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Synthesis and NMR spectral studies of some 2,6-diarylpiperidin-4-one *O*-benzyloximes

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Abstract

Variously substituted 2,6-diarylpiperidin-4-one *O*-benzyloximes were synthesized by the direct condensation of the corresponding 2,6-diarylpiperidin-4-ones with *O*-benzylhydroxylamine hydrochloride. All the synthesized compounds are characterized by IR, Mass and NMR spectral studies. NMR spectral assignments are made unambiguously by their one-dimensional (^{1}H NMR and ^{13}C NMR) and two-dimensional (^{1}H–^{1}H COSY, NOESY, HSQC and HMBC) NMR spectra. All the synthesized compounds are resulted as single isomer, i.e., exclusively *E* isomer (**9**–**14**). The conformational preference of 2,6-diarylpiperidin-4-one oxime ethers with and without alkyl substituents at C-3 and C-5 has also been discussed using the spectral studies. The observed chemical shifts and coupling constants suggest that compounds **8**–**13** adopt normal chair conformation with equatorial orientation of all the substituents while compound **14** contributes significant boat conformation along with the predominant chair conformation in solution. The effect of oximination on ring carbons, their associated protons, alkyl substituents and *ipso* carbons are studied. Every proton in the piperidone ring of the oxime ether is observed as distinct signal due to oximination. The order of chemical shift magnitude in compound **8** is H-2a > H-6a > H-5e > H-3e > H-3a > H-5a. For **9**–**12**, the order is H-6a > H-5e > H-2a > H-3a > H-5a, for **13**, H-6a > H-2a > H-5e > H-3a > H-5a and for **14**, the order is H-2a > H-6a > H-5e > H-3a > H-5a while the ^{13}C chemical shift magnitude for **8**–**14** due to oximination is C-2 > C-6 > C-3 > C-5.

Keywords: 2,6-Diarylpiperidin-4-one; *O*-Benzylhydroxylamine hydrochloride; Oxime ether; ^{1}H NMR; ^{13}C NMR; 2D NMR technique; Conformation; Electronegativity

1. Introduction

Nuclear magnetic resonance spectroscopy is a versatile tool for the structural analysis of most of the organic compounds. The NMR techniques are also useful for the conformational analysis too. ^{1}H NMR and ^{13}C NMR techniques have been extensively applied in deriving stereodynamical information about a wide variety of systems. It gives 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 as it can give an idea about the orientation of the substituents [1,2].

Substituted 2,6-diarylpiperidin-4-ones [3] have been subjected to quite a large number 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]. However, introduction of certain heteroconjugate groups such as –NO, –CHO, $-COCH_3$, $-COC_6H_5$, etc., at the ring nitrogen of 2,6-disubstituted piperidine ring system have reported to cause a major change in ring conformation [16–24]. Similarly, the conversion of the carbonyl group into C=N–OH, $C=N-NH_2$, $C=N-N=CH_2$, C=N–NHPh, $C=NNHCSNH_2$ [26–35] cause 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 the present study, we have converted the carbonyl carbon into bulkier $C=N-O-CH_2-Ph$ in order to establish the impact of the bulkier oximino group on the chemical shift and conformation of the piperidone ring and substituents.

Generally, the decrease in electronegativity of a group or atom on the ring cause major change in chemical shifts on the ring

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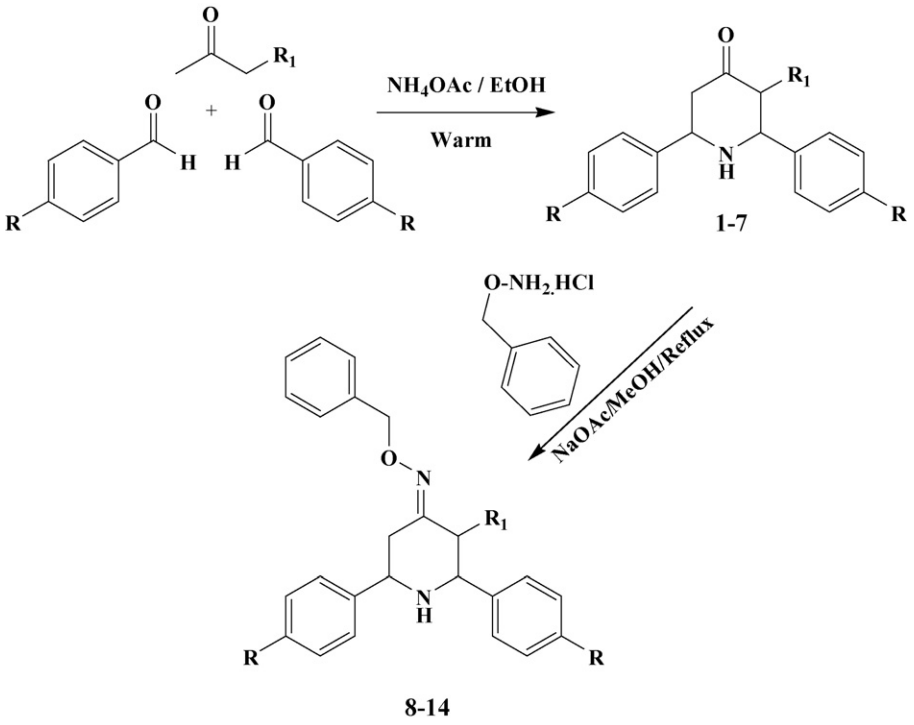

