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Synthesis and NMR spectral studies of polyfunctionalized polymethoxyphenyl piperidones

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Abstract: The piperidine skeleton is a building block that found in various natural products and biologically active compounds. Hence, the synthesis of new molecules with bio-active piperidine nucleus and the investigation of the stereochemistry of synthesized molecules are significant in the field of medicinal chemistry. As stereochemistry of the molecules is a major criterion for their biological response, it is of immense help to establish the stereochemical structure of newly synthesized compounds. Based on the above credentials of piperidine moiety, synthesis of some polyfunctionalized piperidin-4-ones were undertaken to achieve new molecules and to establish their stereochemistry. Since the methoxy groups are responsible pharmacophore for antioxidant property and many biological actions, the synthesis has been targeted towards polyfunctionalized polymethoxyphenylpiperidin-4-ones. Accordingly, the target molecules were achieved as single isomer by successive Mannich condensations with necessary modification in the reaction conditions, reactants and their quantity. Stereochemical investigations were carried out using NMR spectral data. Despite the possibility of chair, boat, twist-boat, and half-boat conformers for the six-membered piperidine, both the new compounds exist in chair conformation with equatorial orientation of both methyl substituents on the active methylene centers and polymethoxyphenyl groups on both sides of the secondary amine group.

Introduction

Nitrogen heterocycles constitute a vital role in organic chemistry especially in the field of medicinal chemistry[1-2]. Nitrogen heterocycles exhibit interesting chemical reactions and important biological actions such as antibacterial, antimycobacterial, antiinflammatory, antiarrhythmic, antifungal, antiallergic, antiprotozoan, anticholinergic, antitumor, anticonvulsant, antiviral, antimalarial, local anesthetic, antineoplastic, hypotensive, cytotoxic, muscle relaxant, analgesic, herbicidal, tyrosinase inhibitor, CNS stimulant/CNS depressant, tranquilizer and nicotinic acetylcholine receptor activity[3-8].

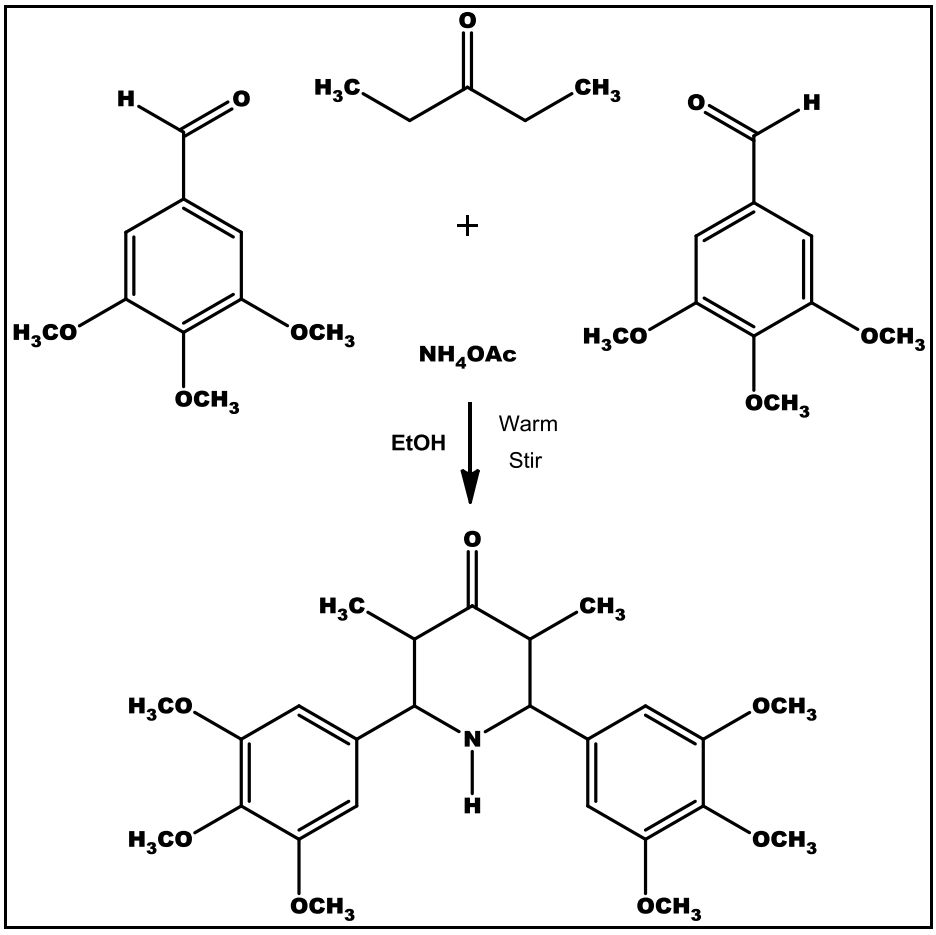
Organic and medicinal chemistry, becoming very essential chemistry, explores the role of organic chemists towards isolation, characterization and synthesis of new compounds that can be used as medicine for the prevention, treatment and cure of diseases. The main concern of an organic chemist normally lies in conceiving an ideal structure of needed drug with negligible or minimal adverse effects usually based on theoretical consideration and in constructing a plausible way for an advantageous synthesis towards that target drug. Hence chemists having specific reason for synthesizing a particular compound, have to work backward starting from the structure of the compound *i.e.*, to adopt retrosynthetic approach.

