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ORIGINAL PAPER

Convenient synthesis and NMR spectral studies of variously substituted *N*-methylpiperidin-4-one-*O*-benzyloximes

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Abstract A series of variously substituted *N*-methylpiperidin-4-one-*O*-benzyloximes were synthesized by three different methods. Among them, the direct conversion of 2,6-diarylpiperidin-4-ones into the corresponding oxime ethers (method A) was proved to be better than the other two methods in the sense of good yield, convenience, easy work-up and quick reaction time. All the synthesized compounds are characterized by IR, Mass and NMR (^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY and HMBC) spectral studies. The conformational preference of the synthesized oxime ethers with/without alkyl and aryl substituents at C-3/C-5 and C-2/C-6 is discussed using the spectral data. The observed chemical shifts and coupling constants suggest that the synthesized oxime ethers adopt chair conformation with equatorial orientation of all the substituents, whereas 1-methyl-3-isopropyl-2,6-diphenylpiperidin-4-one-*O*-benzyloxime also exists in boat conformation. Based on the NMR data, the effects of oximination on ring carbons and their associated protons and alkyl substituents are discussed. In addition, the effect of N*Me* group on the 2,6-diarylpiperidin-4-one-*O*-benzyloximes was also studied.

Keywords *N*-Methylpiperidin-4-ones · Oxime ether · NMR · Effect of oximination · Effect of *N*-methylation

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Introduction

The NMR technique is a versatile tool for the structural elucidation of most of the organic compounds and useful for the conformational analysis also. ^{1}H NMR and ^{13}C NMR techniques have been extensively applied in deriving stereodynamical information about a wide variety of systems. They give information about the influence of electronic and conformational effects on chemical shifts and coupling constants. Vicinal coupling constant values have been used for the conformational analysis which can give an indication of the orientation of the substituents [1, 2].

2,6-Diarylpiperidin-4-ones [3] have been subjected to a variety of synthetic [4–8] and physico-chemical studies [9–11]. 2,6-Diarylpiperidin-4-ones normally adopt chair conformation with equatorial orientation of all the substituents [12–15]. When certain heteroconjucate groups, such as –NO, –CHO, –CO*Me*, –COCH$_2$Cl, –CO*Ph*, etc., are introduced at the ring nitrogen of the 2,6-disubstituted piperidone system they cause a major change in ring conformation [16–25]. Likewise, the conversion of the carbonyl group into C=N–OH, C=N–O*Bn*, C=N–NH$_2$, C=N–N=CH$_2$, C=NNHCSNH$_2$, C=N–NH*Ph*, [26–37] exhibit an abrupt change in the chemical shifts of the ring carbons and associated protons, and also exhibit a change in conformation of the compound and orientation of the substituents.

In general, the change in electronegativity of a particular group or atom on the ring causes a major change in chemical shifts on the ring carbons and their associated protons [28, 35]. In continuation of our earlier work on the spectral [28] and biological [38–41] studies of piperidone oxime ethers, in the present study we report herein a convenient synthesis and complete NMR spectral studies of diversely substituted *N*-methylpiperidin-4-one-*O*-benzyloximes with a view to assign its proton and carbon signals

unambiguously and compare its stereochemical aspects with that of its non-N*Me* analog. In addition, the effects of oximino group at C-4 and *Me* at N-1 have been studied.

Results and discussion

Synthesis

Treatment of ketones with hydroxylamine hydrochloride and sodium acetate in boiling ethanol afforded the corresponding oximes in good yields [42]. Treatment of ketones with hydroxylamine hydrochloride and an ion-exchange resin (Amberlyst A-21) as catalyst in ethanol leads to oxime in 70–100% yield at room temperature and with a simple work-up procedure [43]. In the present study, a series of new piperidone oxime ethers were synthesized. Synthesis of the target compounds was achieved by adopting the following three synthetic strategies as shown in Scheme 1. They are, method A: *N*-methylpiperidin-4-ones are directly refluxed with *O*-benzylhydroxylamine hydrochloride and sodium acetate trihydrate in methanol; method B: the oximes of *N*-methylpiperidin-4-ones are converted into oxime ethers by treating with benzyl bromide in the presence of NaH/*DMF*; and method C: piperidin-4-ones are treated with *O*-benzyl hydroxylamine hydrochloride followed by *N*-methylation.

Condensation of respective ketone, aromatic aldehyde and ammonium acetate in 1:2:1 ratio afforded the formation of 2,6-diarylpiperidin-4-ones [3] **1**–**7**. *N*-Alkylation [44] of **1**–**7** using MeI (methyl iodide) in the presence of anhydrous K_2CO_3 afforded **9**–**15**. Use of MeI over DMS (dimethyl sulphate) is found to be superior in terms of good yield as a single product, convenience and easy work-up procedure.

^{1}H and ^{13}C NMR spectra were recorded for all the synthesized compounds. In addition, for compound **30**, HSQC, and for **32**, HOMOCOSY, HSQC and HMBC, were also recorded. Mass spectra and elemental analyses were recorded for all compounds and are in agreement with their respective proposed molecular formulae. The analytical data are provided as supplementary material. IR spectra of all the synthesized compounds support the formation of oxime ether by the appearance of a band at about 1,639–1,649 cm^{-1}, which is a characteristic stretching band region for the C=N group [28]. Moreover, the formation of the N*Me* group is also confirmed by the disappearance of the characteristic stretching frequency of the piperidone NH at around 3,310 cm^{-1}.

*^{1}H NMR spectral study of 1-methylpiperidin-4-one-O-benzyloxime (**30**)*

The ^{1}H NMR signals are assigned based on their positions, multiplicity and integral values, and by comparing with those of some of the analogs piperidones. In general, the aromatic protons resonate in the downfield region at around 7 ppm due to the magnetic anisotropic effect (ring current effect). Hence, the multiplet appearing in the aromatic region of about 7.23–7.16 ppm (5H) is unambiguously assigned to the *Ph*-H of the O*Bn* moiety.

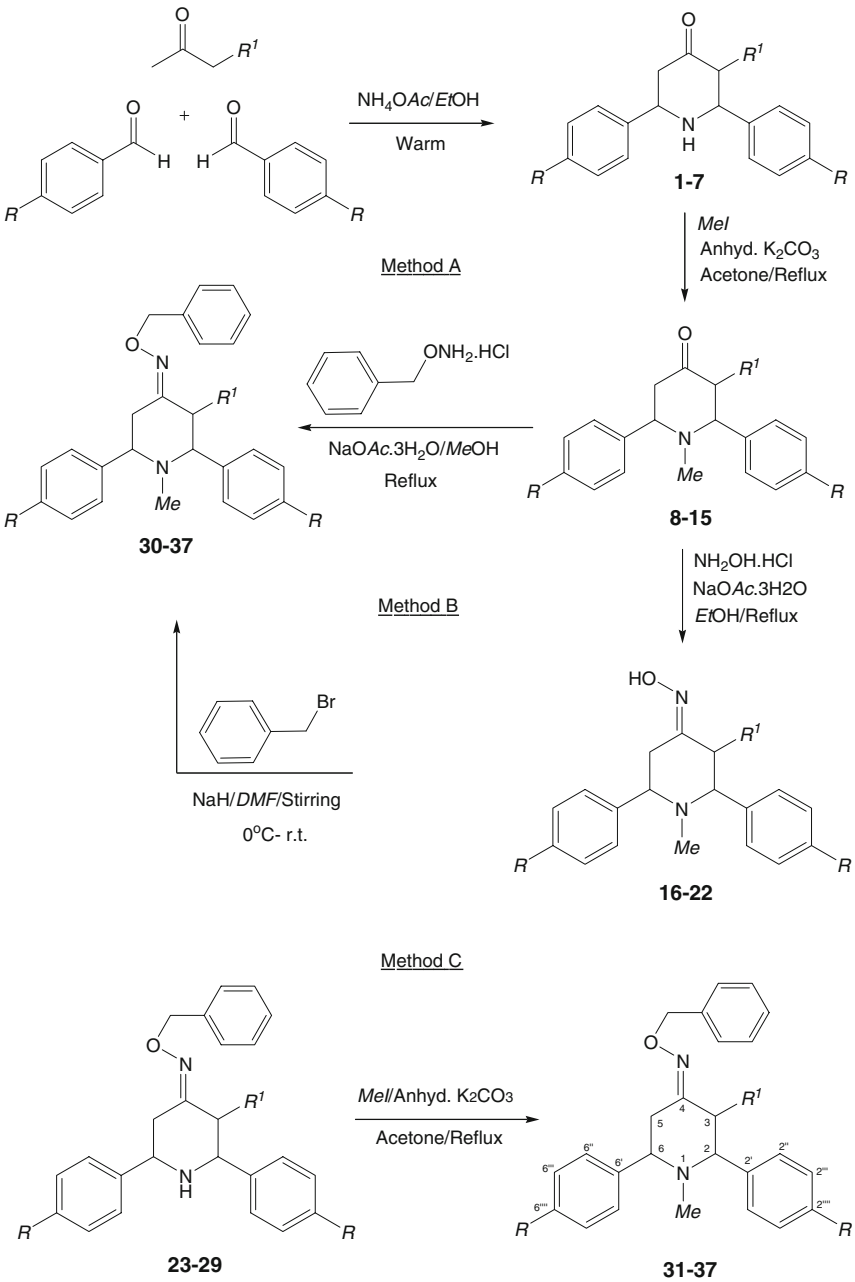
In the aliphatic region, two sharp singlets and four triplets are observed. Of the two singlets at 4.97 (2H) and 2.18 ppm (3H), the downfield singlet is ascribed to the methylene protons of the O*Bn* group. Another singlet at 2.18 ppm is assigned to the N*Me* protons. There are four triplets appearing at 2.55, 2.38, 2.32 and 2.25 ppm (each 2H). Each triplet is raised owing to the splitting of each methylene group protons by the neighboring methylene protons. Actually, an individual signal for each protons of every methylene group is expected, but due to the fast rotation of N–O on the NMR time scale, every two protons of the same methylene groups acquire a similar electronic environment and, thus, an average triplet is observed for each methylene group. Moreover, all the triplets have an average coupling constant in the range between 5.0 and 5.4 Hz. By considering the oximination effect, the triplets at 2.38 and 2.32 ppm are assigned, respectively, to H-2 and H-6 protons. The other two are attributed to the α-protons. Of the two, the 2.55 ppm is unambiguously assigned to the H-5 protons due to the 1,3-spatial proximity effect with N–O bond. And, as a consequence, the most downfield triplet is assigned to H-3 protons. Based on the chemical shifts and coupling constants (Table 1), the conformation of the piperidone heterocycle is proposed as chair (Fig. 1).