Compounds	R	R_1
1, 8	H	H
2, 9	H	CH_3
3, 10	Cl	CH_3
4, 11	CH_3	CH_3
5, 12	OCH_3	CH_3
6, 13	H	CH_2CH_3
7, 14	H	$CH(CH_3)_2$

Scheme 1.

carbons and the attached protons [33]. So, the C=N–O–Bn in place of C=O of the piperidone ring is expected to cause a severe change in their chemical shifts of α-, β- and γ-carbon and their associated protons in addition to the conformational preference of the piperidone ring.

2. Results and discussion

All the oxime ethers were synthesized by the direct condensation of corresponding piperidin-4-ones with *O*-benzylhydroxylamine hydrochloride in the presence of sodium

Table 1
Analytical data for compounds **8–14**

Compound	Molecular formula	mp (°C)	Yield (%)	Elemental analysis					
				Calculated (%)			Found (%)		
				C	H	N	C	H	N
8	$C_{24}H_{24}N_2O$	84	95	80.87	6.79	7.86	80.85	6.71	7.89
9	$C_{25}H_{26}N_2O$	96	94	81.05	7.07	7.56	81.06	7.06	7.57
10	$C_{25}H_{24}N_2OCl_2$	117	92	68.34	5.51	6.38	68.31	5.52	6.40
11	$C_{27}H_{30}N_2O$	132	92	81.37	7.59	7.03	81.39	7.55	7.04
12	$C_{27}H_{30}N_2O_3$	130	94	75.32	7.02	6.51	75.30	7.04	6.51
13	$C_{26}H_{28}N_2O$	102	91	81.21	7.34	7.29	81.20	7.32	7.27
14	$C_{27}H_{30}N_2O$	137–138	89	81.37	7.59	7.03	81.39	7.58	7.04

Table 2
Proton chemical shift values (δ, ppm) of compounds **8**–**14**

Compound	H-2a (d)	H-3a (m)	H-3e (ddd)	H-5a (dd)	H-5e (dd)	H-6a (dd)	Aromatic (m)	*p*-CH_3/*p*-OCH_3 (s)	CH_3at C-3(d)	NH (bs)	O-CH_2-Ph (s)
8	3.93 (dd)	2.34 (dd)	2.58	2.01	3.52 (ddd)	3.85	7.25–7.48	–	–	[a]	5.10
9	3.41	2.40	–	1.93	3.51	3.74	7.12–7.35	–	0.80	1.79	5.03
10	3.33	2.28	–	1.80	3.43	3.65	7.13–724	–	0.75	1.69	5.00
11	3.35	2.36	–	1.89	3.43	3.68	6.99–7.03, 7.16–7.27	2.19, 2.22	0.79	1.74	5.01
12	3.34	2.33	–	1.89	3.46	3.67	6.73–6.77, 7.18–7.28	3.66, 3.68	0.78	1.71	5.02
13	3.59	2.38	–	2.01	3.50	3.78	7.11–7.45	–	0.72 (CH_3, t) 1.17, 1.49 (–CH_2–, m)	[b]	5.04
14	3.82	2.40 (dd)	–	2.18	3.28	3.81	7.12–7.35	–	0.79 (CH_3) 0.94 (CH_3') 1.68 (–CH–, m)	[c]	5.03

[a] Merged with H-5a signal.
[b] Merged with CH_2 signal.
[c] Merged with H-7 signal.

