Journal of Pharmaceutical and Medicinal Research 1(1) (2015) 6–8

ISSN: 2455-0280

Contents List available at JACS Directory

Journal of Pharmaceutical and Medicinal Research

journal homepage: www.jacsdirectory.com/jpmr

Synthesis of Some Novel Piperidones and Pyridinones

K. Kanagalakshmi, S. Ponmuthumariammal, G. Gandhi, M. Valarmathi, A. Vanangamudi*

Center for Research and Postgraduate Studies in Chemistry, Ayya Nadar Janaki Ammal College, Sivakasi – 626 124, TN, India.

ARTICLE DETAILS

Article history:
Received 17 August 2015
Accepted 07 September 2015
Available online 10 September 2015

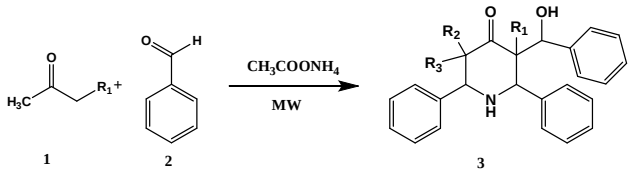
Keywords:
Piperidones
Pyridinones
Microwave Synthesis
Solvent Free Reaction

ABSTRACT

A convenient, fast and high yielding method for the preparation of novel piperidones and pyridinones has been developed by the microwave assisted condensation of a ketone with benzaldehyde/salicyladehyde in the presence of ammonium acetate. All the compounds were characterized with UV, FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

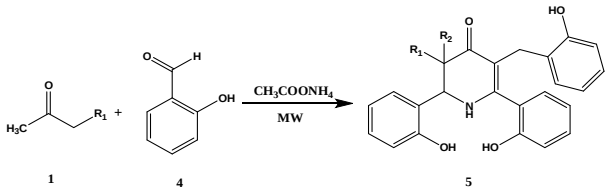
1. Introduction

In recent years, there has been a growing interest pertaining to the synthesis of bioactive compounds in organic chemistry. Among the family of heterocyclic compounds, nitrogen containing heterocyclic especially piperidin-4-ones gaining considerable importance owing to their varied biological properties such as antitumor, analgesic, local anaesthetic, antimicrobial, insecticidal and depressant activities [1-2]. The naturally occurring 2,6-diphenylpiperidine alkaloids show significant biological activity. Watson et al. asserted that during the recent ten years there were thousands of piperidone compounds mentioned in clinical and preclinical studies [3]. Microwave assisted reactions offer a considerable advantages over conventional method reactions because the former results in substantial rate enhancement in a wide range of organic reactions. Moreover, the majority of the microwave assisted reactions is solvent-free reactions; hence they are considered as clean, efficient and economical technology. This methodology has been widely used in a variety of organic reactions [4]. As a part of an on-going synthetic program aimed at the development of new approaches to functioned piperidone and pyridinone ring systems, the authors have explored the use of the microwave in the synthesis of novel piperidones and pyridinones. Mannich reaction involving arylaldehyde, ketone and ammonium acetate is a well-known method for the synthesis of 2,6-diaryl-4-piperidones and 3-substituted-2,6-diaryl-4-piperidones [5]. Review of literature indicated that, the one-pot synthesis of 3,3,5,5-tetrasubstituted-2,6-diaryl-4-piperidones and 3,5-disubstituted-2,6-diaryl-4-pyridinones using Mannich reaction was not reported. Srikrishna and Kumar reported that microwave irradiation changes the course of the reaction thermal process [6-10]. It was observed to be the same during the synthesis of piperidones. Ketone **1**, irradiated with benzaldehyde **2** in the presence of ammonium acetate under the microwave, furnished 3,3,5,5-tetrasubstituted-2,6-diphenyl-4-piperidone **3a-b, 3d** and 3,3-disubstituted-2,6-diphenyl-4-piperidone **3c** (Scheme 1). Irradiation of ketone **1** with salicylaldehyde **4** in the presence of ammonium acetate under microwave gave 3-substituted-2,6-diaryl-4-pyridinones **5a** and 3,5-disubstituted-2,6-diaryl-4-pyridinones **5b-d** (Scheme 2). Using this technique, four new piperidin-4-ones and four new pyridinon-4-ones have been synthesized in the short reaction period under solvent free condition with good yield.