Since biological actions often crucially depend on the stereochemistry of the molecules, the present study was intended to synthesize as well as stereochemical analysis of two polyfunctionalized polymethoxyphenyl piperidones, namely, 3,5-Dimethyl-2,6-*bis*(3,4,5-trimethoxyphenyl)piperidin-4-one (**1**) and 3,5-Dimethyl-2,6-*bis*(2,3,4-trimethoxyphenyl) piperidin-4-one (**2**).

Experimental

Synthesis of 3,5-dimethyl-2,6-bis(3,4,5-trimethoxyphenyl) piperidin-4-one (1)

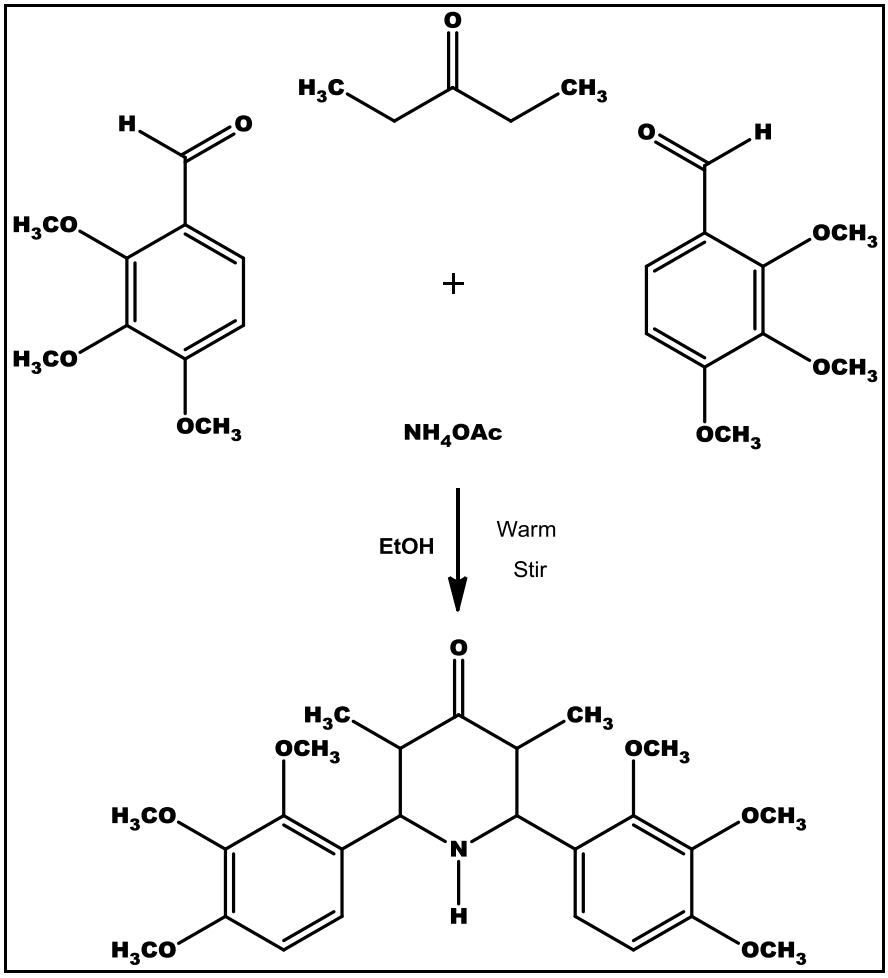
The 3,5-dimethyl-2,6-*bis*(3,4,5-trimethoxyphenyl)piperidin-4-one was synthesized by modified Mannich condensations[9] in one-pot, using 3,4,5-trimethoxybenzaldehyde (0.2 mol), 3-pentanone (0.1 mol) and ammonium acetate (0.1 mol) in 50 ml of absolute ethanol. Initially, the mixture was gently warmed on a hot plate at 318 K (45° C) with moderate stirring then, until the complete consumption of the starting materials, which was stirred at 35-40° C. After the conversion of starting materials, the crude piperidone was separated by filtration and gently washed with cold ethanol-ether mixture. Synthesis of this target molecule is shown in **Scheme 1**.