Table 3
^{13}C chemical shift values of compounds **8**–**14** (δ, ppm)

Compound	C-2	C-3	C-4	C-5	C-6	–O–$\underline{C}H_2$–	$\underline{C}H_3$ at C-3	C-2′	C-6′	O–Bn *ipso*	Aryl carbons
8	61.98	40.41	157.78	34.20	60.67	75.40	–	143.61	143.55	137.99	128.54, 128.31, 127.96, 127.65, 126.74, 126.61
9	69.50	43.37	160.15	34.77	60.94	75.65	11.91	142.84	143.90	138.45	128.52, 128.47, 128.29, 128.01, 127.81, 127.61,126.78
10	68.24	43.04	158.79	34.43	59.81	75.48	11.63	140.90	141.96	138.03	132.94, 133.21 (C_2'''', C_6''''), 129.05, 128.41, 128.10, 127.88, 127.49
11	69.02	43.20	160.16	34.68	60.47	75.43	11.85	139.77	140.86	138.29	136.90, 137.12 (C_2'''', C_6''''), 129.01, 128.95, 128.14, 128.09, 127.72, 127.47, 126.50
12	68.61	43.29	160.19	34.67	60.10	75.40	11.79	134.93	136.00	138.25	158.86, 159.00 (C_2'''', C_6''''), 128.77, 128.13, 128.10, 127.66, 127.47, 113.69, 113.61
13	67.35	49.45	157.93	34.36	60.73	75.46	11.71 (CH_3) 18.89(CH_2)	141.92	142.95	138.36	128.67, 128.31, 128.10, 127.72, 127.50, 127.44, 126.72
14	65.16	53.30	157.98	34.69	59.74	75.50	18.38 (CH_3) 21.03(CH_3') 28.01 (CH)	143.61	144.00	138.70	128.46, 128.41, 128.22, 128.16, 127.93, 127.61, 127.47, 127.10, 126.67

Table 4
IR and Mass spectral data of compounds **8**–**14**

Compound	IR (cm^{-1})	EIMS (*m/z*)
8	2912 (N–H stretching), 2793 (C–H stretching), 1638 (C=N stretching), 1600, 1493, 1453, 1426, 1368, 1299, 1198, 1105, 1043, 936, 878, 757, 700, 574, 494	356 (M^+), 265, 249, 234, 208, 194, 167, 160, 144, 129, 115, 104, 91 (base peak)
9	3310 (N–H stretching), 2810 (C–H stretching), 1640 (C=N stretching), 1601, 1494, 1453, 1371, 1303, 1263, 1208, 1104, 1043, 1018, 983, 921, 863, 783, 748, 699, 556, 476	371 ($M+1$), 263, 194, 174, 156, 143, 129, 117, 106, 91 (base peak)
10	3313 (N–H stretching), 2812 (C–H stretching), 1636 (C=N stretching), 1596, 1490, 1451, 1368, 1303, 1262, 1089, 1015, 923, 827, 751, 697, 582, 511	438 (M^+), 331, 262, 208, 192, 169, 165, 140, 128, 103, 91 (base peak)
11	3312 (N–H stretching), 2808 (C–H stretching), 1647 (C=N stretching), 1597, 1513, 1452, 1369, 1305, 1261, 1208, 1100, 1022, 921, 867, 806, 748, 697, 663, 512.	
12	3313 (N–H stretching), 2808 (C–H stretching), 1635 (C=N stretching), 1601, 1512, 1454, 1361, 1303, 1247, 1175, 1106, 1034, 921, 831, 805, 751, 699, 549	
13	3312 (N–H stretching), 2856 (C–H stretching), 1649 (C=N stretching), 1604, 1514, 1459, 1413, 1262, 1096, 1023, 875, 802, 698, 470	385 ($M+1$)[a]
14	3306 (N–H stretching), 2803 (C–H stretching), 1642 (C=N stretching), 1601, 1493, 1454, 1361, 1301, 1262, 1096, 1023, 801, 752, 699, 662, 607, 490	

[a] Recorded on electron spray mass spectrometer (ESMS), which predominantly gave ($M+1$) only.

acetate trihydrate (Scheme 1). All the synthesized compounds are obtained in good yield. The analytical data are represented in Table 1. Proton and carbon NMR spectra of all the synthesized compounds **8**–**14** were recorded at 400 MHz and 100 MHz, respectively, and are reproduced in Tables 2 and 3, respectively. For compound **8**, HOMOCOSY, NOESY, HSQC and HMBC were also recorded. Mass spectra were recorded for compounds **8**–**10** and **13**. All the obtained Mass spectral data are in agreement with the proposed molecular formula of the respective compounds. IR spectra of all the synthesized compounds support the formation of oxime ether by the appearance of a band at about 1636–1649 cm^{-1}. The IR and Mass spectral values are furnished in Table 4. The numberings of the target compounds are shown in Fig. 1.