	R_1		R_1	R_2	R_3
1a	H	**3a**	C_6H_5CHOH	C_6H_5CHOH	C_6H_5CHOH
1b	CH_3	**3b**	CH_3	C_6H_5CHOH	C_6H_5CHOH
1c	$COOC_2H_5$	**3c**	$COOC_2H_5$	H	H
1d	$COCH_3$	**3d**	$COCH_3$	C_6H_5CHOH	C_6H_5CHOH

Scheme 1 Synthesis of piperidones



	R_1		R_1	R_2
1a	H	**5a**	H	H
1b	CH_3	**5b**	CH_3	H
1c	$COOC_2H_5$	**5c**	$COOC_2H_5$	H
1d	C_2H_5	**5d**	C_2H_5	H

Scheme 2 Synthesis of pyridinones

2. Experimental Methods

Melting points were determined in open capillaries and uncorrected. The IR spectra were recorded on a 8400S SHIMADZU spectrophotometer and the UV spectra on a SHIMADZU UV-1700 UV-Vis spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker 300 MHz spectrometer in $CDCl_3$ (Chemical shifts in δ, ppm relative to TMS as an internal standard). Elemental analyses were done on Elementar Vario EL III.

*Corresponding Author
Email Address: sudhakanivanangamudi@gmail.com (A. Vanangamudi)

Cite this Article as: K. Kanagalakshmi, S. Ponmuthumariammal, G. Gandhi, M. Valarmathi, A. Vanangamudi, Synthesis of some novel piperidones and pyridinones, J. Pharm. Med. Res. 1(1) (2015) 6–8.

*2.1 General Procedure for the Synthesis of Piperidones **3a-d**/Pyridinones **5a-d***

A mixture of ketone (10 mmol), benzaldehyde (20 mmol) / salicyaldehyde (20 mmol) and ammonium acetate (10 mmol) were taken in a 50 mL conical flask. A funnel was kept in the conical flask over which a small round bottom flask filled with ice water was kept which acted as a condenser. The mixture was irradiated in a microwave oven (SAMSUNG M 197 DL) at 180 W for 2-7 minutes / 7-14 minutes in the interval of 10 seconds. After the reaction was completed, the reaction mixture was treated with ice-water. The solid obtained was filtered and crystallized from ethanol.

*3,3,5,5-Tetra [hydroxy (phenyl) methyl] -2,6-diphenyl-4-piperidone **(3a)***

It was obtained as a colorless solid, m.p 212 °C, yield 85%. ^{1}H NMR : (δ, ppm, $CDCl_3$), 1.60 (4H, s, C-1', 1", 1'", 1^{IV} -OH); 2.16 (1H, s, NH); 2.88 (2H, s, H-2, H-6); 4.38 (2H, s, H-1', 1^{IV}); 4.73 (2H, s, H-1", 1'"); 6.70-7.60 (30H, m, C-2, C-6, C-1', 1", 1'", 1^{IV}-phenyl ring protons); ^{13}C NMR : (δ, ppm, $CDCl_3$), 58.59 (C-3, 5); 61.70 (C-2, 6); 63.23 (C-1', 1", 1'", 1^{IV}); 126.2-145.3 (C-1', 1", 1'", 1^{IV}-phenyl ring carbons); 185.00 (carbonyl carbon); IR (KBr) ν_{max} : 3427 (OH), 3306 (NH), 3040, 2960, 1714 (CO); UV (methanol) λ_{max} : 254, 266.

*3,3,5-Trihydroxy(phenyl)-5-methyl-2,6-diphenyl-4-piperidinone **(3b)***

It was obtained as a yellow solid, m.p 218 °C, yield 80%. ^{1}H NMR : (δ, ppm, $CDCl_3$), 0.66 (3H, s, CH_3); 1.57 (3H, s, C-1', 1", 1'", -OH); 2.14 (1H, s, NH); 3.00 (1H, s, H-2); 3.86 (1H, s, H-6); 4.36 (1H, s, H-1'"); 4.75 (1H, s, H-1'); 5.30 (1H, s, H-1"); 6.69-7.73 (25H, m, C-2, C-6, C-1', 1", 1'", -phenyl ring protons) ^{13}C NMR : (δ, ppm, $CDCl_3$), 18.35 (CH_3); 54.81 (C-5); 58.63 (C-3); 61.60 (C-2); 62.43 (C-6); 63.24 (C-1'); 70.24 (C-1", 1'"); 126.2-139.69 (phenyl ring carbons); 212.53 (carbonyl carbon); IR (KBr) ν_{max} : 3431 (OH), 3308 (NH), 3063, 2920, 1710 (CO); UV (methanol) λ_{max}: 252, 265.

