ISSN: 2348-8948
Vol: 2; Issue: 9

RESEARCH ARTICLE

Microwave induced synthesis of 3-arylidene-4-piperidone derivatives as promising antimicrobial analogs

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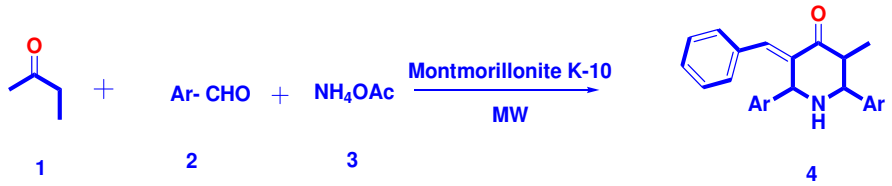
Date Received:	Date of Accepted:	Date Published:
12-Sep-2014	25-Sep-2014	30-Sep-2014

Abstract:
A new class of novel 3-benzylidene-3-methyl-2, 6-diarylpiperidin-4-ones has been efficiently synthesized in the presence of eco friendly Montmorillonite clay catalyst by means of mannich reaction. The synthetic method provides the basis and advantages of a simple experimental procedure and easy recovery and reuse of catalyst, which makes it a highly practical and environmentally benign pathway for the synthesis of substituted 4-piperidones. Besides, the synthesized compounds were evaluated for their antibacterial and antifungal activities against a spectrum of microbial organisms.

Keywords: Mannich reaction ● Solvent free ● Reusable ● Antibacterial studies ● Montmorillonite K-10



Ar= C_6H_5, 3-$MeOC_6H_5$, 2-OHC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$

Introduction

The three-component coupling Mannich reactions are the most important carbon-carbon bond forming reactions in organic synthesis and are conventionally used for the development of construction of nitrogenous molecules as well [1-2]. Various methodologies have been adopted for Mannich reactions via organic and mineral acids [3], such as proline [4,5], acetic acid [6], dodecylbenzenesulfonic acid [7], Bronsted acids, some Lewis acids, and Lewis base catalysis. [8-10]. However, these methods often suffer from the drawbacks of long reaction times and harsh reaction conditions, toxicity, and difficulty in product separation, which limit their use in the synthesis of complex molecules.

This has led to search for economical, cheap and better catalysts, and we utilized to Montmorillonite K-10 (MK-10) clay as a catalyst under controlled reaction condition for Mannich reactions.

MK-10 is widely considered as a green heterogeneous catalyst which is commercially available as smectite clay, used as a catalyst in organic synthesis [11] is reflected in a huge number of reports and reviews [12]. However in our research group we have recently reported the catalytic properties of montmorillonite clay in mannich reaction for synthesis of *N*-methyl-4-piperidones [13]. In continuation of our efforts towards the synthesis of bioactive compounds [14-15],

we report herein a simple and practical new synthetic method for the preparation of 3-arylidene-4-piperidone derivatives involving MK-10 catalyzed condensation of 4-piperidones with aldehydes under microwave irradiation according to scheme1.

2. MATERIALS AND METHODS

Required chemicals were purchased from Sigma-Aldrich, Merck. Melting points of the 3-benzylidene piperidin-4-ones were recorded are uncorrected. Column chromatography was performed on silica gel (230–400 mesh). FTIR spectra in KBr pellets were recorded on Nucon Infrared spectrophotometer. Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Avance III 500 MHz (AV 500) spectrometer. HRMS were recorded on Finnegan Mat 8230 mass spectrometer (EI mode)

2.1 General procedure: Synthesis of 3-benzylidenepiperidin-4-ones 4a-4e

Ammonium acetate **3** (1 mmol), freshly distilled aromatic aldehyde**2** (3.5 mmol), ketone**1** (1 mmol), and montmorinollite K–10 (10 mmol %) were mixed thoroughly and irradiated in microwave oven at 130 °C and 80W power for the specified time (Table 1). On completion, ethyl acetate was added to the reaction mixture, and the granules of the catalyst were filtered. The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure; the solid obtained was purified by column chromatography using petroleum ether: ethyl acetate as eluent to give the 3-benzylidenepiperidin-4-ones **4a-4e** in high yield.