*^{1}H NMR spectral study of 1-methyl-2,6-diphenylpiperidin-4-one-O-benzyl oxime (**31**)*

The multiplet appears in the range 7.37–7.17 ppm (15H) is obviously assigned to the *Ph*-H at C-2, C-6 and O*Bn* group. A sharp singlet with two protons integral at 5.01 ppm is conveniently assigned to the O*Bn* methylene protons by comparing with the corresponding signal in compound **30**. In **31**, the singlet for N*Me* appears at 0.49 ppm upfield compared with **30**, due to the pavement of the equatorial *Ph* substituents on either side of the N*Me*.

In **1**, the resonances of benzylic protons (H-2a, H-6a) and methylene protons (H-3, H-5) were reported to observe, respectively, at 4.01 and 2.45 ppm [46] whereas the same of its N*Me* analog observed at 3.30 and 2.60 ppm. Hence, the introduction of a *Me* at NH shields H-2a,6a by 0.71 ppm and deshields H-3,5 by 0.15 ppm. The similar effect is also observed in 2,6-diphenylpiperidine [48]. In **31**, the doublet of doublets appears at 3.17 ($^{3}J_{2a,3a}$ = 9.3 Hz, $^{3}J_{2a,3e}$ = 5.4 Hz) and 3.09 ppm ($^{3}J_{5a,6a}$ = 11.5 Hz, $^{3}J_{5e,6a}$ = 2.2 Hz). Both are 0.76 ppm shielded compared with the benzylic protons H-2a (3.93 ppm, dd) and H-6a (3.85 ppm, dd) of **23**. Hence,

Scheme 1



Compounds	*R*	*R*^{1}
8 30	-	H
1, 9, 16, 23, 31	H	H
2, 10, 17, 24, 32	H	*Me*
3, 11, 18, 25, 33	Cl	*Me*
4, 12, 19, 26, 34	*Me*	*Me*
5, 13, 20, 27, 35	O*Me*	*Me*
6, 14, 21, 28, 36	H	*Et*
7, 15, 22, 29, 37	H	^{i}*Pr*

Table 1 Coupling constant values of compounds **30–37, 15, 22** and **29** (*J*, Hz)

Compound	$^3J_{2a,3a}$	$^3J_{2a,3e}$	$^3J_{5a,6a}$	$^2J_{5a,5e}$	$^3J_{5e,6a}$	$^3J_{3a,Me}/^3J_{3a,7}$
30	5.3 ($J_{2,3}$)		5.4 ($J_{5,6}$)			–
31	9.3	5.4	11.5	14.1	2.2	–
32	10.3	–	11.9	13.8	2.9	6.4
33	10.3	–	12.0	13.9	3.2	6.5
34	10.1	–	–[a]	13.8	3.0	6.5
35	10.2	–	11.9	13.8	3.2	6.5
36	10.1	–	11.7	13.7	2.7	–
37	7.2	–	10.7	11.7	3.5	7.1
15	10.6	–	11.7	13.4	3.6	2.8
22	7.6	–	11.0	11.0	4.4	6.0
29	8.9	–	11.3	14.6	3.6	3.9

[a] Could not be determined due to overlapped signals

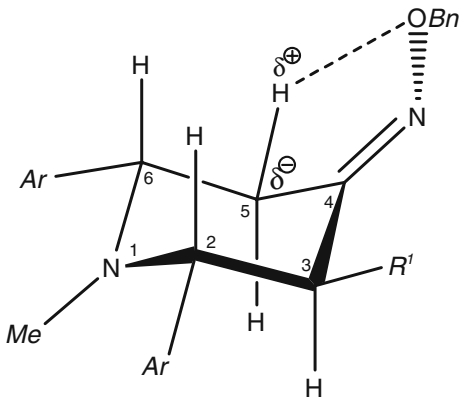


Fig. 1 Chair conformation

the doublet of doublets at 3.17 and 3.09 ppm are respectively assigned to the H-2a and H-6a of **31**.

The vicinal and geminal coupling constants of benzylic protons are significantly varied from the corresponding non-N*Me* oxime ether **23**. The vicinal diaxial coupling constant is decreased on the *anti* side ($^3J_{2a,3a} = 9.3$ Hz) rather than the *syn* side ($^3J_{5a,6a} = 11.5$ Hz), whereas the vicinal axial-equatorial coupling constant ($^3J_{2a,3e} = 5.4$ Hz) of *anti* side is greater than the *syn* side ($^3J_{5e,6a} = 2.2$ Hz). The decrease in $^3J_{2a,3a}$ is about 2.2 Hz compared with $^3J_{5a,6a}$ and this may be due to the puckering about the C(2)–C(3) bond by means of the introduction of a *Me* group at NH. By comparing compound **23** and considering the effect of N*Me* group, the higher frequency doublet at 3.36 ppm ($^2J_{5a,5e} = 14.1$ Hz) is designated to the *syn* α-equatorial proton H-5e. The higher δ value for H-5e is due to the interaction of the N–O bond with the C–H(5e) bond (Fig. 1). Hence, H-5e appears in the downfield region and, as a consequence, the upfield signal at 2.09 ppm is attributed to the *syn* α-axial proton H-5a. Obviously, another signal at 2.40 ppm is designated to the methylene protons at C-3.

Eventhough the chemical shifts are in favor for chair conformation, the coupling constants are considerably varied from the expected/literature values. Particularly, the $^3J_{2a,3a}$ and $^3J_{2a,3e}$ deviate considerably from the expected range. In **23**, the $^3J_{2a,3a}$ and $^3J_{2a,3e}$ are 11.5 and 2.9 Hz whereas in **31** they are 9.3 and 5.4 Hz, respectively. There is a significant decrease (2.2 Hz) in vicinal diaxial coupling and increase (2.2 Hz) in vicinal axial-equatorial coupling. At the same time, there is no notable variation in *syn* side vicinal and geminal couplings except $^3J_{5e,6a}$ ($^3J_{5e,6a}$ of **31** and **23** are 2.2 and 2.8 Hz, respectively). Based on the chemical shifts and the rest of the coupling constants, we can suggest that the compound is in chair conformation with puckering about the C(2)–C(3) bond.

*^{1}H NMR spectral study of 1,3-dimethyl-2,6-diphenylpiperidin-4-one-O-benzyloxime (**32**)*

In Fig. 2, a multiplet appears in the range 7.31–7.09 ppm with 15 protons. Hence, it is assigned to the *Ph*-H at C-2, C-6 and O*Bn* moiety. The sharp singlets at 5.00 (2H) and 1.58 ppm (3H) are respectively assigned to the O*Bn* methylene and N*Me* protons by comparing with these protons resonance in **31**.

The doublet at 0.71 ppm (3H, $J = 6.4$ Hz) is designated to the *Me* substituent at C-3 by comparing with **2**. Due to the introduction of a *Me* group at C-3, the nature of splitting of piperidone ring protons of **32** is drastically varied from the previous compound **31**. In this spectrum, there are five signals between 3.41 and 2.02 ppm (each 1H), which shows that every proton in the piperidone ring gives individual signals unlike **31**. In **32**, the doublet at 2.70 ppm with (diaxial) coupling constant of 10.2 Hz may be assigned to the H-2a proton, which is shielded by 0.47 ppm compared with the H-2a resonance in **31** [49].

There are two doublets of doublets appearing in the higher frequency region at 3.41 and 3.05 ppm. In 2,6-diarylpiperidin-4-one systems, the diaxial and axial-equatorial coupling constants are observed at about 12 and 3 Hz, respectively. Hence, the doublet of doublet at 3.05 ppm may be designated to H-6a and this is raised due to the coupling of H-6a with H-5a ($^3J_{5a,6a} = 11.9$ Hz) and H-5e ($^3J_{5e,6a} = 2.9$ Hz). Therefore, the doublets of doublet at 3.41 ppm ($^2J_{5e,5a} = 13.8$ Hz, $^3J_{5e,6a} = 2.9$ Hz) can be assigned to the H-5e proton by considering the 1,3-spatial proximity effect. Of the two signals between 2 and 2.5 ppm, the triplet at 2.02 ppm ($J_{ave} = 12.9$ Hz) may be assigned to H-5a owing to the induced polarity on C(5)–H(e) bond (Fig. 1). The sextet at 2.48 ppm is attributed to the methinic proton H-3a.