*Ethyl-3-(hydroxy(phenyl)methyl)-4-oxo-2,6-diphenylpiperidine-3-carboxylate **(3c)***

It was obtained as a yellow colored crystal, m.p 149 °C, yield 75%. ^{1}H NMR : (δ, ppm, $CDCl_3$), 0.92 (3H, t, CH_3 protons); 2.30 (1H, dd, H-5eq); 2.90 (1H, dd, H-5ax); 3.96 (2H, q, -OCH_2); 5.36 (1H, s, H-1'); 6.80 (3H, s, NH, H-2, OH); 4.12 (1H, dd, H-6); 7.3-8.2 (m, 15H, three phenyl ring protons) ^{13}C NMR : (δ, ppm, $CDCl_3$), 13.9 (CH_3); 30.4 (C-5); 50.4 (C-6); 30.8 (C-3); 58.8 (C-1'); 126.6-132.8 (phenyl ring carbons); 55.9 (C-2); 168.4 (ester carbonyl carbon); 200.2 (C-4); IR (KBr) ν_{max} : 3410 (OH), 3298 (NH), 1680 (CO), 1622, 3034, 2978, 1602.; UV (methanol) λ_{max} : 281.

*3-Acetyl-3,5,6-tri[hydroxyphenyl]-2,6-diphenyl-4-piperidone **(3d)***

It was obtained as a colorless solid, m.p 165 °C, yield 85%. ^{1}H NMR : (δ, ppm, $CDCl_3$), 1.98 (3H, s, NH, C-1'-OH, C-1"-OH); 2.49 (3H, s, CH_3); 4.75 (2H, s, H-1', H-6); 4.95 (2H, s, H-2, C-1'"-OH); 5.10 (2H, s, H-1", 1'"); 7.2-7.9 (25H, m, Phenyl ring protons) ^{13}C NMR : (δ, ppm, $CDCl_3$), 22.7 (CH_3); 28.6 (C-5); 56.9 (C-6, C-2); 64.2 (C-1',1",1'"); 104.2 (C-3); 126.5-153.3 (aryl ring carbons); 192.0 (acetyl carbonyl carbon); 194.9 (ring carbonyl carbon); IR (KBr) ν_{max} : 3400 (OH), 3232 (NH), 3037, 2906, 1693 (CO), 1654; UV (methanol) λ_{max} : 303.

*5-(2-hydroxybenzyl)-2,6-bis(2-hydroxyphenyl)-2,3-dihydropyridin-4(1H)-one **(5a)***

It was obtained as a yellow solid, m.p 213 °C, yield 80%. ^{1}H NMR : (δ, ppm, $CDCl_3$), 1.73 (2H, s, CH_2); 2.17 (1H, dd, H-3ax); 2.57 (1H, t, H-3eq); 4.28 (1H, dd, H-2); 6.84-7.38 (12H, m, aryl ring protons) 8.37 (2H, s, 2"-OH); 8.55 (2H, s, 2'-OH); 12.98 (2H, s, 2'"-OH & NH) ^{13}C NMR : (δ, ppm, $CDCl_3$), 29.45 (CH_2); 40.39 (C-3); 61.10 (C-2); 89.56 (C-5); 116.43-132.81 (three aryl ring carbons); 151.47 (C-6); 160.56 (C-2"); 160.91 (C-2"');161.06 (C-2'); 166.77 (carbonyl carbon); IR (KBr) ν_{max} : 3437 (OH), 3363 (NH), 3063, 2985, 1627 (CO); UV (methanol) λ_{max} : 260, 320.

*5-(2-Hydroxybenzyl)-2,6-bis(2-hydroxyphenyl)-3-methyl-2,3-dihydropyridin-4(1H)-one **(5b)***

It was obtained as a pale yellow solid, m.p 224 °C, yield 75%. ^{1}H NMR : (δ, ppm, $CDCl_3$), 1.26 (3H, d, CH_3); 1.68 (2H, s, CH_2); 2.45 (1H, m, H-3); 3.84 (1H, d, H-2); 6.83-7.39 (12H, m, three aryl ring protons); 8.41 (2H, s, C-2"-OH); 8.49 (1H, s, C-2'-OH); 13.10 (2H, s, C-2'"-OH & NH) ^{13}C NMR : (δ, ppm, $CDCl_3$), 13.00 (CH_3); 28.0 (CH_2); 41.50 (C-3); 67.90 (C-2); 2.47 (C-5); 116.30-132.80 (three aryl ring carbons); 151.00 (C-6); 160.00 (C-2"); 160.00 (C-2"'); 161.40 (C-2'); 167.00 (carbonyl carbon); IR (KBr) ν_{max} : 3440 (OH), 3360 (NH), 3059, 2987, 1627 (CO); UV (methanol) λ_{max} : 258, 321.