*2.1. ^{1}H NMR spectral study of 2,6-diphenylpiperidin-4-one O-benzyloxime (**8**)*

The signals (double doublet and multiplet) appeared in the region of 7.25–7.48 ppm with 15 protons integral are due to the phenyl group protons at C-2, C-6 and in *O*-benzyl group. Of the two signals, the double doublet at 7.46–7.48 ppm has strong nOe with the double doublets at 3.93 and 3.85 ppm, which suggest that the double doublet at 7.46–7.48 ppm with four protons integral is due to the *ortho* protons of the phenyl groups at C-2 and C-6. Deshielding of the *ortho* protons has been attributed to the lone pair of electrons on the nitrogen in the piperidone heterocycle. The rest of the phenyl protons and *O*-benzyl moiety phenyl protons are merged together to give multiplet at about 7.25–7.36 ppm.

The two doublets at 3.93 ppm and 3.85 ppm (Fig. 2) are appeared with the coupling constant of $^3J_{aa} = 11.5$ Hz, $^3J_{ae} = 2.9$ Hz and $^3J_{aa} = 11.7$ Hz, $^3J_{ae} = 3.0$ Hz, respectively, which may be due to the benzylic protons H-2a and H-6a and are having correlation, respectively, with 2.58/2.34 and 3.52/2.01 ppm signals of the methylene protons at C-3 and C-5. Of the four methylene proton signals, the two lower frequency signals (2.01 ppm $^3J_{aa} = 11.8$ Hz, $^2J_{ae} = 13.9$ Hz and 2.34 ppm, $^3J_{aa} = 11.6$ Hz, $^2J_{ae} = 13.5$ Hz) are appeared as double doublets, which is due to the splitting of one methylenic proton by another methylenic proton on the same carbon and also with the benzylic proton of the adjacent position, while rest of the two are appeared as doublets of double doublets (ddd) instead of the expected double doublets due to the long-range coupling between them. This is possible only when both the protons are in "W" arrangement presumably with equatorial disposition at C-3 and C-5. This is substantiated by the observed weak HOMO correlation (Fig. 3) between these two signals (2.58 and 3.52 ppm). Consequently, the double doublets at 2.01 and 2.34 ppm are due to the axial methylenic protons H-3a and H-5a, which is confirmed by its nOe with the *ortho* protons of the phenyl group at C-2 and C-6 (Fig. 4). Of the two sets of axial and equatorial protons at C-3 and C-5, the higher frequency ddd at 3.52 ppm is assigned to the H-5e proton owing to the interaction of the N–O bond with the C–H(5e) bond (Fig. 5). Due to this interaction, the C–H(5e) bond is polarized consequently the *syn* α-proton H-5e gets positive charge and the *syn* α-carbon C-5 gets negative charge. Further, the H-5a proton is highly shielded due to the transmittance of negative charge from C-5 to H-5a. From this, the higher frequency ddd at 3.52 ppm is assigned to the H-5e whereas the lower frequency ddd at 2.58 ppm is assigned to the *anti* α-equatorial proton H-3e. From the HOMO correlations of the signals at 3.52 and 2.58 ppm, respectively, with double doublets at 2.01 and 2.34 ppm, it is concluded that the former one (2.01 ppm dd) is due to H-5a and the latter one (2.34 ppm dd) is due to H-3a proton.

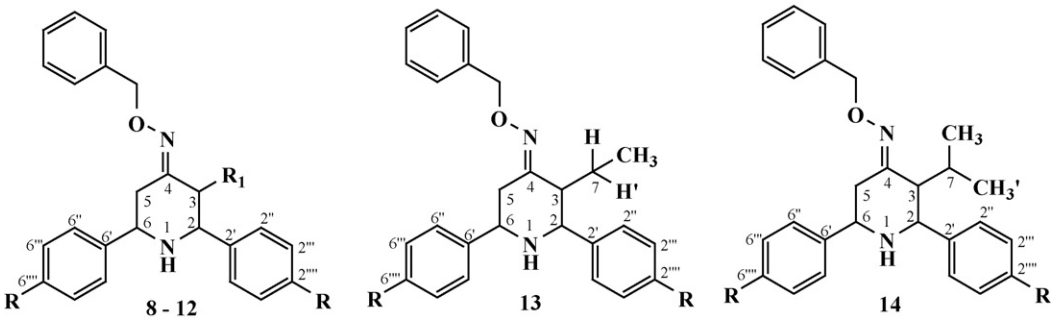

Fig. 1. Numberings of the target compounds **8**–**14**.