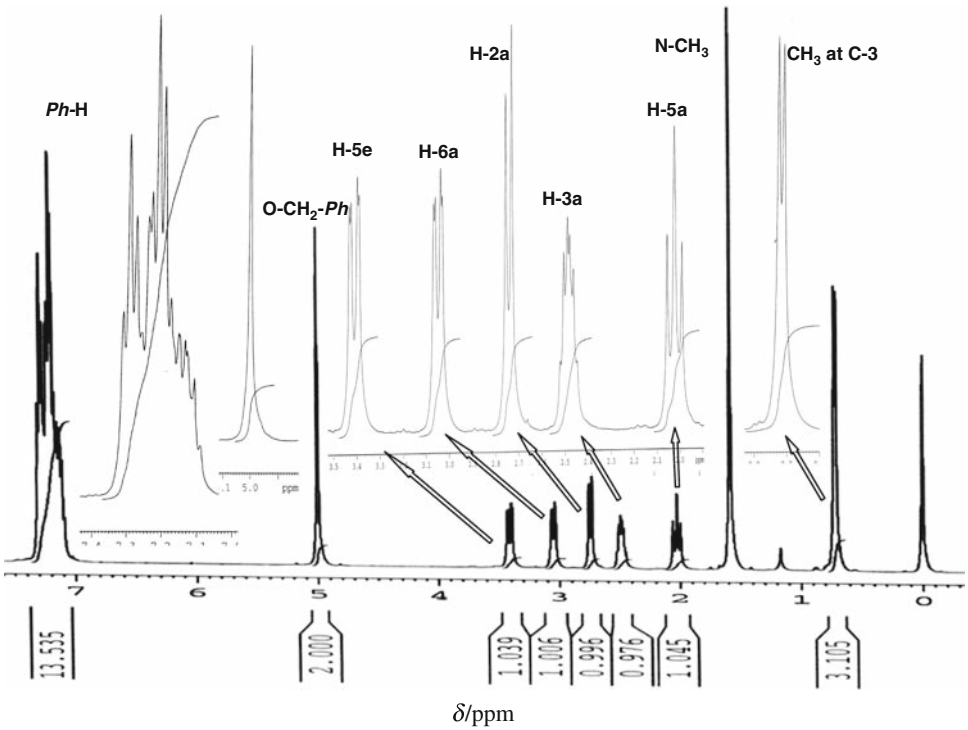


Fig. 2 ^{1}H NMR spectrum of compound **32**

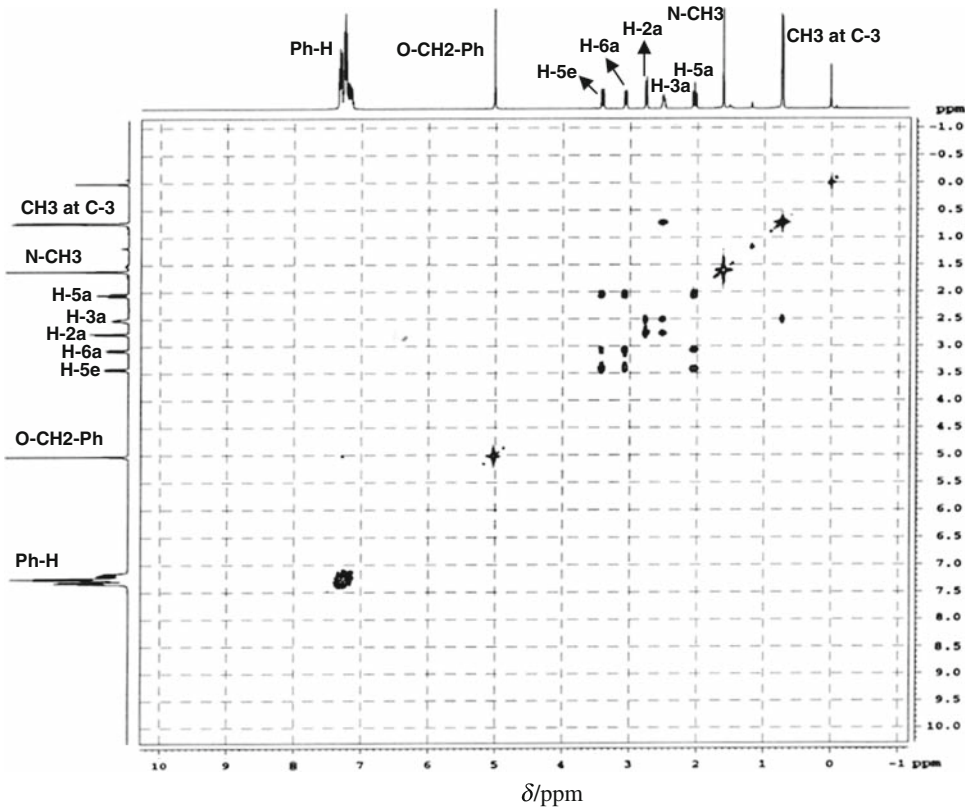


Fig. 3 HOMOCOSY spectrum of compound **32**

The HOMO correlations (Fig. 3; Table 2) between the sextet at 2.48 ppm and the doublets at 2.70 (H-2a) and 0.71 ppm (*Me* at C-3) clearly shows that the resonance at 2.48 ppm is only due to the H-3a proton. The benzylic proton H-6a has strong and weak correlations with 2.02 and 3.41 ppm, which unambiguously confirm the assignment of 2.02 and 3.41 ppm, respectively, for H-5a and H-5e. The strong correlation between the doublet of doublet at

Table 2 Correlations in the HOMOCOSY spectrum of compound **32** (δ, ppm)

Signal	Correlations
7.31–7.09 (*Ph*-H)	–
3.41 (dd, 1H, H-5e)	2.70, 3.05
3.05 (dd, 1H, H-6a)	2.02, 3.41
2.70 (d, 1H, H-2a)	2.48
2.48 (sextet, 1H, H-3a)	2.70, 0.71
2.02 (t, 1H, H-5a)	3.41, 3.05
1.58 (N–CH_3)	–
0.71 (CH_3 at C-3)	2.48

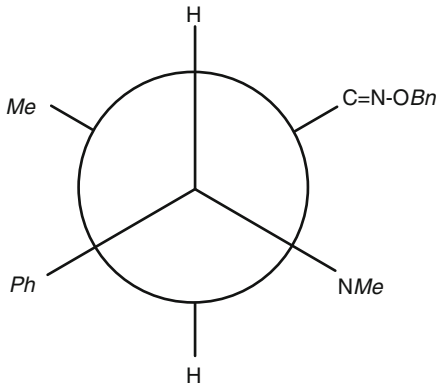


Fig. 4 Flattening about the C(2)–C(3) bond

3.41 ppm (H-5e) and the triplet at 2.02 ppm also explain that the triplet is ascribed to the H-5a proton. The absence of correlation for the sharp singlet at 1.58 ppm with any of the proton signals clearly shows that the signal at 1.58 ppm is due to the N*Me* protons.

The observed splitting pattern, chemical shifts and coupling constants clearly suggest that the compound adopts chair conformation with equatorial orientation of all the substituents (Fig. 1). The chemical shift difference (1.6 Hz) between $^3J_{2a,3a}$ and $^3J_{5a,6a}$ is obviously due to the introduction of a *Me* group at C-3, which leads to flattening of the ring about the C(2)–C(3) bond to decrease the *Ph-Me gauche* interaction (Fig. 4).

*^{1}H NMR spectral study of 1,3-dimethyl-2, 6-diarylpiperidin-4-one-O-benzyloximes (**33**–**35**)*

Notwithstanding the substitution in phenyl rings, all the proton resonance of compounds **33**, **34** and **35** are assigned in a similar manner of **32**. The *Ph* protons are assigned by considering the nature of the substituent. Generally, in *para* substituted phenyl rings, protons *ortho* to the substituents are chemically equivalent. Similarly, protons *meta* to the substituents are also chemically equivalent. Hence, two sets of signals are quite obvious for that kind of *Ph*.

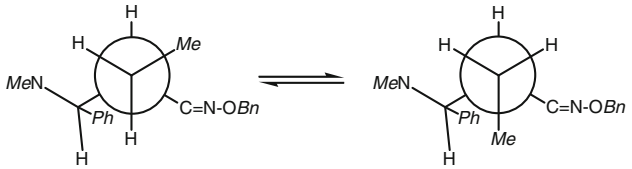


Fig. 5 Ethyl group conformation of compound **36**

In **34** and **35**, the upfield doublet of doublets with four protons integral are assigned to the protons *ortho* to the *Me*/O*Me* substituents (i.e., H-2′′′/H-6′′′). However, more shielding (about 0.31 ppm) for **35** is akin to the *ortho* effect of the O*Me* group. Due to the effect of oximination, in **34** and **35**, the *Me*/O*Me* groups at C-2′′′′/C-6′′′′ appear as separate signals.