*Ethyl-5-(2-hydroxybenzyl)-2,6-bis(2-hydroxyphenyl)-4-oxo-1,2,3,4-tetrahydropyridine-3-carboxylate **(5c)***

It was obtained as a yellow solid, m.p 209 °C, yield 85%. ^{1}H NMR : (δ, ppm, $CDCl_3$), 1.22 (3H, t, CH_3 protons); 1.78 (2H, s, CH_2 protons); 3.35 (1H, d, H-5); 4.25 (2H, q, -OCH_2 protons); 4.65 (1H, d, H-6); 6.7-7.5 (12H, m, aryl ring protons); 8.4 (1H, s, C-2'" -OH proton); 8.6 (2H, s, C-2' -OH proton); 12.7 (1H, s, -NH proton); 12.8 (1H, s, C-2"-OH proton) ^{13}C NMR : (δ, ppm, $CDCl_3$), 14.1 (CH_3); 28.5 (CH_2); 54.0 (O-CH_2); 61.4 (C-5); 63.8 (C-6); 89.5 (C-3); 16.3-133.0 (phenyl ring carbons); 150.3 (C-2); 160.6 (C-2'"-OH); 160.9 (C-2"-OH); 161.1 (C-2'-OH); 168.9 (ester carbonyl carbon); 169.7 (ring carbonyl carbon); IR (KBr) ν_{max} : 3431 (OH), 3340 (NH), 2920, 2378, 1734, 1627 (CO), 1581; UV (methanol) λ_{max} : 257.

*3-Ethyl-5-(2-hydroxybenzyl)-2,6-di(2-hydroxyphenyl)1,2,3,4-tetrahydro-4-pyridinone **(5d)***

It was obtained as a pale yellow colored crystal, m.p 198 °C, yield 70%. ^{1}H NMR : (δ, ppm, $CDCl_3$), 1.05 (3H, t, methyl protons); 1.4-1.5 and 1.9-2.05 (2H, m, CH_2 protons); 1.8 (2H, s, benzyl methylene protons); 2.2 (1H, m, H-5); 3.95 (1H, d, H-6); 6.8-7.5 (12H, m, aryl ring protons); 8.4 (1H, s, C-2'-OH); 8.6 (1H, s, C-2'"-OH); 13.0 (2H, s, NH, C-2"-OH protons) ^{13}C NMR : (δ, ppm, $CDCl_3$), 14.2 (CH_3); 21.8 (Benzyl CH_2 carbon); 28.2 (CH_2); 48.2 (C-5); 67.9 (C-6); 92.8 (C-3); 116.3-132.9 (aryl ring carbons); 151.0 (C-2); 160.5 (C-2'); 161.1 (C-2"); 161.4 (C-2'"); 167.1 (carbonyl carbon); IR (KBr) ν_{max} : 3441 (OH), 3330 (NH), 2933, 1626 (CO), 1587; UV (methanol) λ_{max} : 252.

3. Results and Discussion

3.1 Synthetic Chemistry

The formation of piperidones **3a-d** was confirmed by recording elemental analysis (Table 1) and UV, FT-IR, ^{1}H NMR and ^{13}C NMR spectra. As a representative example, the characterization of compound **3a** has been discussed. The IR spectrum of piperidone **3a** showed the presence of hydroxyl (3427 cm^{-1}), amino (3306 cm^{-1}) and carbonyl (1714 cm^{-1}) groups. In ^{1}H NMR spectrum, three singlets present at 2.88 δ (2H), 4.38 δ (2H) and 4.73 δ (2H) were assigned to H-2,6, H-1',1^{IV} and H-1", 1'" respectively. The presence of a singlet at 2.16 δ (1H) was due to NH proton and a remaining singlet at 1.60 δ (4H) was corresponding with C-1', 1", 1'", 1^{IV} –hydroxyl protons. In the ^{13}C NMR spectrum a signal observed in 180.00 δ apart from the expected aromatic and aliphatic carbons was due to the carbonyl carbon of piperidone.