The H-5a proton signal has almost two protons integral, contrary to other ring proton signals (each signal corresponds to one proton integral). This may be due to the overlapping of NH proton signal with that of H-5a at 2.01 ppm. Generally, in 2,6-diarylpiperidin-4-ones the NH proton appeared at about 2 ppm. Moreover, this NH proton signal is unambiguously identified by D_2O exchange. Besides, the sharp singlet appeared at 5.10 ppm, which integrates as two protons, is obviously assigned to the methylene protons of the *O*-benzyl moiety. Moreover, this singlet has nOe with its phenyl protons merged with the *meta* protons of the phenyl group at C-2 and C-6 in the range of 7.34–7.36 ppm. The HOMOCOSY and NOESY spectra correlations of **8** are reproduced in Table 5.

2.2. ^{1}H NMR spectral study of 3-alkyl-2,6-diarylpiperidin-4-one O-benzyloximes (**9**–**14**)

In the ^{1}H NMR spectrum of compound **9** (Fig. 6), besides the aryl protons signal at 7.12–7.35 ppm [7.33–7.35 (t) and 7.12–7.30 (m), the triplet is due to the *ortho* protons of the phenyl at C-2 and C-6 while the multiplet is due to the rest of the phenyl protons] and the *O*-benzyl methylene protons signal at 5.03 ppm, all the piperidone ring protons signals (splitting pattern and chemical shifts) are varied drastically due to the introduction of an equatorial methyl group at C-3. This methyl protons signal appeared as a doublet at 0.80 ppm with coupling constant of 6.5 Hz. The NH proton signal is appeared separately as a broad singlet at 1.79 ppm.