*^{1}H NMR spectral study of 1-methyl-3-ethyl-2, 6-diphenylpiperidin-4-one-O-benzyloxime (**36**)*

The protons assignment of **36** is carried out with reference to **32**. Except H-2a and H-3a, all other protons are resonated in the same region as in **32**. The *anti* β-axial benzylic proton H-2a and *anti* α-axial methine proton H-3a are respectively deshielded and shielded by 0.21 and 0.11 ppm, due to the replacement of the equatorial *Me* by *Et* group at C-3. Moreover, the *syn* β-axial benzylic proton H-6a also been deshielded by 0.06 ppm. The upfield triplet at 0.68 ppm (3H) and multiplets centered at 1.06 and 1.44 ppm (each 1H) are corresponding to *Et* protons. Among the signals, the triplet is due to the *Me* protons whereas the multiplets are caused by the methylene protons of the *Et*; both the multiplets are interchangeable. Since the observed coupling constants are similar to **32**, compound **36** is also suggested as adopting chair conformation with equatorial orientation of the *Ph* and *Et* groups, respectively, at C-2, C-6 and C-3 as in Fig. 1. The conformation of the *Et* group is depicted in Fig. 5.

*^{1}H NMR spectral study of 1-methyl-3-isopropyl-2, 6-diphenylpiperidin-4-one-O-benzyloxime (**37**)*

In **37**, other than piperidone ring protons, all appear in the expected chemical shift region. The doublets at 1.07 (3H, $J = 6.5$ Hz) and 1.23 (3H, $J = 6.5$ Hz) are conveniently assigned to the *Me* protons of the ^iPr group by comparing **22** and **29**. Owing to the diastereotopic nature, both the *Me* signals are interchangeable. The expected sharp singlet for the N*Me* is overlapped with the multiplet of H-7 centered at 1.73 ppm.

There are two signals at 3.44 and 3.46 ppm corresponding to one proton each. Of the two, the downfield signal is a doublet of doublet ($^3J_{5a,6a} = 10.7$ Hz; $^3J_{5e,6a} = 3.5$ Hz), which suggests that the signal is due to

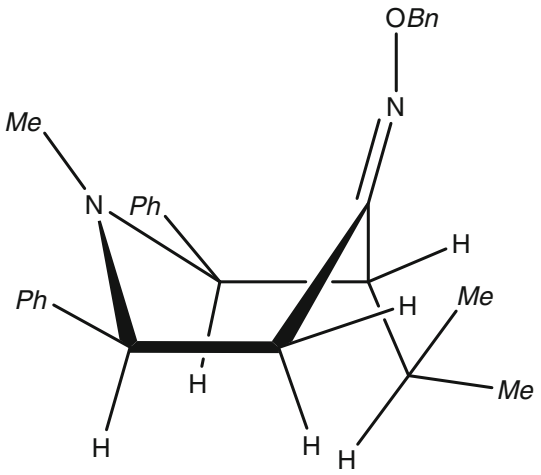


Fig. 6 Boat conformation

the benzylic proton H-6. Obviously the doublet at 3.44 ppm ($^3J_{2a,3a} = 7.2$ Hz) is postulated to another benzylic proton H-2. The decrease in vicinal coupling constants compared with other 3-substitituted analogs and the downfield signal of H-6 over H-2 clearly suggest that the compound is significantly populated in boat form. While comparing the vicinal coupling constant ($^3J_{2a,3a}$) for the doublets of **15, 22, 29** and **37**, compound **37** shows a significant decrease in $^3J_{2a,3a}$ and also an appreciable decrease in $^3J_{5a,6a}$, which strongly indicate that the compound is, to a considerable extent, in boat form.

Among the three doublets of doublets at 3.23, 2.63 and 2.44 ppm (each 1H), the 2.44 ppm is assigned to the H-3a proton by its coupling constants. Of the remaining two doublets of doublets, the downfield and upfield signals are respectively designated to H-5e and H-5a. In chair form, the H-5e and H-5a experiences a pronounced deshielding and shielding, respectively, but in boat conformation (Fig. 6), the *syn* α-axial proton H-5a would not be perfectly in axial position and seems to occupy an equatorial position and, as a consequence, this proton is involved in interaction with the N–O bond. Hence, the H-5a in boat form is deshielded compared with H-5e. As a sum of boat and chair conformations, this deviation is observed in **37**. This also

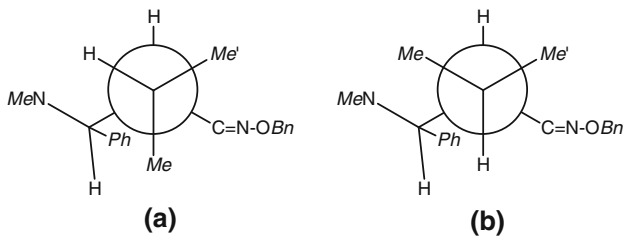


Fig. 7 Isopropyl group conformation of compound **37**; **a** in chair form, **b** in boat form

Table 3 Correlations in the HSQC spectrum of compound **30** (δ, ppm)

Signal	Correlations
7.23–7.16 (m, 5H, *Ph*-H)	127.82 (*meta*), 127.45 (*para*), 127.14 (*ortho*)
4.97 (s, 2H, –O–CH_2-*Ph*)	74.83
2.55 (t, 2H, H-5)	55.41
2.38 (t, 2H, H-2)	31.01
2.32 (t, 2H, H-6)	24.96
2.25 (t, 2H, H-3)	54.09
2.18 (N–CH_3)	45.41

again proves that the compound is largely populated in boat form.

The $^3J_{3a,7}$ of **15** is only 2.8 Hz whereas it is 7.1 Hz for **37**. This coupling constant is also very significantly an added support for the existence of boat form. From this coupling constant, we can get one more interesting fact i.e., in **15** (which was reported to adopt chair conformation), according to the *gauche* proton coupling ($J = 2$–4 Hz), the conformation of the ^iPr was depicted as in Fig. 7a, but in **37**, $^3J_{3a,7}$ clearly suggests that the ^iPr exists in both the conformations shown in Fig. 7a and b. This can be explained as follows. In boat conformation, the H-7 is *anti* to H-3 and hence the *anti* proton coupling is experienced by this ^iPr group; it should be around 10–12 Hz (characteristic coupling constant value for *anti* protons). Due to the significant population of boat form, a drastic increase is observed in $^3J_{3a,7}$ when compared to **15, 22** and **29**. Owing to the presence of both chair and boat conformation in solution, ^iPr group adopts the conformation of Fig. 7a and b in chair and boat forms, respectively.

*^{13}C NMR spectral study of 1-methylpiperidin-4-one-O-benzyloxime (**30**)*

The *Ph* and quaternary carbons are unambiguously assigned by their HSQC correlations (Table 3). In its HSQC spectrum, the carbon resonance at 74.83 ppm has a cross peak with the singlet at 4.97 ppm, which indicates that the signal at 74.83 ppm is due to the O*Bn* methylene carbon. There are five intense signals in the aliphatic region at 55.41, 54.09, 45.41, 31.01 and 24.96 ppm. Among the signals, one at 45.41 ppm is assigned to the N*Me* carbon, which only correlates with the singlet at 2.18 ppm.

The signals at 55.41 and 54.09 ppm are respectively assigned to C-2 and C-6 carbons by comparing parent ketone. According to the expected electronegativity effect, the *anti* and *syn* β-carbons are respectively deshielded (0.90 ppm) and shielded (1.33 ppm). Similarly, the *anti* and *syn* α-carbons are also assigned by considering the

decrease in electronegativity on C-4. The assignments are done by comparing with similar type of compounds and cyclohexanone oximes [50], which are further, unambiguously confirmed by ^{1}H-^{13}C correlations (Table 3).

*^{13}C NMR spectral study of 1-methyl-2, 6-diphenylpiperidin-4-one-O-benzyloxime (**31**)*

The carbon resonances beyond 127 ppm are due to the phenyl rings at C-2, C-6 and O*Bn* moiety. The less intense signals at 156.78, 144.20 and 143.99 ppm are respectively assigned to the quaternary carbons C-4, C-2′ and C-6′. The still less intense signal at 138.15 ppm is conveniently assigned to the O*Bn ipso* carbon by comparing with **30**. Similarly, the intense signal at 75.48 ppm is assigned to the O*Bn* methylene carbon.

By comparing with **23**, the higher frequency aliphatic region signals at 70.71 and 69.34 ppm are assigned to the benzylic carbons C-2 and C-6, respectively. The signals at 41.27 and 35.36 ppm are respectively assigned to the methylenic carbons C-3 and C-5. The benzylic (C-2, C-6) and methylenic (C-3, C-5) carbons are deshielded by 8.73, 8.67 and 0.86, 1.16 ppm, respectively. This is obviously due to the introduction of a *Me* group in the ring nitrogen of compound **23**. Generally, the N*Me* carbon resonates at about 41 ppm in 1-methyl-2,6-diphenylpiperidin-4-one [51] whereas the same is reported to be observed at about 45 ppm in 1-methylpiperidin-4-one [44]. Here, the *Me* group is flanked either side by the *Ph* rings at C-2 and C-6; hence, the *Me* carbon is shielded by about 4 ppm.