Scheme 1: Synthesis of the target compound 1

Synthesis of 3,5-dimethyl-2,6-bis(2,3,4-trimethoxyphenyl) piperidin-4-one (2)

The 3,5-dimethyl-2,6-*bis*(2,3,4-trimethoxyphenyl)piperidin-4-one was synthesized by modified Mannich condensations in one-pot, using 2,3,4-trimethoxybenzaldehyde (0.2 mol), 3-pentanone (0.1 mol) and ammonium acetate (0.1 mol) in 50 ml of absolute ethanol. Initially, the mixture was gently warmed on a hot plate at 318 K (45° C) with moderate stirring then, until the complete consumption of the starting materials, which was stirred at 35-40° C. At the end, the crude piperidone was separated by filtration and gently washed with cold ethanol-ether mixture. Synthesis of this target molecule is schematically represented (**Scheme 2**).



Scheme 2: Synthesis of the target compound 2.

Results and Discussion

Physical properties and elemental composition of the target compounds 1 and 2

The nature and physical appearance, color, melting point, yield and elemental composition of the target piperidones **1** and **2** are presented in **Table 1**. The observed C, H, N and O percentages are in good agreement with the theoretical values and empirical formula of the target compounds.

Table 1: Physical properties and elemental analysis data of compound 1 and 2.

Properties	**Compound 1**	**Compound 2**
Molecular formula	$C_{25}H_{33}NO_7$	$C_{25}H_{33}NO_7$
Molecular weight	459.53	459.53
Color	White	Off-white
Physical appearance and nature	Amorphous powder	Amorphous powder
Melting point	170 °C	217 °C
Yield	80%	78%
Elemental composition: C	65.24 (65.34)	65.40 (65.34)
H	7.20 (7.24)	7.22 (7.24)
N	3.06 (3.05)	3.05 (3.05)
O	24.39 (24.37)	24.33 (24.37)

The values within the brackets are calculated values.

IR spectral assignments of target compounds

In 3,5-dimethyl-2,6-*bis*(3,4,5-trimethoxyphenyl)piperidin-4-one (compound **1**), the characteristic vibrational band at 1710 cm^{-1} is supported by the reported stretching frequency of the C=O group of the unsubsubstituted 2,6-diphenylpiperidin-4-one. Also the absence of the stretching frequency of the C=O group of the starting material 3,4,5-trimethoxybenzaldehyde at 1683 cm^{-1} supports the complete consumption of aldehyde starting material and formation of the expected cyclic ketone. Similarly, a sharp band observed at 1707 cm^{-1} for the compound **2** instead of the sharp band at 1679 cm^{-1} for the aldehyde.

The strong absorption band observed at about 3300 cm^{-1} in the IR spectrum is normally assigned to the N-H stretching mode of the secondary amine. Hence, the appeared characteristic IR band at 3322 and 3323 cm^{-1} are assigned to the N-H stretching of the secondary amine of the target molecules **1** and **2**, respectively.

NMR spectral assignments of target compound 1

^{1}H NMR:

For a better comprehension of NMR spectral assignments, the complete labelling of the target compound **1** is depicted in **Figure 1** and its NMR spectrum and assignments are reproduced in **Figure 2** and **Table 2**.