(Z)-3-benzylidene-2,6-diphenyl-5-methylpiperidin-4-ones(4a):

Yellow solid, mp123-124 °C, IR ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (d, 3H, *J* = 8 Hz, CH_3), 2.11 (s, 1H, NH), 2.63-2.80 (m, 1H, H-3), 3.63 (d, 1H,*J* = 4, H-6) 4.08 (d, 1H, *J* =11 Hz, H-2), 7.02 (m, CH=CH), 7.11-7.35, ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.9, 141.8, 141.7, 138.1, 136.4, 134.2, 131.6, 130.3, 129.1, 128.9, 128.7, 128.5, 128.4, 127.8, 127.7, 127.4, 127.2, 63.1, 54.2, 47.1, 42.4; IR (KBr,cm^{-1}) ν = 3298, 1702, 1638, 700;HRMS: m/z = 353.3991 (M^+).

3-(3-Methoxybenzylidene-2,6-bis(3-methoxyphenyl))-5-methylpiperidin-4-one (4b) :

White solid, mp 128-129 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (d, 3H, *J* =3.8 Hz, CH_3), 2.08 (s, 1H, NH), 3.83, 3.85, 3.91 (s, 9H, 3X OCH_3), 2.84 (m, 1H, H-3), 3.75 (d, 1H, *J* =10.9 Hz, H-2), 4.19 (dd, 1H, *J* = 3 and 11 Hz, H-6), 7.09 (m, CH=CH), 6.48-7.65 (m, 12H);^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 160.6, 160.5, 145.3, 143.4, 140.3, 129.3, 128.5, 127.4, 126.7, 125.4, 112.5, 112.1,68.5, 61.8, 55.2, 54.9, 52.8, 10.1;IR (KBr cm^{-1}) : ν 3305, 1708, 1635, 702; HRMS: m/z 443.4538 (M^+).

(Z)-3-(2-Hydroxyphenylbenzylidene)-2,6-bis(2-hydroxyphenyl)-5-methylpiperidin-4-one(4c):

Pale yellow solid, mp 145-146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.1 (s, 1H, CH_3), 3.88,3.89 (d, 2H, *J* =11.1 Hz, H-2&6), 2.4 (d, 1H, *J* =10.8 Hz, H-3), 6.75-8.47 (m, 12H), 7.11 (m, CH=CH), 8.54 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.1, 167.4, 161.5, 161.18, 160.6, 151.1, 132.9, 132.8, 132.4, 131.78, 129.3, 127.7, 122.7, 121.5, 121.2, 118.9, 117.1, 116.4, 68.1, 65.1, 41.8, 13.22; IR (KBr, cm^{-1}): ν 3297, 1701, 1631, 698, HRMSm/z: 401.7643 (M^+).

(Z)-3-(4-Chlorobenzylidene)-2,6-bis(4-chlorophenyl)-5-methylpiperidin-4-one (4d):