The formation of pyridinones **5a-d** was also confirmed by recording elemental analysis (Table 1) and UV, FT-IR, ^{1}H NMR and ^{13}C NMR spectra. As a representative example, the characterization of compound **5b** has been discussed. The IR spectrum of pyridinone **5b** showed the presence of hydroxyl, amino (3360- 3440 cm^{-1}) and carbonyl (1627 cm^{-1}) groups. In ^{1}H NMR spectrum apart from the expected aromatic, OH and NH protons, a singlet at 1.68 δ (2H) and a doublet at 1.26 δ (3H) were assigned to methylene and methyl protons respectively. A doublet present at 3.84 δ (1H) and a multiplet at 2.45 δ (1H) were readily assigned to H-2 and H-3 respectively. The ^{13}C NMR spectrum showed the carbonyl carbon at 167.00 δ and methyl and methylene carbons at 13.00 δ and 28.00 δ respectively.

Table 1 Elemental analysis of compounds

Compound	Reaction Period MW (min.)	Molecular Formula	% of Elements observed*		
			C	H	N
3a	7	$C_{45}H_{41}NO_5$	79.98 (79.91	6.11 6.13	2.07 2.09)
3b	7	$C_{39}H_{37}NO_4$	80.25 (80.20	6.39 6.37	2.40 2.43)
3c	4	$C_{27}H_{27}NO_4$	75.50 (75.53	6.34 6.37	3.26 3.30)
3d	2	$C_{40}H_{37}NO_5$	78.54 (78.53	6.10 6.13	2.29 2.33)
5a	7	$C_{24}H_{21}NO_4$	74.40 (74.53	5.46 5.43	3.62 3.56)
5b	7	$C_{25}H_{23}NO_4$	74.79 (74.73	5.77 5.71	3.49 3.53)
5c	13	$C_{27}H_{25}NO_6$	70.58 (70.63	5.48 5.55	3.05 3.15)
5d	14	$C_{26}H_{25}NO_4$	75.16 (75.10	6.06 6.01	3.37 3.35)

*The values inside the bracket indicate the calculated values.

4. Conclusion

The present study demonstrates a quick and simple method for the synthesis of novel piperidones and pyridinones with good yield in a solvent-free environment assisted by microwave irradiation.

Acknowledgement

The authors are thankful to the Management, Principal of the Ayya Nadar Janaki Ammal College, Sivakasi, Tamil Nadu, India for providing the necessary facilities to carry out this work.

References

[1] N.P. Hari, D. Umashankar, J. Wilson Quail, M. Kawase, H. Sakagami, J.R. Dimmock, Cytotoxic 3,5-bis(benzylidene)piperidin-4-ones and N-acyl analogs displaying selective toxicity for malignant cells, Eur. J. Med. Chem. 43(1) (2008) 1-7.

[2] G. Aridoss, P. Parthiban, R. Ramachandran, M. Prakash, S. Kabilan, Y.T. Jeong, Synthesis and spectral characterization of a new class of N-(N-methylpiperazinoacetyl)-2,6-diarylpiperidin-4-ones: antimicrobial, analgesic and antipyretic studies, Eur. J. Med. Chem. 44(2) (2009) 577-592.

[3] P.S. Watson, B. Jiang, B. Scott, A diestereoselective synthesis of 2, 4–disubstituted piperidines: scaffolds for drug discovery, Org. Lett. 2 (2000) 3679 - 3681.

[4] A. Loupy, A. Petit, F. Hamelin, F. Texier-Boullet, P. Jacquault, D. Mathe, New solvent free organic synthesis using focused microwaves, Synthesis 9 (1998) 1213-1234.

[5] C.R. Noller, V. Baliah, The preparation of some piperidine derivatives by the mannich reactions, J. Am. Chem. Soc. 70 (1948) 3853-3855.

[6] A. Srikrishna, P.P. Kumar, Napthalenes via microwave irradiation induced rearrangement on montmorilonite K–10, Tetrahed. Lett. 36 (1995) 6313-6316.

[7] J. Heilmann, I. Merfort, M. Weiss, Radical scavenger activity of different 3',4'–dihydroxy flavonols and 1,5 dicaffeoylquinic acic studied by inhibition of chemiluminescenc, Planta Med. 15 (1995) 435-438.

[8] R. Larson, The antioxidants of higher plants, Phytochem. 7 (1988) 969-978.

[9] K. Kanagalakshmi, M. Premanathan, R. Priyanka, B. Hemalatha, A. Vanangamudi, Synthesis anticancer and antioxidant activities of 7-methoxyisoflavone and 2,3-diarylchromanone, Eur. J. Med. Chem. 45 (2010) 2447-2452.

[10] M.M. Compton, A biochemical hallmark of apoptosis: internucleosomal degradation of the genome, Cancer Metastasis Rev. 11 (1992) 105-119.