrum of *N*-acetyl-3-benzylidene-5-methyl-2,6-diphenylpiperidin-4-one (5) revealed that the aromatic protons were resonated at 6.85-7.74 ppm. The H(2) proton was appeared as singlet at 5.00 ppm. The doublet at 4.5 ppm was assigned to H(6) proton. The H(5) proton was resonated at 3.07 ppm as multiplet and the doublet in the region at 0.89 ppm was observed for H(5)-methyl group. The appearance of singlet at 1.89 ppm for N-acetyl group and another singlet at 8.19 ppm for 3-methylene group confirm the formation N-acetyl-3-benzylidene-5-methyl-2,6-diphenylpiperidin-4-one (**5**). Akin to compound 5, the structure of rest of the synthesized compounds (**6-10**) was assigned. In addition, the mass spectrum of compounds (**5-10**) revealed that the observed molecular ion peak was in good agreement with

TABLE-1
PHYSICAL DATA AND *in vitro* ANTIOXIDANT ACTIVITY OF COMPOUNDS **5-10**

Compounds	Reaction time		Yield (%)		Antioxidant activity (%)
	Grind (min)	Reflux (h)	Grind	Reflux	
5	35	11	86	66	10.22
6	30	8	82	68	64.24
7	25	10	84	62	28.48
8	25	10	82	64	7.04
9	40	9	81	72	51.62
10	35	7	81	68	32.54
Ascorbic acid	–	–	–	–	76.31

the calculated mass and their purity was confirmed by elemental analysis.

The physical data of synthesized compounds are given in Table-1. The data showed that solvent free grinding technique gave more yield than conventional reflux method with short reaction time.

The *in vitro* antioxidant activity of synthesized compounds was studied based on the radical scavenging effect of stable DPPH free radical using ascorbic acid as a standard [16]. The results (Table-1) showed that *N*-acetyl-3-(furan-2-ylmethylene)-5-methyl-2,6-diphenylpiperidin-4-one (**6**) and *N*-acetyl-3-(furan-2-yl-methylene)-5-methyl-2,6-di(4-methoxyphenyl)-piperidin-4-one (**9**), which possess furfuryl moiety were showed good antioxidant activity. However, *N*-acetyl-3-benzylidene-5-methyl-2,6-diphenylpiperidin-4-one (**5**) and *N*-acetyl-3-benzylidene-5-methyl-2,6-di(4-methoxyphenyl)piperidin-4-one (**8**) showed very less antioxidant activity.

Conclusion

The ^{1}H NMR spectrum and other spectral studies confirm the formation of *N*-acetyl-3-arylidene-5-methyl-2,6-diarylpiperidin-4-one (**5-10**) under solvent free grinding technique with short reaction rime and simple work up procedure. The synthesized compounds showed considerable antioxidant activity.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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