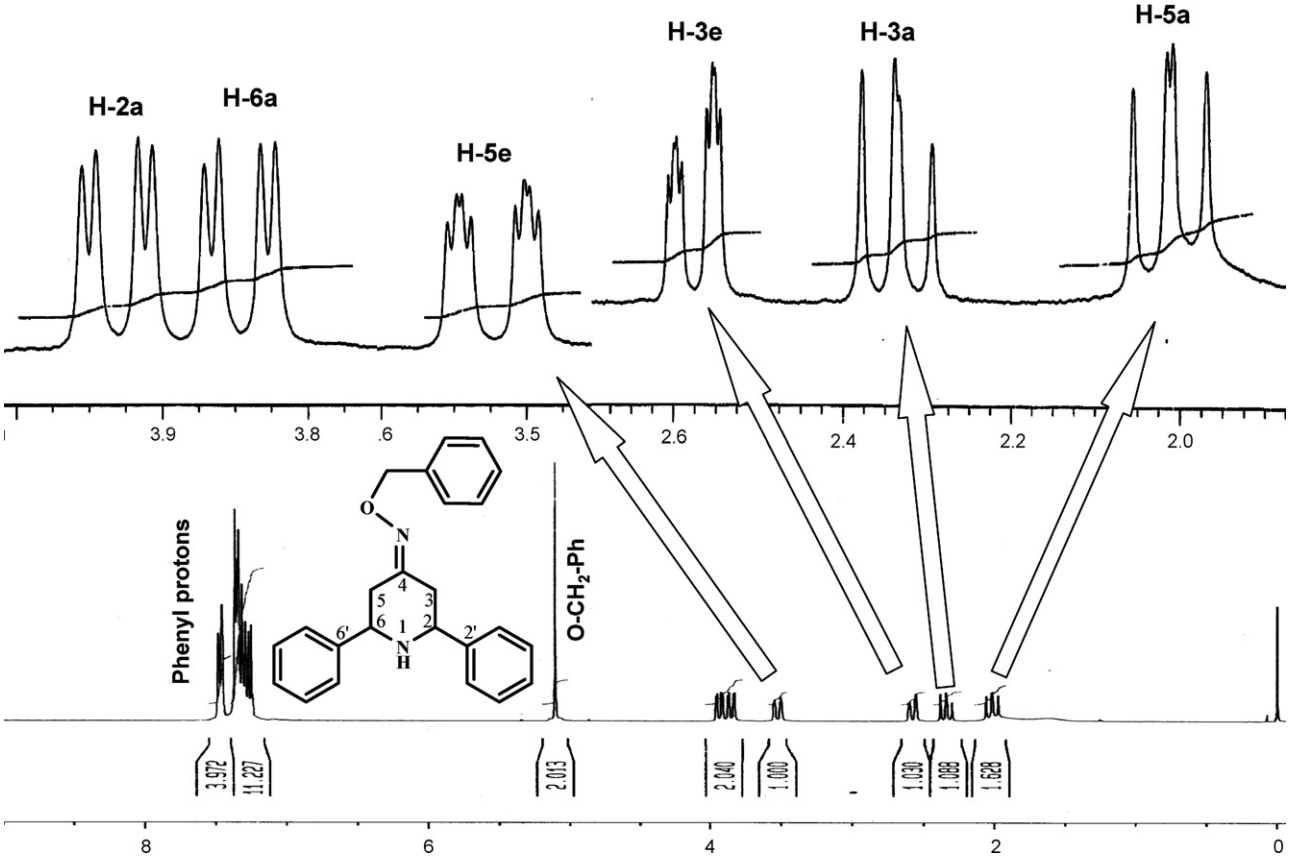

Fig. 2. ^{1}H NMR spectrum of compound **8**.

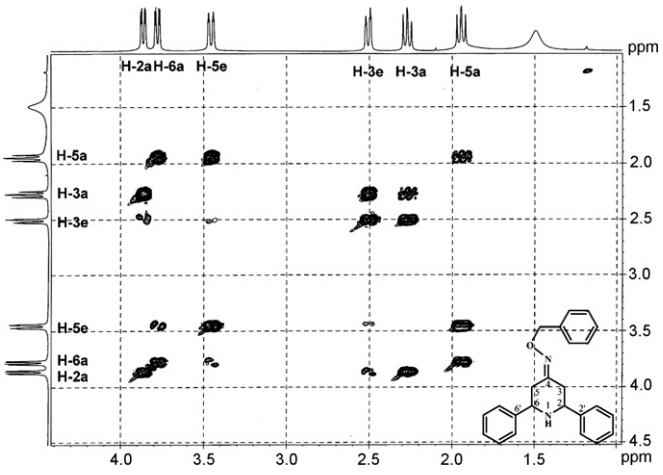

Fig. 3. HOMOCOSY spectrum of compound **8**.

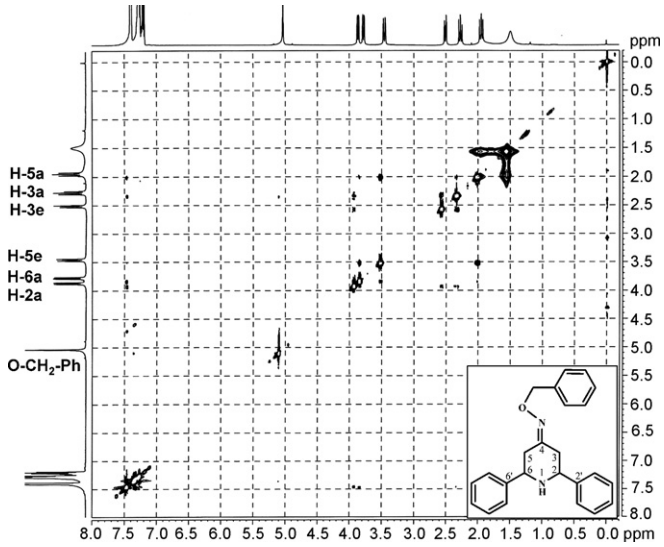

Fig. 4. NOESY spectrum of compound **8**.

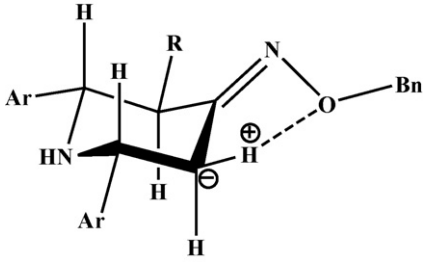

Fig. 5. H(5e)–NO bond interaction.

In the higher frequency region there are two double doublets and one doublet at 3.74 (^3J = 11.7 Hz, 2.8 Hz), 3.51 (^2J = 13.7 Hz, ^3J = 2.8 Hz) and 3.41 ppm (^3J = 10.1 Hz), respectively. Of the three signals, 3.41 ppm doublet and 3.74 ppm doublet of doublet are assigned to the H-2a and H-6a benzylic protons, respectively, while 3.51 ppm (^2J = 13.7 Hz, ^3J = 12.1 Hz) double doublet is assigned to H-5e (*syn* α) proton on the basis of their splitting pattern and vicinal coupling constant. Consequently, the other double doublet at 1.93 ppm is assigned to the methylenic proton of H-5a on the basis of their position nature of splitting, coupling constants and in comparison with **8**. Obviously, the sextet centered at 2.40 ppm is designated to the H-3a. This is deshielded by about 0.06 ppm than **8** due to the introduction of an equatorial methyl group at C-3 [35].