*^{13}C NMR spectral study of 1,3-dimethyl-2, 6-diphenylpiperidin-4-one-O-benzyloxime (**32**)*

In the ^{13}C NMR spectrum of **32**, the most upfield resonance at 12.62 ppm is assigned to the *Me* group at C-3. In addition, there are six signals observed in the aliphatic region at 77.66, 75.47, 69.31, 43.13, 41.44 and 35.22 ppm. In its HSQC spectrum (Fig. 8), the carbon signals at 77.66 and 69.31 ppm have cross peaks with the proton resonances at 2.70 (H-2a) and 3.05 ppm (H-6a), respectively. Hence, they are conveniently assigned to the C-2 and C-6 carbons, respectively. Since the carbon resonance at 75.47 ppm has a cross peak with the singlet at 5.00 ppm, it is conveniently assigned to the O*Bn* methylene carbon. The sextet at 2.48 (H-3a) and a sharp singlet at 1.58 ppm (N*Me*) have correlations with 43.13 and 41.44 ppm, respectively. Hence, the carbon resonances at 43.13 and 41.44 ppm are respectively assigned to C-3 and N*Me* carbons.

The signals from 128.48 to 127.02 ppm have correlations with the *Ph* protons multiplet. However, the signals beyond 128.48 ppm have no correlation with any of the proton signals. Hence, they are identified as quaternary carbons. In order to carry out unambiguous assignment of the quaternary carbon signals, the HMBC spectrum (Fig. 9) has been recorded.

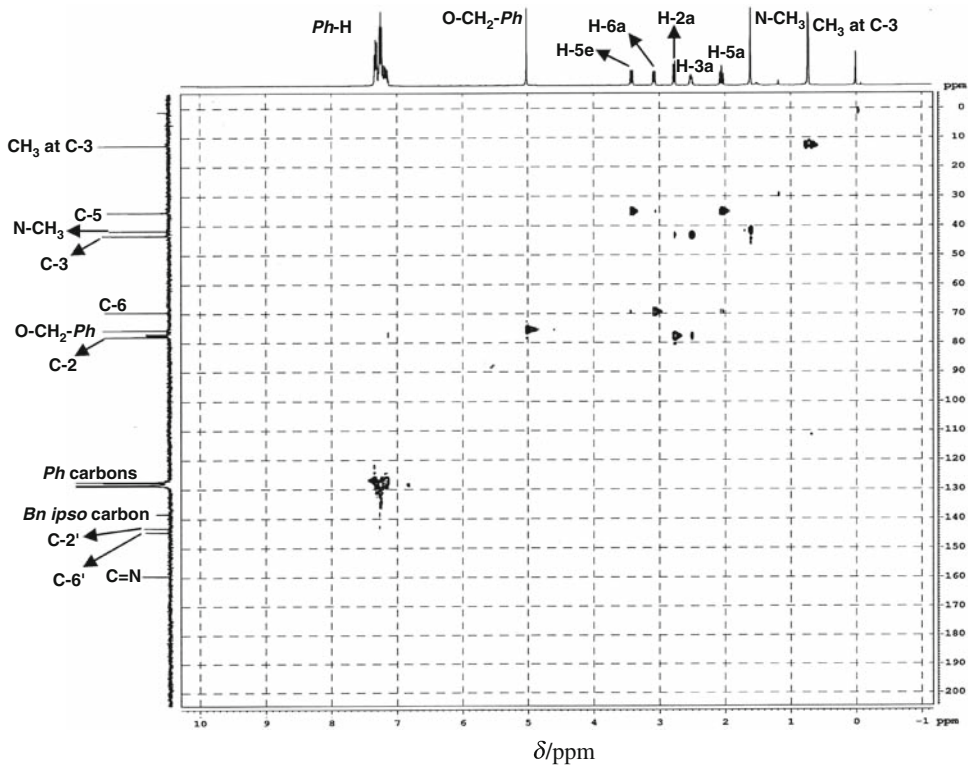


Fig. 8 HSQC spectrum of compound **32**

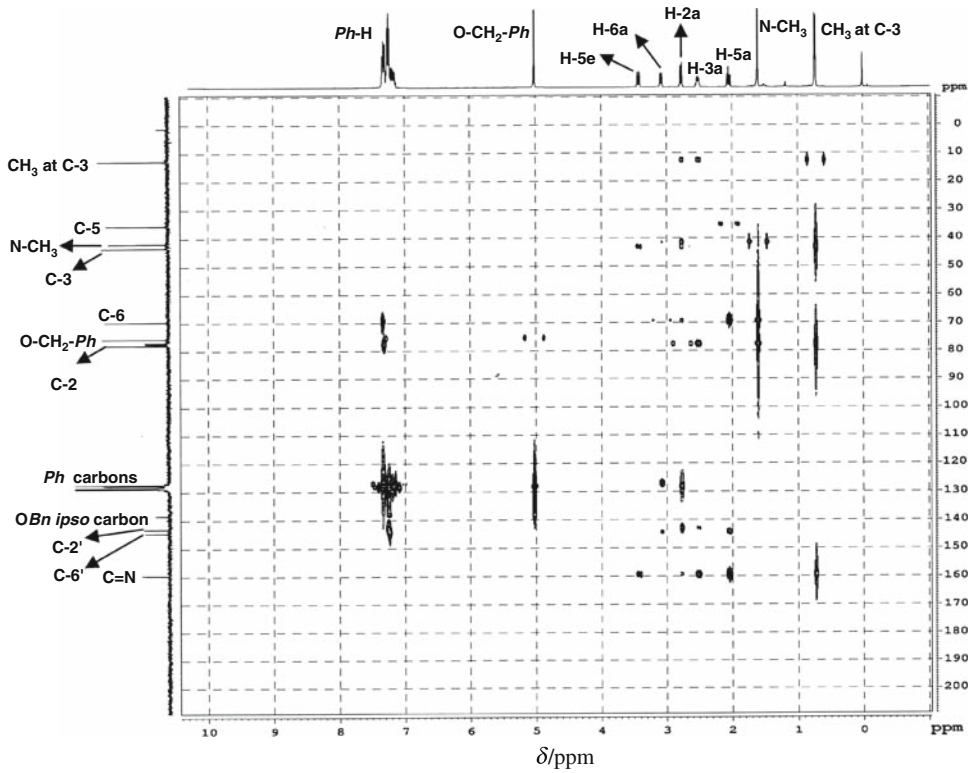


Fig. 9 HMBC spectrum of compound **32**

Table 4 Correlations in the HSQC and HMBC spectra of compound **32** (δ, ppm)

Signal	Correlations in HSQC	Correlations in HMBC
7.31–7.09 (*Ph*-H)	128.48–127.02	144.23(α), 142.85(α), 138.28(α,β), 77.66(β), 75.47(β), 69.31(β)
5.01 (–O–CH_2-*Ph*)	75.47	138.28(α), 128.48–127.02(β)
3.41 (dd, 1H, H-5e)	35.13	158.78(α), 43.13(β)
3.05 (dd, 1H, H-6a)	69.31	144.23(α), 128.48–127.02(β)
2.70 (d, 1H, H-2a)	77.66	158.78(β), 142.85(α), 128.48–127.02(β), 69.31(β), 41.44(β), 12.62(β)
2.48 (sextet, 1H, H-3a)	43.13	158.78(α), 142.85(β), 77.66(α), 12.62(α)
2.02 (t, 1H, H-5a)	35.13	158.78(α), 144.23(β), 69.31(α)
1.58 (N–CH_3)	41.44	77.66(β), 69.31(β)
0.71 (CH_3 at C-3)	12.62	158.78(β), 77.66(β), 43.13(α)

α α-Correlation
β β-Correlation
γ γ-Correlation

The lower frequency resonance at 138.28 ppm has good correlation with the O*Bn* methylene protons signal (α-correlation) and with the *Ph* protons signal (α-correlation); this clearly indicates that the signal is ascribed to the O*Bn ipso* carbon. The higher frequency resonance at 158.78 ppm has α-correlations with H-3a (2.48 ppm), H-5a (2.01 ppm) and H-5e (3.41 ppm), and also a strong and weak β-correlation, respectively, with *Me* at C-3 (0.71 ppm) and H-2a (2.70 ppm). Thus, the above correlations clearly explain that the signal at 158.78 ppm is obviously due to the C=N carbon. From the multiple bond correlations, the resonances at 142.85 and 144.23 ppm are respectively designated to the *ipso* carbons C-2′ and C-6′. All the HSQC and HMBC correlations are listed in Table 4.

*^{13}C NMR spectral study of 1,3-dimethyl-2, 6-diarylpiperidin-4-one-O-benzyloximes (**33**–**35**)*

All the carbon signals are assigned with respect to **32**. Owing to the introduction of Cl/*Me*/O*Me* substituents at C-2′′′′/C-6′′′′, aryl carbons resonances vary from **32**. All the assignments are summarized in the respective compounds experimental section.

*^{13}C NMR spectral study of 1-methyl-3-ethyl-2,6-diphenylpiperidin-4-one-O-benzyloxime (**36**)*

The carbon signals are assigned by comparing the corresponding carbon signals in compound **28** with the impact

of *Me* at N-1 and *Et* at C-3. The replacement of *Me* by *Et* group at C-3 in **24** (i.e., compound **28**) deshields the *anti* α-carbon C-3 by 6.08 ppm whereas it shields the *anti* β-carbon C-5 by 1.74 ppm. In **36**, also, due to the decrease in the electropositive nature of the *Et* substituent compared with *Me*, the C-3 (α-carbon) is deshielded by 7.06 ppm while the C-2 (β-carbon) is shielded by 1.74 ppm. Hence, the signals at 67.35, 60.73, 49.45 and 34.36 ppm are respectively assigned to the C-2, C-6, C-3 and C-5 carbons.