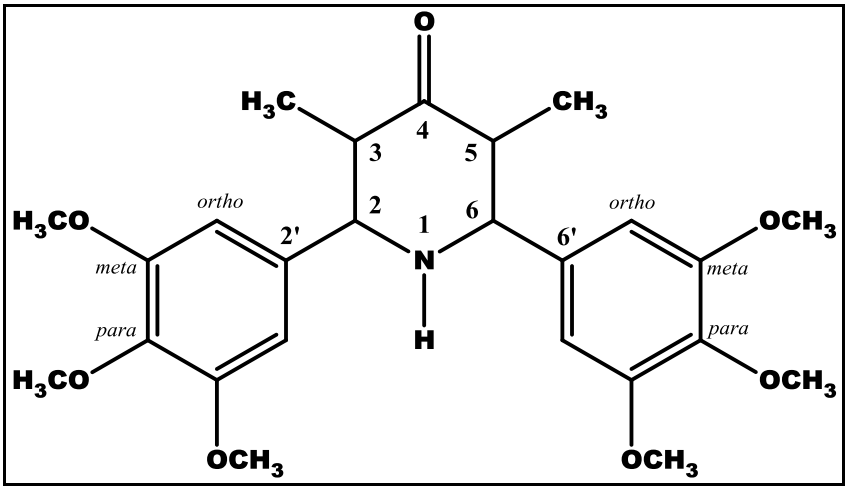


Fig. 1: Numberings of the target compound 1.

Only one singlet observed in the aryl region at 6.67 ppm with four protons integral. Since the aryl substituent is 3,4,5-trimethoxyphenyl, obviously the aryl protons resonances are due to the *ortho* protons of the phenyl groups at C-2 and C-4.

The high intensity sharp singlets at 3.88 (12H) and 3.83 (6H) ppm are obviously due to the presence of methoxy groups at *meta* and *para* positions of the phenyl group attached to C-2 and C-4.

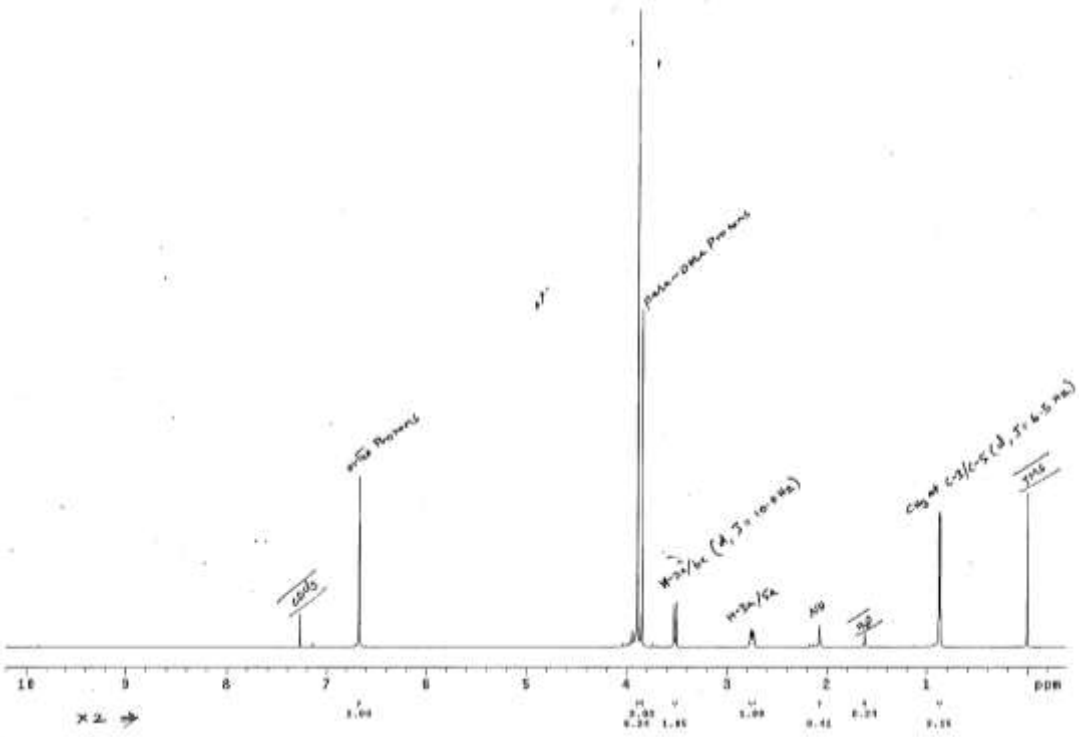


Fig. 2: ^{1}H NMR spectrum of the target compound 1.