Unlike **9**, compound **10** gave a single multiplet with integral value for 13 protons (*p*-chlorophenyl at C-2 and C-6). But in compound **11** (*p*-methylphenyl at C-2 and C-6) and **12** (*p*-methoxyphenyl at C-2 and C-6) two sets of aryl signals are observed with 13 protons integral value. Of the two set of aryl signals, the upfield triplet is due to the protons *ortho* to the substituent in **11**, while in **12** the triplet appeared in the upfield region is due to the protons *meta* to the methoxy substituents i.e., H-2″ and H-6″. Contrary to **11**, in **12**, the *ortho* protons are observed in the downfield region due to the *ortho* effect of the methoxy group. In parent piperidones **4** and **5**, only one singlet with six protons integral was observed for the CH_3/OCH_3 at C-2‴″ and C-6‴″ whereas, two closely merged singlets (appeared as like that of a doublet), each corresponds to three protons appeared at 2.19, 2.22 and 3.66, 3.88 ppm, respectively, for the methyl and methoxy protons at C-2‴″ and C-6‴″ due to the oximino effect.

Compound **13** also has similar kind of splitting as like that of **9**. The side chain ethyl at C-3 gave three kinds of signals (Fig. 7) viz., a septet and a multiplet centered, respectively, at 1.49 and 1.17 ppm for the methylene protons (H-7 and H′-7) in the ethyl group while the methyl group gave a triplet with three protons integral in the most upfield region of about 0.72 ppm.

In compound **14**, all the phenyl ring protons are merged to give a multiplet in the region 7.12–7.35 ppm. Two doublets at 0.94 ppm (J = 6.9 Hz) and 0.79 ppm (J = 6.9 Hz), each represent three protons are assigned to the two-methyl group protons in the isopropyl moiety. The separate signals for the two-methyl groups are due to their diastereotopic nature. Further, the isopropyl methine proton and the ring NH proton were merged to give a multiplet centered at 1.68 ppm (Fig. 8). All the ring protons are assigned similar to that of compound **9**.

2.3. Analysis of coupling constants

All the observed coupling constant values for **8**–**14** are furnished in Table 6.

Table 5
Correlations in the HOMOCOSY and NOESY spectra of compound **8** (δ, ppm)

Signal	Correlations in the HOMOCOSY spectrum	Correlations in the NOESY spectrum
7.46–7.48 (dd, 4H)	7.28–7.36	3.93, 3.85, 2.34, 2.01
7.25–7.36 (m, 11H)	7.46–7.48	–
5.10 (s, 2H)	–	7.28–7.36
3.93 (dd, 1H)	2.58, 2.34	2.58, 2.34
3.85 (dd, 1H)	3.52, 2.01	3.52, 2.01
3.52 (ddd, 1H)	3.85, 2.58, 2.01	2.01, 3.85
2.58 (ddd, 1H)	3.93, 3.52, 2.34	2.34, 3.93
2.34 (dd, 1H)	3.93, 2.58	2.58, 2.01, 3.85
2.01 (dd, 1H)	3.85, 3.52	3.52