*^{13}C NMR spectral study of 1-methyl-3-isopropyl-2, 6-diphenylpiperidin-4-one-O-benzyloxime (**37**)*

The carbon resonances beyond 126 ppm are assigned by comparing its analogs 3-*Me* (**32**) and 3-*Et* oxime ethers (**36**). There are three signals in the upfield region at 29.08, 21.44 and 18.44 ppm. Of the three signals, the one at 29.08 ppm is assigned to the ^{i}Pr methine carbon as in the case of its non-N*Me* analog **29**. Similarly, the resonances at 21.44 and 18.44 ppm are designated to *Me* and *Me′* of the ^{i}Pr side chain at C-3; both the *Me* signals are interchangeable.

Among the signals at 72.64, 67.08, 54.06, 41.93 and 35.27 ppm, the 41.93 ppm carbon resonance is unambiguously assigned to the N*Me* carbon. The remaining four signals are attributed to the piperidone ring carbons. The effect of the ^{i}Pr group in place of *Me* in **32** and also the effect of *N*-methylation on the piperidone ring carbons in **29** have been taken into account for the assignment of the ring carbons signal in addition to the oximination effect.

Introduction of a *Me* at N-1 in compound **7** (i.e., compound **15**) deshields the C-2 and C-6 by 8.16 and 8.37 ppm, respectively. Similarly in **29**, the introduction of a *Me* at ring nitrogen, respectively deshields the benzylic carbons C-2 and C-6 by 7.48 and 7.34 ppm. Therefore, the signals at 72.64 and 67.08 ppm are conveniently assigned to C-2 and C-6 carbons, respectively. According to *N*-methylation, shielding is observed on C-5 and C-3. In **32**, due to the replacement of *Me* by ^{i}Pr at C-3, the C-3 and C-5 are shielded by 0.76 and 0.58 ppm when compared to **29**. Hence, the signals at 54.06 and 35.27 ppm are respectively assigned to C-3 and C-5.

Effect of oximination

Decrease in electronegativity of a particular group in the six-membered heterocyclic ring skeleton shields the α-carbons and deshields the β- and γ-carbons [52]. According to the less polar nature of the C=N than the C=O bond, the electronegativity of the C=N–O*Bn* group must be less than that of the C=O group. All the $\Delta\delta$ ($\delta_{N\text{-methylpiperidone}} - \delta_{\text{oxime ether}}$) values for the piperidone ring carbons of the synthesized compounds **30–32** and **36** are represented in Table 5. (Due to lack of all the data for parent ketones, we did not compare the effect for **33–35**. However, as the piperidone carbons chemical shifts of **33–35** are similar to **32**, the oximination effect should also be same as **32**.)

The α-carbons are shielded and γ-carbons are deshielded according to the expected electronegativity effect on C-4 carbon (electronegativity on C-4 carbon is reduced by oximination). Not withstanding the decrease in electronegativity on C-4, the *syn* β-carbon is shielded by the polarization of the C–H(5e) bond. Moreover, the then polarized C–H(5e) bond causes severe impact on *syn* α-carbon over *syn* β-carbon. Oximination effects on the *N*-methylpiperidone oxime ether ring carbons (α and β), substituent at C-3 (β and γ) and *ipso* carbons (γ) are reported in Table 5.

α-Effect

By comparing the chemical shifts of α-carbons (C-3 and C-5) of the oxime ether with the corresponding piperidones, the α-effect was analyzed. Due to the diminished electronegativity of C=N compared with C=O, the α-carbons are significantly shielded in oxime ether compared with their respective *N*-methyl piperidones. Though the shielding of α-carbons is in accord with the expected electronegativity effect, the *syn* α-carbon is more pronounced than that of *anti* α-carbon. This is substantiated by the interaction of the N–O bond with the *syn* α C–H(e) bond (Fig. 5). This interaction induces a polarity in the *syn* α C–H(e) bond so that the *syn* α-equatorial proton (H-5e) acquires a slight positive charge and the C-5 carbon acquires a slight negative charge. And, as a consequence, the proton and carbon are respectively deshielded and shielded.

Table 5 ^{13}C Chemical shift difference between *N*-methylpiperidone and corresponding oxime ether ($\delta_{N\text{-methylpiperidone}} - \delta_{\text{oxime ether}}$) [$\Delta\delta$, ppm]

Compound	C-2	C-3	C-4	C-5	C-6	C-2′	C-6′	*Me* at C-3
30	−0.09	10.04	50.86	16.09	1.23	–	–	–
31	−0.82	9.21	49.03	15.12	0.55	−1.36	−1.16	–
32	−0.48	7.75	48.70	15.41	1.10	−0.80	−1.13	−1.62
36	−0.44	7.50	49.42	15.62	1.30	−1.16	−2.38	−1.24 (–CH_2)

Negative sign denotes deshielding

Table 6 Chemical shift differences between piperidone ring protons of oxime ethers **31–37** ($\Delta\delta$, ppm)

Compound	$\Delta\delta_{5e,5a}$	$\Delta\delta_{3a,5a}$	$\Delta\delta_{2a,6a}$
31	1.27	0.31	0.08
32	1.39	0.46	−0.35
33	1.40	0.47	−0.30
34	1.37	0.47	−0.31
35	1.37	0.45	−0.30
36	1.37	0.32	−0.20
37	0.60	−0.19	−0.02

Negative sign denotes deshielding

The sum of shielding experienced on *syn* α-carbon is about 15–16 ppm for all compounds whereas the shielding experienced on *anti* α-carbon is only about 7.5–10 ppm. Particularly in 3-substituted compounds, the shielding of anti α-carbon is about 7.5 ppm while in the symmetric ketoximes the shielding magnitude increased to 9–10 ppm. This variation is solely due to the effect of the alkyl substituents at the *anti* α-carbon (C-3).

Owing to the interaction of N–O bond with the *syn* α C–H(e) bond, the *syn* α-equatorial proton (H-5e) gets a slight positive charge and the C-5 carbon gets a slight negative charge. Akin to this, H-5e deshielded about 1 ppm and appeared at around 3.5 ppm in all compounds while the *syn* α-axial proton (H-5a) is shielded by the negative charge on the *syn* α carbon. The difference between the H-5e and H-5a is about 1.3 ppm in **31–36** while the difference is considerably decreased in **37**. This indicates that the conformation of the compound deviates from predominant chair form. The differences between all the α-protons are represented in Table 6. The differences between the axial α-protons are about 0.4 ppm, which is in good agreement with our earlier report on non-N*Me* analogs [28].

β-Effect

The *β*-effect can be studied by comparing the chemical shifts of the *β*-carbons C-2 and C-6 of the piperidone oxime ether with corresponding piperidones. In six-member heterocycles, a decrease in electronegativity of a group in the ring deshields *β*-carbons and shields *β*-protons [26, 27]. The deshielding of *anti* *β*-carbon is in accordance with the expected electronegativity effect, and the magnitude of deshielding is less than 1 ppm. The *syn* *β*-carbons are shielded and the shielding magnitude is about 1 ppm for compounds **30, 32** and **36**, but **31** is deshielded by only 0.55 ppm, probably due to the puckering in its conformation. The reason for the shielding is due to the negative charge on the *syn* α-carbon, which is transmitted to a small extent on the *syn* *β*-carbon. Thus, the shielding produced on the *syn* *β*-carbon by the transmittance of the negative charge outweighs the deshielding produced by the electronegativity effect. Table 6 sets out the chemical shift difference between the benzylic protons.

γ-Effect

The *γ*-effect is studied by comparing the chemical shifts of the *ipso* carbons C-2′ and C-6′ in *N*-methylpiperidones with corresponding oxime ethers. The *ipso* carbons are deshielded in all oxime ethers, with the expected electronegativity effect. The *γ*-effect magnitude is about 1 ppm for all compounds and the values are reported in Table 5.

Oximino group effect on alkyl group

According to the electronegativity effect, the observed *β*-effect (deshielding) on methyl carbon of **32** (*Me* at C-3) is about 1.62 ppm and on methylene carbon (CH_2 of *Et* at C-3) of **36** is 1.24 ppm. Due to the decrease in electronegativity, the *γ*-effect is also observed on the alkyl group. In **36,** the *Me* carbon of the *Et* substituent at C-3 is deshielded by 0.13 ppm.

Effect of N-methyl group on piperidone ring

The introduction of a *Me* at ring nitrogen of compounds **31–37** causes a significant effect on the benzylic and methylenic/methinic carbons and their associated protons. The N*Me* group gives a better deshielding on the C-2, C-6 carbons and a poor deshielding on the C-3, C-5 carbons while a little shielding is exerted on the C-4 carbon. As a consequence, H-2a and H-6a are shielded whereas H-3a and H-5a are deshielded.