There are two doublets observed at 3.51 and 0.87 ppm. The former one corresponds to two protons whereas the latter is meant for six protons. Hence, by comparing with 3,5-dimethyl-2,6-diphenylpiperidin-4-one, 3,5-dimethyl-2,6-*bis*(3-methoxyphenyl)piperidin-4-one and 3,5-dimethyl-2,6-*bis*(4-methoxyphenyl) piperidin-4-one, the two protons doublet is assigned to the protons at C-2 and C4, which are in axial position (i.e., H-2a and H-4a, $^{3}J_{2a,3a}$ = 10.0 Hz). Hence it is clear by the diaxial vicinal coupling constant that the protons at C-2 and C-6 are in axial position, which indicates that the polyfunctionalized phenyl groups attached to C-2 and C-4 are obviously adopt the equatorial disposition.

Interesting information from the observed vicinal coupling constant is, the protons at C-3 and C-5 adopt axial and thus, it is clear that the methyl groups at C-3 and C-5 engaged equatorial position. Since the molecule is symmetric, the methyl groups at C-3 and C-5 appear at 0.87 ppm (d, J = 6.5 Hz). The protons at C-3 and C-5 split the methyl signal as doublet, whereas, the methyl groups split the protons at C-3 and C-5 as a quartet and further splitted by the protons at C-2 and C-6, thus a multiplet formed and appears at 2.75 ppm.

The singlet at 2.07 (1H) ppm is allocated to the secondary amine group (i.e., NH proton in the first position. In the proton NMR spectrum of compound **1**, the water (moisture) peak in $CDCl_3$ appears at 1.62 ppm and the residual $CHCl_3$ of $CDCl_3$ appears at 7.26 ppm. Since TMS is used as internal reference in $CDCl_3$, the spectrum is corrected to 0.00 ppm for TMS.

Table 2: ^{1}H NMR spectral assignments of 3,5-dimethyl-2,6-*bis*(3,4,5-trimethoxyphenyl) piperidin-4-one 61 in $CDCl_3$.

Chemical shift [δ (ppm)]	**Proton**
6.67, s, 4H	*ortho* protons of the phenyl groups at C-2 and C-6
3.88, s, 12H	*meta*-OMe protons
3.83, s, 6H	*para*-OMe protons
3.51, d, 2H, $^{3}J_{2a,3a}$ = 10.0 Hz	H-2a and H-4a (benzylic protons)
2.75, m, 2H	H-3a and H-5a (methinic protons)
2.07, s, 1H	NH
0.87, d, J = 6.5 Hz	Methyl groups at C-3 and C-5

By considering the coupling constant along with the comparison of benzylic and methinic protons of compound **1** with analogous molecules, it is suggested that the compound **1** adopts a chair conformation with equatorial orientation of the 3,4,5-trimethoxyphenyl group at C-2/C-4 and methyl group at C-3/C-5.

^{13}C NMR:

In the ^{13}C NMR spectrum of **1** (**Figure 3**), there are five resonances in the aryl region beyond 100 ppm including the carbonyl carbon (C=O) of C-4 at 210.86 ppm. Of the remaining four signals at 153.18, 137.66, 134.47 and 104.51, the most intensed as well as most downfield signal at 153.18 ppm is attributed to the OMe bearing *ipso* carbons in the *meta* positions, whereas, the carbon resonance at 137.47 ppm belongs to the OMe bearing *ipso* carbons in the *para* position. The upfield aryl region signal at 104.51 ppm is assigned to the *ortho* carbons of the phenyl groups at C-2 and C-4. The detailed ^{13}C NMR spectral assignments of all the carbon signals are presented in **Table 3**.