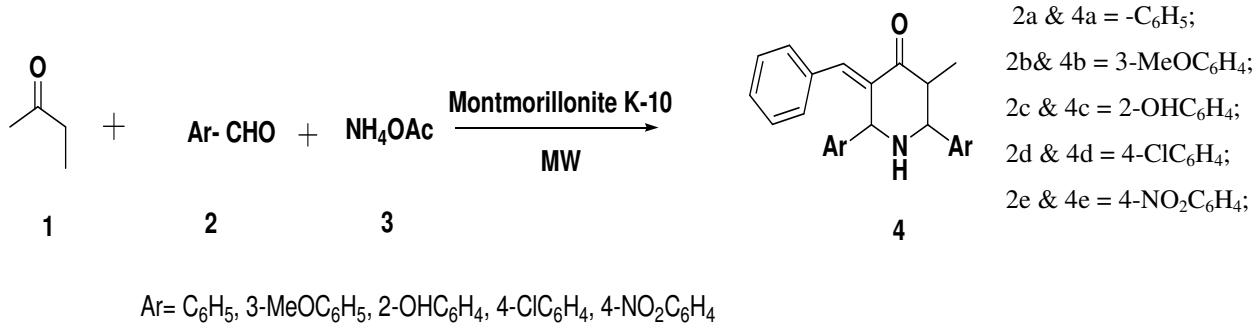
White solid, mp 133-134 °C;^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (d, 3H, CH_3),2.22 (s, 1H, NH), 2.71 (m, 1H, H-3), 3.77 (d, 1H, *J* =11 Hz, C_2-H), 3.84 (d, 1H, *J* =10.5 Hz, H-6), 6.88-7.99 (m, 12H), 6.98 (m, CH=CH);^{13}C NMR (125 MHz, $CDCl_3$): δ 209.5, 135.7, 135.6, 132.7, 131.4, 131.1, 130.9, 130.1, 129.3, 128.8, 128.6, 128.3, 127.9, 127.6, 126.2, 68.3, 61.9, 51.4, 10.2; IR (KBr, cm^1): ν = 3298, 1708, 699; HRMS *m/z*: 456.8756 (M^+).

(Z)-3-(3-Nitrobenzylidene)-2,6-bis(3-nitrophenyl)-5-methylpiperidin-4-one(4e):

Pale yellow solid, mp 135-136°C; IR (KBr): ν = 3296, 1701 cm^{-1}, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (d, 3H, CH_3), 2.12 (s, 1H, NH), 3.82 (m, 2H, H-2&6), 3.55 (m, 1H, H-3), 6.75-8.13 (m, 12H), 7.11 (m, CH=CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.1, 148.5, 140.7, 138.5, 137.2, 136.2, 134.4, 132.7, 129.7, 123.7, 121.7, 120.5, 119.6, 118.6, 66.5, 63.4, 53.1, 10.3; HRMS *m/z* : 488.3498 (M^+).

3. RESULTS AND DISCUSSION

In order to formulate the effective conversion system, the synthesis of 3-benzylidene-5-methyl-2,6-diarylpiperidine-4-ones, (**4a**) from ketone (**1a,** 1 mmol), aldehyde (**2a,** 3.5mmol) and ammonium acetate(**3a,** 1 mmol) was chosen as a model reaction to evaluate the influence of different catalyst loadings under solvent free condition. Initially, we carried out the reaction under microwave irradiation (110 ºC, 55 W) for 5 min under solvent free conditions in the presence of 10 mol% of Montmorillonite K-10 (MK-10) catalyst, and 85% yield was detected (Table 2, entry 1). The usage of 9, 8 and 5 mol% of catalyst resulted in 82, 78 and 73% yield, respectively (Table 2, entry 2), which indicates that the decreased catalyst loadings lead to reduced yields. Further, an increase of catalyst loadings (11mol %) did not improve the yield significantly (Table 2, entry 3).



Scheme 1. Synthesis of 3-benzylidene-5-methyl-2, 6-diarylpiperidine-4-ones, **4a-e**

Obviously, the use of 10 mol% of catalyst is considered to be sufficient to promote the reaction. The reaction under catalyst-free condensations failed to yield the expected product even after a prolonged reaction time (Table 2, entry 4). The reaction was also performed under green chemical microwave irradiation which resulted better yield than the conventional method (Table 1). The results indicate that the reaction efficiency and yields in solution are lower than those obtained under solvent free conditions under microwave irradiation. The advantage of this method is economical and eco-friendly as neither any byproduct was formed nor any toxic material was used during the synthesis and the reactions were carried out at ambient temperature.

With the availability of the best reaction conditions in hand, we tried to recover and reuse the MK-10 catalyst. Aftercompletion of the reaction for the first run, diethyl ether was added to the resulting mixture to separate the product.