The effect of the introduction of a *Me* at N-1 of compounds **23–29** (i.e., compounds **31–37**) is reported in Tables 7 and 8, respectively, for the ring carbons of the piperidone moiety and their associated protons. The

Table 7 The effect of *N*-methylation on ring carbons of oxime ethers **31–37** (δ, ppm)

Compound	C-2	C-3	C-4	C-5	C-6	*Me* at C-3
31	−8.73	−0.86	1.00	−1.16	−8.67	–
32	−8.16	0.24	1.37	−0.43	−8.37	−0.71
33	−8.74	−0.18	0.31	−0.74	−8.82	−0.94
34	−8.46	−0.02	0.60	−0.63	−8.66	−0.79
35	−8.53	−0.07	0.57	−0.74	−8.67	−0.93
36	−8.57	−0.74	0.12	−1.26	−8.62	−0.90 (–CH_2)
37	−7.48	−0.76	0.61	−0.58	−7.34	−1.07 (–CH)

Negative sign denotes deshielding

Table 8 The effect of *N*-methylation on ring protons of oxime ethers **31**–**37** (δ, ppm)

Compound	H-2a	H-3a	H-3e	H-5a	H-5e	H-6a	*Me* at C-3
31	0.76	−0.06	0.18	−0.08	0.16	0.76	–
32	0.71	−0.08	–	−0.09	0.10	0.69	0.09
33	0.50	−0.23	–	−0.24	−0.02	0.52	−0.04
34	0.50	−0.17	–	−0.27	−0.10	0.52	−0.07
35	0.56	−0.21	–	−0.20	0	0.59	−0.01
36	0.68	0.01	–	−0.04	0.08	0.67	0.11 (–CH_2)
37	0.38	−0.04	–	−0.45	0.05	0.35	−0.05 (–CH)

Negative sign denotes deshielding

oximino carbon (γ-position to the N*Me*) is also shielded about 0.12 to 1.37 ppm due to *N*-methylation; the magnitude of shielding depends on the substitution at C-3.

Conclusion

All the synthesized oxime ethers (**30**–**37**) were characterized by their IR, Mass and NMR studies. All the spectral studies and elemental analysis reports strongly confirm the formation of the target compounds. Based on the observed chemical shifts and coupling constants, the conformation of the six-member heterocycle and alkyl substituent at C-3 are proposed. The compounds **30**–**36** adopt normal chair conformation (**31** is not in perfect chair form; there is a slight puckering observed about the C(2)–C(3)bond) with equatorial orientation of the substituents at C-2, C-3 and C-6, whereas **37** contributes a significant boat conformation along with the chair conformation in solution and its population in boat form is significantly higher than its non-N*Me* analog **29** [28]. Moreover, the NMR spectral studies clearly reveal that the unsymmetrical oxime ethers **32**–**37** are exclusively in *E* form. The oximination effect on the piperidone ring carbons, their attached protons and alkyl substituents are recorded and are also found to be significant beyond the γ-position. In addition, the effect of *N*-methylation on the above is also very significant.

Experimental

All the reported melting points were taken in open capillaries. IR spectra were recorded in a Thermo Nicolet AVATAR-330 FT-IR spectrophotometer by KBr pellet technique and only noteworthy absorption levels are listed in reciprocal centimeters. ^{1}H and ^{13}C NMR spectra were recorded respectively at 400 and 100.6 MHz on a BRUKER AMX 400 spectrometer using $CDCl_3$ as solvent and *TMS* as internal standard. ^{1}H-^{1}H COSY, HSQC and HMBC were recorded on a BRUKER DRX 500 NMR spectrometer with standard parameters using 0.05 M solutions of the samples prepared in $CDCl_3$. The tubes used for recording NMR spectra are of 5 mm diameter. Electro Spray Mass Spectra (ESMS) were recorded on an API 3000 series mass spectrometer while Electron Impact Mass Spectra (EIMS) were recorded on a mass engine HP 5989 series. Microanalyses were performed on a Heraeus Carlo Erba 1108 CHN analyzer.

*Preparation of 2,6-diarylpiperidin-4-ones (**1–7**)*

All the parent 2,6-diarylpiperidin-4-ones were prepared by the condensation of respective ketones, aldehydes and ammonium acetate in warm ethanol in the ratio of 1:2:1.

*Preparation of 1-methyl-2,6-diarylpiperidin-4-ones (**8–15**)*

A mixture of respective 2,6-diarylpiperidin-4-ones **1**–**7** (0.01 mol), anhydrous potassium carbonate (2 g) and MeI (0.01 mol) in acetone (30 ml) was refluxed for 3 h. Removal of acetone by distillation, dilution with water and treatment with aqueous ammonia afforded corresponding 1-methyl-2,6-diarylpiperidin-4-ones **9**–**15**. 1-Methyl piperidin-4-one **8** was procured from Fluka and used as such.

*Preparation of 1-methyl-2,6-diarylpiperidin-4-one oximes (**16–22**)*

1-Methyl-2,6-diarylpiperidin-4-one (1 equiv), sodium acetate trihydrate (3 equiv) and hydroxylamine hydrochloride (1.2 equiv) were refluxed for minimum 30 min in ethanol. After completion of the reaction, the mixture was poured into water and the solid thus obtained was filtered and recrystallized from ethanol to afford 1-methyl-2,6-diphenylpiperidin-4-one oximes.

*Synthesis of 2,6-diarylpiperidin-4-one-O-benzyloximes (**23–29**)*

A mixture of 2,6-diarylpiperidin-4-one (1 equiv), *O*-benzylhydroxylamine hydrochloride (1 equiv) and sodium acetate trihydrate (3 equiv) in methanol was refluxed until

completion of the reaction. After completion, water was added and extracted with ether, dried with anhydrous sodium sulphate and evaporated.

*Synthesis of 1-methyl-2,6-diarylpiperidin-4-one-O-benzyloximes (**30–37**)*

Method A: A mixture of ketone (1 equiv), *O*-benzylhydroxylamine hydrochloride (1 equiv) and sodium acetate trihydrate (3 equiv) in methanol was refluxed for about 7–20 h (depending upon the nature of substituents at C-3). After the completion of reaction, excess of solvent was removed under reduced pressure then water was added and extracted with chloroform. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuum. The residue thus obtained was triturated with diethyl ether to afford the solid product.

Method B: One equivalent of the respective oxime (**16–22**) in *DMF* was added slowly to a suspension of NaH (1 equiv) in *DMF* at 0 °C. Then the reaction mixture was stirred for about half an hour and a solution of benzyl bromide (1 equiv) in *DMF* was added. The reaction mixture was stirred at room temperature for about 1–2 days (depending upon the nature of substituent at C-3). Later, the reaction mixture was poured into water and extracted with chloroform. The organic phase was washed with brine, dried over anhydrous sodium sulphate and concentrated in vacuum. The obtained product was purified over neutral alumina using 5:1 mixture of *n*-hexane–ethyl acetate as eluent.

Method C: A mixture of 2,6-diarylpiperidin-4-one-*O*-benzyloxime (**23–29**) (0.001 mol), anhydrous potassium carbonate (0.2 g) and methyl iodide (0.001 mol) in acetone (10 ml) was refluxed until the completion of *N*-methylation. Then, the excess of solvent was removed and the residue was washed with water, aqueous ammonia and again by water. After that, the reaction mass was extracted with dichloromethane (DCM), dried with anhydrous sodium sulphate and concentrated. Thus, the obtained *N*-methylpiperidone oxime ether was purified by column chromatography using neutral alumina as adsorbent and *n*-hexane–ethyl acetate (2:1) as eluent.

1-Methylpiperidin-4-one-O-benzyloxime (**30**, $C_{13}H_{18}N_2O$)
Yield: 96%; Semi-solid; IR (KBr):$\bar{\nu} = 3,062$, 3,031, 2,941, 2,847, 2,787, 2,753 (C–H stretching); 1646 (C=N stretching); 1563 (C=C stretching-*Ph*); 1,497, 1,456, 1,427, 1,371, 1,328, 1,279, 1,214, 1,134, 1,042, 909, 872, 804; 740 (N–O stretching); 700, 614, 540, 472; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.23$–7.16 (m, *Ph*-H), 4.97 (s, OCH_2), 2.55 (t, H-5), 2.38 (t, H-2), 2.32 (t, H-6), 2.25 (t, H-3), 2.18 (N–CH_3) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 156.24$ (C-4), 137.73 (O*Bn ipso* carbon), 127.82, 127.45, 127.14 (*Ph* carbons), 74.83 (OCH_2), 55.41 (C-2), 54.09 (C-6), 45.41 (N–CH_3), 31.01 (C-3), 24.96 (C-5) ppm; MS (ES): $m/z = 219.0$ (M + 1).

1-Methyl-2,6-diphenylpiperidin-4-one-O-benzyloxime (**31**, $C_{25}H_{26}N_2O$)
Yield: 95%; M.p.: 80 °C; IR (KBr): $\bar{\nu} = 3,061$, 3,029, 2,963, 2,912, 2,850, 2,785 (C–H stretching); 1644 (C=N stretching); 1,601 (C=C stretching-*Ph*); 1,493, 1,453, 1,423, 1,361, 1,304, 1,262, 1,201, 1,036, 931, 802; 754 (N–O stretching); 698, 618, 509, 466; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$–7.17 (m, *Ph*-H), 5.01 (s, OCH_2), 3.36 (d, H-5e), 3.17 (dd, H-2a), 3.09 (dd, H-6a), 2.40 (m, H-3), 2.09 (t, H-5a), 1.69 (N–CH_3) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 156.78$ (C-4), 144.20 (C-2′), 143.99 (C-6′), 138.15 (O*Bn ipso* carbon), 128.67, 128.36, 128.03, 127.70, 127.40, 127.34 (*Ph* carbons), 75.48 (OCH_2), 70.71 (C-2), 69.34 (C-6), 41.27 (C-3, N–CH_3), 35.36 (C-5) ppm; MS (ES): $m/z = 371.2$ (M + 1).