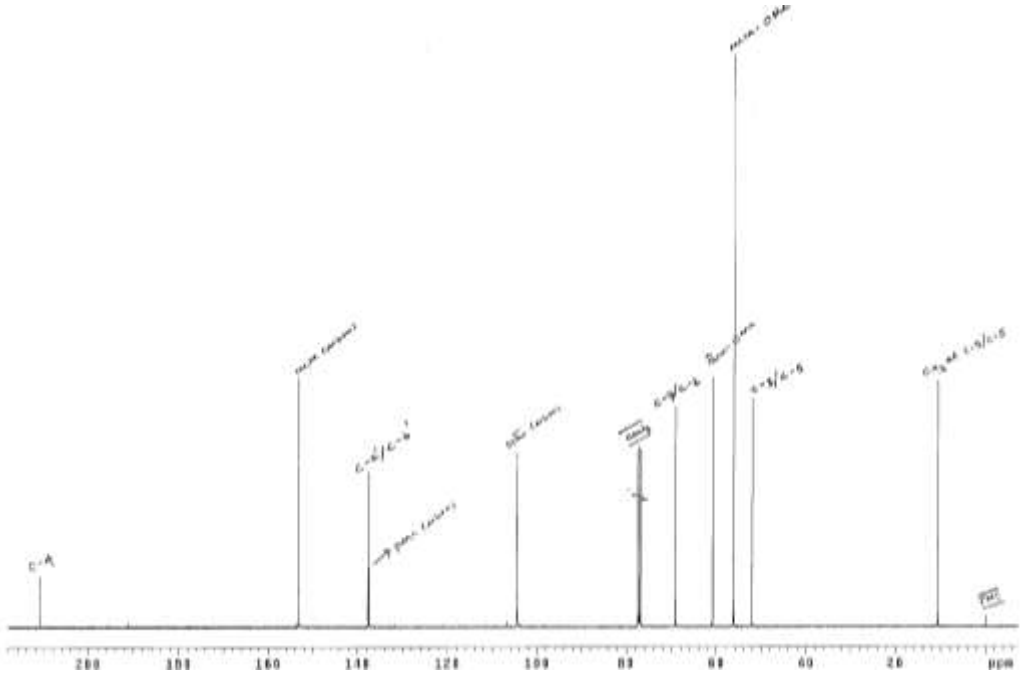


Fig. 3: ^{13}C NMR spectrum of the target compound 1.

Table 3: ^{13}C NMR spectral assignments of 3,5-dimethyl-2,6-*bis*(3,4,5-trimethoxyphenyl) piperidin-4-one 1 in $CDCl_3$.

Chemical shift [δ (ppm)]	Carbon
210.86	C-4
153.18	OMe bearing *ipso* carbons in the *meta* position
137.66	Phenyl *ipso* carbons (C-2' and C-6')
137.47	OMe bearing *ipso* carbons in the *para* position
104.51	*ortho* carbons
69.13	C-2 and C-6
60.86	OMe groups at *para* position
56.16	OMe groups at *meta* positions
52.05	C-3 and C-5
10.64	Methyl groups at C-3 and C-5

The resonances at 69.13 and 52.05 ppm are assigned to the C-2/C-6 and C-3/C-5, respectively. These assignments have been arrived by comparing the carbon resonances of analogous compounds such as 3,5-dimethyl-2,6-diphenylpiperidin-4-one, 3,5-dimethyl-2,6-*bis*(3-methoxyphenyl)piperidin-4-one and 3,5-dimethyl-2,6-*bis*(4-methoxyphenyl)piperidin-4-one.

The upfield resonance in the ^{13}C NMR spectrum at 10.64 ppm is unambiguously assigned to the methyl groups at C-3 and C-5. There are two resonances remain unresolved at 60.86 and 56.16 ppm, which are assigned to the OMe groups at *para* position and *meta* positions, respectively.

Based on the analysis of ^{1}H and ^{13}C NMR spectra of compound **1**, along with the comparison of analogous molecules, it is clear that the target molecule exists in a chair conformation with equatorial orientation of the polymethoxyphenyl groups at C-2 and C-4 as represented in **Figure 4**.