The remaining solid catalyst was recovered by filtration and reused in the next run without further purification under the optimized reaction conditions. This procedure was repeated six times, and the results are outlined in Table 1 (entry 9). The detected yields were observed to be close in proximity to the initial value in the previous four cycles, and subsequently a slight gradual decrease in the yields was observed in the two latter cycles. Hence, the catalyst could be effectively recycled for at least four times without any loss of activity.

To investigate the generalization of this synthetic method under optimized reaction conditions , various aliphatic ketones 1, and aromatic aldehydes bearing strong electron withdrawing groups (such as $–NO_2$, -Cl) or electron releasing groups such as ($-CH_3$, $-OCH_3$,-OH) were employed for the synthesis of benzylidene piperidones. The aryl aldehydes possessing electron donating groups showed faster reactions and results the product formation in short time 5h (Table 1, entry 1, 2, 3) which might be attributed to more easy formation of benzylidene piperidones.

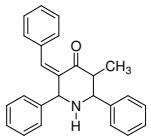
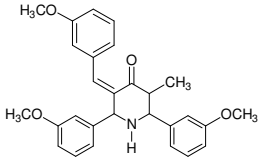
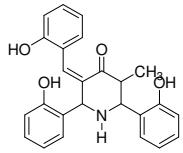
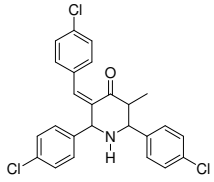
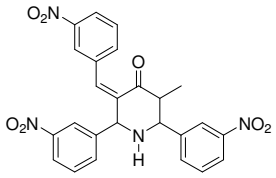
The structures of compounds **4a-e** were deducted from their elemental analyses, and their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The IR spectral investigation for the compound **4a** shows the peaks at 3293.34, 1703.21 and 1628.29 cm^{-1} which corresponds to NH, -C=O and –CH=CH- peaks respectively. In ^{1}H NMR methyl group appears at 1.09 as a doublet and NH peaks appears at 2.1 as singlet, aliphatic protons appears at 2.4ppm, 3.9 and aromatic peaks appears from 6.751 to 8.477 ppm whereas –OH group occurs at 13.2 ppm and also the appearance of 7.27 in aromatic region shows the presence of -CH=CH. In ^{13}C NMR aliphatic carbons appears at 8.91, 13.22, 28.12, 41.85, 65.18 and 68.02 peaks respectively. Aromatic carbons represented at 116.44 to 167.48, whereas carbonyl group appears at 210.1 ppm and the CH=CH group were also found at aromatic region 141.84 ppm for compound **4a**. Likewise same pattern has been observed in all other derivatives.

3.1 Antimicrobial activity

All the synthesized 3-benzylidenepiperidin-4-ones **4a-e** were tested for their antibacterial activity in vitro against *Staphylococcus aureus* (ATCC 25923), *Staphylococcus epidermidis* (ATCC 3583), *Bacillus subtilis* (ATCC 2063) (Gram-positive bacteria) and *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 13883), and *Pseudomonas aeruginosa* (ATCC 27853) (Gram-negative bacteria) by a well-diffusion method (Barry, 1976; Dhar et al., 1968). *Ampicillin* was used as a standard drug. The antifungal activity was screened against *Aspergillusniger*, *Aspergillus flavus*, *Aspergillus fumigatus*, and *Candida albicans*. *Amphotericin B* (25 µg mL^{-1}) was used as a standard drug.

For the bioassay, the compounds were dissolved in DMSO. The two-fold dilution of the compounds was prepared (2.0µg/mL, 1.0 µg/mL, 0.5µg/mL, 0.25µg/mL, 0.125µg/mL, 0.062µg/mL, 0.031µg/mL, 0.015µg/mL, 0.0078 µg/mL, 0.0039µg/mL). No antimicrobial activity was observed in the solvent employed. The results of MIC values are given in Table 2 in comparison with those of *amphicillin* and *amphotericin B* was used as standard drugs for bactericidal and fungicidal activity.