1,3-Dimethyl-2,6-diphenylpiperidin-4-one-O-benzyloxime (**32**, $C_{26}H_{28}N_2O$)
Yield: 93%; M.p.: 76–77 °C; IR (KBr): $\bar{\nu} = 3,061$, 3,029, 2,971, 2,928, 2,871, 2,781 (C–H stretching); 1,639 (C=N stretching); 1,601 (C=C stretching-*Ph*); 1,493, 1,453, 1,423, 1,362, 1,308, 1,234, 1,125, 1,045, 1,017, 922, 875; 753 (N–O stretching); 699, 619, 554, 508; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$–7.09 (m, *Ph*-H), 5.00 (s, OCH_2), 3.41 (dd, H-5e), 3.05 (dd, H-6a), 2.70 (d, H-2a), 2.48 (m, H-3a), 2.02 (t, H-5a), 1.58 (N–CH_3), 0.71 (d, CH_3 at C-3) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 158.78$ (C-4), 144.23 (C-6′), 142.85 (C-2′), 138.28 (O*Bn ipso* carbon), 128.48, 128.29, 128.10, 128.04, 127.43, 127.27, 127.15, 127.02 (*Ph* carbons), 77.66 (C-2), 75.47 (OCH_2), 69.31 (C-6), 43.13 (C-3), 41.44 (N–CH_3), 35.20 (C-5), 12.62 (CH_3 at C-3) ppm; MS (EI): $m/z = 384$ (M^+).

1,3-Dimethyl-2,6-bis(4-chlorophenyl)piperidin-4-one-O-benzyloxime (**33**, $C_{26}H_{26}N_2OCl_2$)
Yield: 89%; M.p.: 136 °C; IR (KBr): $\bar{\nu} = 3,030$, 2,970, 2,930, 2,871, 2,787 (C–H stretching); 1,639 (C=N stretching); 1,599 (C=C stretching-*Ph*); 1,485, 1,447, 1,372, 1,299, 1,259, 1,016, 921, 830; 750 (N–O stretching); 699; 580 (C–Cl stretching); 509; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$–7.20 (m, *Ar*–H), 5.09 (s, OCH_2), 3.45 (dd, H-5e), 3.13 (dd, H-6a), 2.83 (d, H-2a), 2.51 (m, H-3a), 2.04 (dd, H-5a), 1.66 (N–CH_3), 0.79 (d, CH_3 at C-3) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 158.48$ (C-4), 142.77 (C-6′), 141.45 (C-2′), 138.22 (O*Bn ipso* carbon), 133.11 (C-6′′′′), 132.97 (C-2′′′′), 129.51, 128.86, 128.72, 128.55, 128.30, 127.72 (*Ar* carbons), 76.98 (C-2), 75.70 (OCH_2), 68.63 (C-6), 43.22 (C-3), 41.54 (N–CH_3), 35.17 (C-5), 12.57 (CH_3 at C-3) ppm; MS (ES): $m/z = 453.2$ (M + 1).

1,3-Dimethyl-2,6-bis(4-methylphenyl)piperidin-4-one-O-benzyloxime (**34**, $C_{28}H_{32}N_2O$)
Yield: 91%; M.p.: 124 °C; IR (KBr): $\bar{\nu} = 3,027$, 2,970, 2,922, 2,868, 2,789 (C–H stretching); 1,646 (C=N stretching); 1,599 (C=C stretching-*Ph*); 1,509, 1,457, 1,370, 1,306, 1,259, 1,211, 1,025, 919, 870, 805; 746 (N–O stretching); 698, 660, 515; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$–7.31 (m, *Ar*–H), 7.19–7.17 (dd, H-2′′′′, H-6′′′′), 5.14 (s, OCH_2), 3.53 (dd, H-5e), 3.16 (dd, H-6a), 2.85 (d, H-2a), 2.63 (m, H-3a), 2.39, 2.37 (*p*-CH_3), 2.16 (t, H-5a), 1.74 (N–CH_3), 0.86 (d, CH_3 at C-3) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 159.56$ (C-4), 141.49 (C-6′), 140.03 (C-2′), 138.30 (O*Bn ipso* carbon), 136.75 (C-2′′′′, C-6′′′′), 129.19, 129.02, 128.12, 128.06, 127.68, 127.50, 113.82 (*Ar* carbons), 77.48 (C-2), 75.45 (OCH_2), 69.13 (C-6), 43.18 (C-3), 41.43 (N–CH_3), 35.31 (C-5), 21.07 (*p*-CH_3), 12.64 (CH_3 at C-3) ppm; MS (ES): $m/z = 413.3$ (M + 1).

1,3-Dimethyl-2,6-bis(4-methoxyphenyl)piperidin-4-one-O-benzyloxime (**35**, $C_{28}H_{32}N_2O_3$)
Yield: 90%; M.p.: 112 °C; IR (KBr): $\bar{\nu} = 3,065$, 3,000, 2,965, 2,932, 2,835, 2,781 (C–H stretching); 1,645 (C=N stretching); 1,610 (C=C stretching-*Ph*); 1,511, 1,456, 1,363, 1,302, 1,248, 1,174, 1,087, 1,035, 923; 751 (N–O stretching); 694, 619, 544, 461; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.28 (m, *Ar*–H), 6.89–6.85 (dd, H-2′′′, H-6′′′), 5.09 (s, OCH_2), 3.83, 3.79 (*p*-OCH_3), 3.46 (dd, H-5e), 3.08 (dd, H-6a), 2.78 (d, H-2a), 2.54 (m, H-3a), 2.09 (t, H-5a), 1.67 (N–CH_3), 0.79 (d, CH_3 at C-3) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 159.62$ (C-4), 158.85 (C-2′′′′, C-6′′′′), 138.38 (O*Bn ipso* carbon), 136.66 (C-6′), 135.25 (C-2′), 129.96, 129.12, 128.25, 127.61, 113.96, 113.78 (*Ar* carbons), 77.14 (C-2), 75.54 (OCH_2), 68.77 (C-6), 55.24 (*p*-OCH_3), 43.36 (C-3), 41.41 (N–CH_3), 35.41 (C-5), 12.72 (CH_3 at C-3) ppm; MS (ES): $m/z = 445.3$ (M + 1).

1-Methyl-3-ethyl-2,6-diphenylpiperidin-4-one-O-benzyloxime (**36**, $C_{27}H_{30}N_2O$)
Yield: 85%; M.p.: 124 °C; IR (KBr): $\bar{\nu} = 3,027$, 2,963, 2,924, 2,852, 2,781 (C–H stretching); 1,645 (C=N stretching); 1,563 (C=C stretching-*Ph*); 1,519, 1,448, 1,412, 1,261, 1,095, 1,023, 866, 802; 759 (N–O stretching); 699, 558, 465; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$–7.15 (m, *Ph*-H), 5.03 (s, OCH_2), 3.42 (dd, H-5e), 3.11 (dd, H-6a), 2.91 (d, H-2a), 2.37 (m, H-3a), 2.05 (t, H-5a), 1.59 (N–CH_3), 1.44, 1.06 (m, CH_2), 0.68 (t, CH_3) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 157.81$ (C-4), 144.59 (C-6′), 143.21 (C-2′), 138.62 (O*Bn ipso* carbon), 128.58, 128.41, 128.26, 127.59, 127.27 (*Ph* carbons), 75.92 (C-2), 75.47 (OCH_2), 69.35 (C-6), 50.19 (C-3), 41.63 (N–CH_3), 35.62 (C-5), 19.79 (CH_2), 11.92 (CH_3) ppm; MS (ES): $m/z = 399.2$ (M + 1).

1-Methyl-3-isopropyl-2,6-diphenylpiperidin-4-one-O-benzyloxime (**37**, $C_{28}H_{32}N_2O$)
Yield: 87%; M.p.: 116 °C; IR (KBr): $\bar{\nu} = 3,061$, 3,030, 2,959, 2,925, 2,869, 2,786 (C–H stretching); 1,649 (C=N stretching); 1,559 (C=C stretching-*Ph*); 1,495, 1,454, 1,364, 1,261, 1,208, 1,021, 946, 916, 803; 752 (N–O stretching); 696, 606, 459; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$–7.32 (m, *Ph*-H), 5.17 (s, OCH_2), 3.46 (dd, H-6a), 3.44 (d, H-2a), 3.23 (dd, H-5e), 2.63 (dd, H-5a), 2.44 (dd, H-3a), 1.73 (m, CH of ^{i}*Pr*, N–CH_3), 1.23 (d, CH_3), 1.07 (d, CH_3') ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 157.37$ (C-4), 144.68 (C-6′), 144.31 (C-2′), 138.81 (O*Bn ipso* carbon), 128.67, 128.57, 128.41, 128.22, 127.96, 127.49, 127.14, 126.84 (*Ph* carbons), 76.45 (OCH_2), 72.64 (C-2), 67.08 (C-6), 54.06 (C-3), 41.44 (N–CH_3), 35.27 (C-5), 29.08 (CH), 21.44 (CH_3), 18.44 (CH_3') ppm; MS (ES): $m/z = 413.2$ (M + 1).

Compounds **31**–**37** were synthesized by adopting all the above three methods while **30** was synthesized by method A only. The summarized data of all the compounds are obtained by Method A.

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