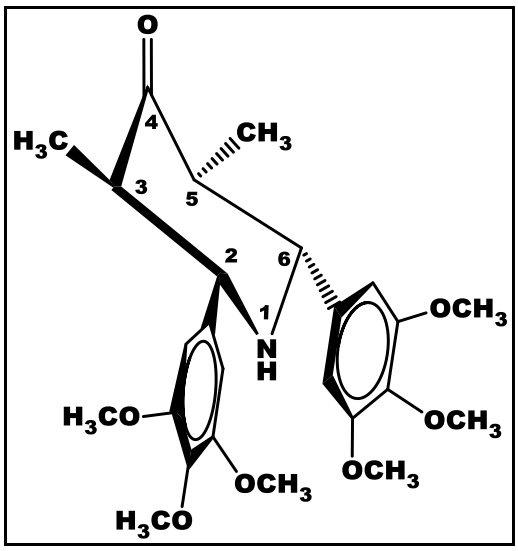


Fig. 4. Chair conformation of the synthesized target compound 1 with equatorial orientations of the 3,4,5-trimethoxyphenyl groups.

NMR spectral assignments of target compound 2

For unambiguous comprehension of the atoms in the new molecule **2**, the numberings annotated and is represented in **Figure 5**.

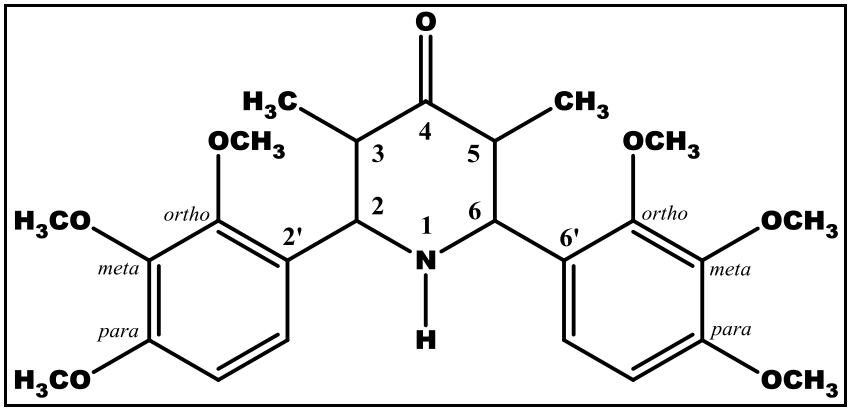


Fig. 5: Numberings of the target compound 2.

^{1}H NMR:

The proton resonance at 7.20 ppm that corresponds to two protons is the *ortho* protons of the phenyl groups at C-2 and C-6. The 6.67 (d, J = 5.5 Hz) ppm resonance corresponds to four protons, which is assigned to the *meta* protons of the phenyl groups at C-2 and C-6. By the interaction of *ortho* protons and nitrogen lone pair electrons, the *ortho* protons are deshielded and appeared at 7.20 ppm. Therefore, a downfield shift of 0.53 ppm than the *meta* protons has been observed, which is due to the foresaid interaction and as a consequence the signal becomes broader.

There are three broad singlets appear in the upfield region of 4.03, 2.82 and 1.95 ppm. Of them, the first two signals correspond to two protons each while the last one at 1.95 ppm corresponds to one proton, which is assigned to NH by comparing with compound **1**. The 2.82 ppm broad singlet is assigned to H-3a and H-5a (methinic protons) since it is appeared similar to that of compound **1** at 2.75 ppm while the H-2a and H-4a (benzylic protons) are deshielded 0.52 ppm and appears at 4.03 ppm. The singlets at 3.90, 3.85 and 3.84 ppm are assigned to the *ortho*-OMe, *para*-OMe and *meta*-OMe protons, respectively; each signal is integrated to six protons. All the above assignments of compound **2** are summarized in **Table 4**.

Table 4: ^{1}H NMR spectral assignments of compound 2 in $CDCl_3$

Chemical shift [δ (ppm)]	**Proton**
7.20, br s, 2H	*ortho* protons of the phenyl groups at C-2 and C-6
6.67, d, *J* = 5.5 Hz, 4H	*meta* protons of the phenyl groups at C-2 and C-6
4.03, br s, 2H	H-2a and H-4a (benzylic protons)
3.90, s, 6H	*ortho*-OMe protons
3.85, s, 6H	*para*-OMe protons
3.84, s, 6H	*meta*-OMe protons
2.82, br s,	H-3a and H-5a (methinic protons)
1.95, br s, 1H	NH
0.87, d, *J* = 6.5 Hz, 6H	Methyl groups at C-3 and C-5

^{13}C NMR:

The complete carbon resonance assignments of compound **2** is reproduced in reproduced in **Table 5** for better understanding of the assignments.