Table 1 :Synthesis of 3-benzylidene-5-methyl-2, 6-diarylpiperidine-4-ones, 4a-e

		Conventional[a]		Microwave[a]	
		Time/h	Yield[b]	Time/min	Yield[b]
1	 **4a**	10	73	5	85
2	 **4b**	9	65	3	78
3	 **4c**	8	63	3.5	78
4	 **4d**	9	45	4	75
5	 **4e**	8	58	4	70

Reaction Condisitions: [a]benzaldehyde (3.5 mmol) and ethyl methyl ketone (1 mmol), ammonium acetate (1 mmol), MK 10 (10mmol %) [b]Isolated Yield

Table 2 Screening optimized reaction conditions for the synthesis of 4a-gand investigation for the reuse of catalyst.

Entry	Catalyst loadings/ mol %	Catalyst	Yield % [a]
1	10	Montmorinollite K-10	85
2	9,8,7	Montmorinollite K-10	82, 78, 73
3	11	Montmorinollite K-10	
4	-	-	-[b]
5	10	Montmorillonite KSF	-
6	10	Acidic alumina	25
7	10	Silica	35
8	10	Bentonite	28
9	10	Acetic Acid	51
10	10	Ethanol	32
11	10	MK-10	83,81,78,76,73[c]

Reaction conditions: benzaldehyde (3.5 mmol) and ethyl methyl ketone (1 mmol), ammonium acetate (1 mmol), were irradiated at 120 C, 55W for 5 min. [a]Yields % ; [b] The reaction was carried out without catalyst ; [c] Yields % as the MK-10 catalyst was reused for 6 cycles

Table 3:Biological screening of 3-benzylidene-5-methyl-2,6-diphenylpiperidin-4-ones, 4a-f

Compd.	Minimum Inhibition Concentration (µg mL^{-1})									
	Bacterial strains*						Fungi strains**			
	A	B	C	D	E	F	G	H	I	J
4a	-	0.5	0.5	-	-	0.25	-	0.25	-	-
4b	-	0.5	-	-	0.25	-		0.5	-	0.25
4c	-	0.25	-	0.25	-	-	0.25	0.25	0.5	0.5
4d	0.25	0.5	-	-	0.25	-	-	-	0.5	-
4f	0.125	0.25	0.25	-	-	0.5	0.25	0.25	0.5	0.25
Std 1	0.125	0.125	0.125	0.125	0.125	0.125	-	-	-	-
Std 2	-	-	-	-	-	-	0.031	0.031	0.031	0.031

*- **A**- *S. aureus*, **B**- *S. epidermidis*, **C**- *Bacillus*, **D**-*E.Coli*, **E**-*Klebsila*, **F**- *Pseudomonas aeruginosa;* ** - **G**- *A. flavus*, **H**- *A. fumigatus*, **I**- *A. niger*, **J**- *Candida albicans;* **std 1**- *Amphicillin*; **std 2**: *Amphotericin B*

In general all the synthesized compounds exerted a wide range of modest antimicrobial activity in vitro against the tested organisms (Table 3). Compounds **4b, 4d** shown potent bacterial activity against *klebsiella* and the compounds **4c, 4d** also were shown good activity towards bacteria *S. epidermis* and the compound **4f** were more active against gram positive bacteria as well as fungi strains. Compounds **4c, 4f** shown good activity against *A.flavus* and compounds **4b, 4d** was more active against *C.albanical*. These results shown that electron withdrawing groups such as $–NO_2$ and –OH groups were shown potent activity against bacteria and fungi strains, whereas other compounds were shown moderate activity. All other compounds were almost active.