Table 5: ^{13}C NMR spectral assignments of compound 2 in $CDCl_3$

Chemical shift [δ (ppm)]	**Carbon**
212.04	C-4
153.03, 152.00, 141.94, 127.89, 122.31, 107.63	Phenyl carbons
61.35	C-2 and C-6
60.78	OMe group at *meta* positions
56.04	OMe groups at *meta/para* positions
51.61	C-3 and C-5
10.89	Methyl groups at C-3 and C-5

In the ^{13}C NMR spectrum of **2**, there are five resonances in the aryl region beyond 100 ppm. Other than the carbonyl carbon (C=O) of C-4 at 212.04 ppm, the remaining signals at 153.03, 152.00, 141.94, 127.89, 122.31 and 107.63 ppm are allocated to the phenyl carbons. The signals at 61.78 and 51.61 ppm are assigned to the carbon resonances of C-2/C-6 and C-3/C-5, respectively by comparing the spectrum of compound **1**. Similarly, the 10.89 ppm carbon resonance is assigned to the methyl groups at C-3 and C-5. Of the two signals at 60.78 and 56.04, the less intensed signal of 60.78 ppm is assigned to the OMe group at *meta* positions whereas the intensed signal at 56.04 ppm is designated to the OMe groups at *meta* and *para* positions.

Based on proton and carbon NMR spectral studies of compound **2** along with the comparison of analogous molecules, it is suggested that the target molecule **2** exists in a chair conformation with equatorial disposition of the methyl groups at C-3 and C-5, and the bulkiest aryl groups (i.e., 2,3,4-trimethoxyphenyl) at C-2 and C-4 as shown in **Figure 6**.

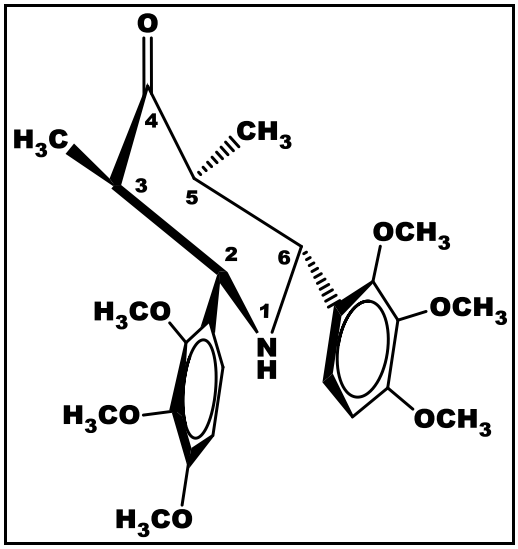


Fig. 6. Stereochemistry of the synthesized compound 2.

Summary and Conclusion

By considering the biological importance of the piperidine nucleus, synthesis of some functionalized piperidin-4-ones such as 3,5-dimethyl-2,6-*bis*(3,4,5-trimethoxyphenyl) piperidin-4-one (compound **1**) and 3,5-dimethyl-2,6-*bis*(2,3,4-trimethoxyphenyl)piperidin-4-one (compound **2**) were achieved by modified, improved and optimized Mannich condensation using 3-pentanone, ammonium acetate and appropriated benzaldehyde in warm ethanolic medium.

After the preliminarily identification of the synthesized target compounds by their physical, elemental composition and IR data. The compounds were studied by ^{1}H and ^{13}C NMR techniques, to explore their stereochemistry.

There are a number of stereomers are possible as witnessed by the stereogenic centers in the target molecules, however, they were achieved as single isomer with high yield. Another interesting result from this study is, even though a strong possibility for these molecules to adopt either boat or twist-boat, both the target molecules **1** and **2** adopt a chair conformation with equatorial disposition of the highly functionalized phenyl groups (i.e., 3,4,5-trimethoxyphenyl in compound **1** and 2,3,4-trimethoxyphenyl in compound **2**). The methyl groups at C-3 and C-5 also adopted equatorial disposition in the chair conformation.

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