4. CONCLUSION

In conclusion, we describe a simple and efficient preparation of benzylides**4a-g**, from ketones, aldehydes and ammonium acetate under mild conditions, using a MK-10 as catalyst. The catalyst can be recovered and reused at least four times without apparent loss of activity. Use of a clay catalyst for this preparation has several advantages, it avoids use of either strongly acidic or basic conditions and the reaction has carried out under solvent-free condition. Simple work up, ease of recovery, and reuse of this catalyst are expected to contribute to the development of a green strategy for preparation of benzylidenes.

ACKNOWLEDGEMENTS

The authors wish to express their thanks to the Technology Business Incubator, VIT University and the SAIF, Indian Institute of Technology, Madras, for providing analytical facilities.

REFERENCES

1. Arend M, Westermann B, Risch P. Modern Variants of the Mannich Reaction, *Angew. Chem. Int. Ed.*1998, 37, 1044-1070.
2. Kobayashi S, IshitaniH.Catalytic Enantioselective Addition to Imines, *Chem. Rev.*1999, 99, 1069-1094.
3. Mitsumori S,Zhang H, Cheong P. H,HoukK. N.,TanakaF.,BarbasC. F. Direct Asymmetric *anti*-Mannich-Type Reactions Catalyzed by a Designed Amino Acid,*J Am Chem Soc.*2006, 128 (4), 1040–1041.
4. List B, Pojarliev P,Biller W. T, MartinH. J.The Proline-Catalyzed Direct Asymmetric Three-Component Mannich Reaction: Scope, Optimization, and Application to the Highly Enantioselective Synthesis of 1,2-Amino Alcohols,*J. Am. Chem. Soc.*2002, 124 827-833.
5. List B.The Direct Catalytic Asymmetric Three-Component Mannich Reaction, *J. Am.Chem. Soc*.2000, 122, 9336-9337.
6. Duthaler R. O.Proline-Catalyzed Asymmetric α-Amination of Aldehydes and Ketones—An Astonishingly Simple Access to Optically Active α-Hydrazino Carbonyl Compounds,*Angew. Chem. Int. Ed.* 2002, 42, 975-978.
7. Mogilaiah K. Kankaiah G.Synthesis and antibacterial activity ofnovel Mannich bases containing 1,8-naphthyridine moiety,*Indian J. Het. Chem.*2002, 1, 283-286.
8. Manabe K,Mori Y, Kobayashi S.Three-component carbon±carbon bond-forming reactionscatalyzed by a Brùnstedacid-surfactant-combined catalyst in water,*Tetrahedron* 2001, 57, 2537-2544.
9. Kobayashi S,Hamada T, Manabe K. The Catalytic Asymmetric Mannich-Type Reactions in Aqueous Media, *J. Am. Chem. Soc*. 2002, 124 (20) 5640-5641.
10. Ishimaru K, Kojima T.Stereoselective synthesis of *trans*-2,6-diaryl-4-piperidones by usingbenzaldiminetricarbonylchromium derivatives, J.Chem.Soc.Perkin Trans. 2000, 1, 24, 2105.
11. RaquelA. P. C. et al., Improved methodologies for synthesis of prenylatedxanthones by microwave irradiation and combination of heterogeneous catalysis (K10 clay) with microwave irradiation, Tetrahedron 2009, 65,3848–3857.
12. Toshima K. et al., A highly stereoselective synthesis of β-olivosides by glycosidations of 2-iodo-olivosyl fluoride using montmorillonite K-10 as an environmentally benign solid acid, Green. Chem. 2002, 4, 27–29.
13. Nithya. P, Mohanaroopan S, Khan F. N., et al., Environmentally benign one-pot synthesis and antimicrobial activity of 1-methyl-2,6-diarylpiperidin-4-ones, Chem. Papers 2011, 65, 743–746.
14. Nithya P., et al., 1, 3-Dimethyl-2, 6-diphenylpiperidin-4-one, ActaCrystE65: o43
15. Khan F. N, Nithya P, et al., Synthesis of 2- Amino- 1, 3, 4-thiadiazoles,Indian J. Het. Chem.2009, 19, 83-84.