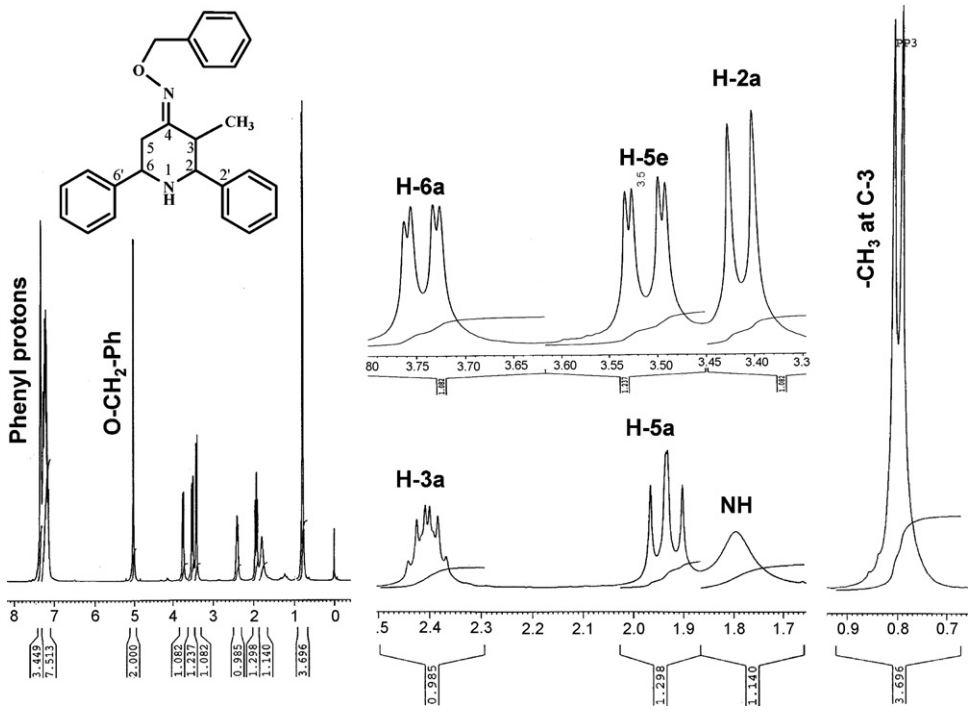

Fig. 6. ^{1}H NMR spectrum of compound **9**.

For compound **8**, the observed vicinal diaxial coupling constants $J_{2a,3a}$ and $J_{5a,6a}$ are 11.5 and 11.7 Hz, respectively (almost same) and the vicinal axial–equatorial coupling constants $J_{2a,3e}$ and $J_{5e,6a}$ are, respectively, 2.9 and 3.0 Hz, whereas the geminal axial–equatorial coupling constants $J_{3a,3e}$ and $J_{5a,5e}$ are, respectively, 12.9 and 14.0 Hz (slightly varied due to the bulkier oximino group in place of the carbonyl carbon). Based on the obtained coupling constant values, normal chair conformation is proposed for compound **8** as depicted in Fig. 9.

In **9–12**, due to the introduction of methyl group, $J_{2a,3a}$ is considerably decreased by about 1.4 ppm. The difference between $J_{2a,3a}$ and $J_{5a,6a}$ also in the same magnitude (1.4 Hz). Obviously, this is due to the flattening of the ring about C(2)–C(3) bond to decrease the Ph–Me *gauche* interaction while introducing an equatorial methyl group at C-3 as depicted in Fig. 10. This is also supported by the force field calculations [36] and X-ray diffraction data [37]. The observed vicinal coupling constants suggest that **9–12** adopts normal chair conformation.

In **13**, there is no appreciable variation in coupling constants and are almost similar to that of **9**, which suggest that the ethyl substituent does not alter the conformation. To find the ethyl group conformation at C-3, the coupling constants between the methine proton H-3a and methylene protons H-7/H′-7 are found as 2.7 Hz ($J_{3a,7H}$) and 8.4 Hz ($J_{3a,7H'}$). These values suggest that the conformation of ethyl group exist as an equilibrium mixture of the two forms as in Fig. 11. This conclusion is conformed by the earlier report on the 3-ethyl 2,6-diphenylpiperidin-4-one [28].

But in **14**, the coupling constants are appreciably varied from compound **9**. The considerable decrease in $J_{2a,3a}$ (1.2 Hz) and $J_{5a,6a}$ (0.4 Hz) and also an increase in $J_{5a,5e}$ (0.9 Hz) are observed when compared to **9**. The coupling constant is decreased about 1.4 Hz and 0.4 Hz, respectively, for $J_{2a,3a}$ and $J_{5a,6a}$ compared to corresponding piperidone. Moreover the increasing magnitude of $J_{3a,7}$ is 1.7 Hz and $J_{5a,5e}$ is 0.9 Hz compared to piperidone. These values strongly suggest that **14** contribute boat conformation (Fig. 12) along with the predominant chair conformation in solution. The conformational preference of the isopropyl substituent at C-3 is found from the vicinal coupling constant between H-3a and isopropyl methine proton H-7. The observed

Table 6
Coupling constant (Hz) values of compounds **8–14**

Compound	$^{3}J_{2a,3a}$	$^{3}J_{2a,3e}$	$^{2}J_{3a,3e}$	$^{4}J_{3e,5e}$	$^{3}J_{5a,6a}$	$^{2}J_{5a,5e}$	$^{3}J_{5e,6a}$	$^{3}J_{3a,7}$
8	11.5	2.9	12.9	1.7	11.7	14.0	3.0	–
9	10.1	–	–	–	11.7	13.7	2.8	–
10	10.1	–	–	–	11.5	13.6	2.5	–
11	10.1	–	–	–	11.5	13.6	2.5	–
12	10.1	–	–	–	[a]	13.7	2.8	–
13	10.3	–	–	–	11.6	13.6	2.7	–
14	8.9	–	–	–	11.3	14.6	3.6	3.9

[a] Could not be determined due to overlapped signal.

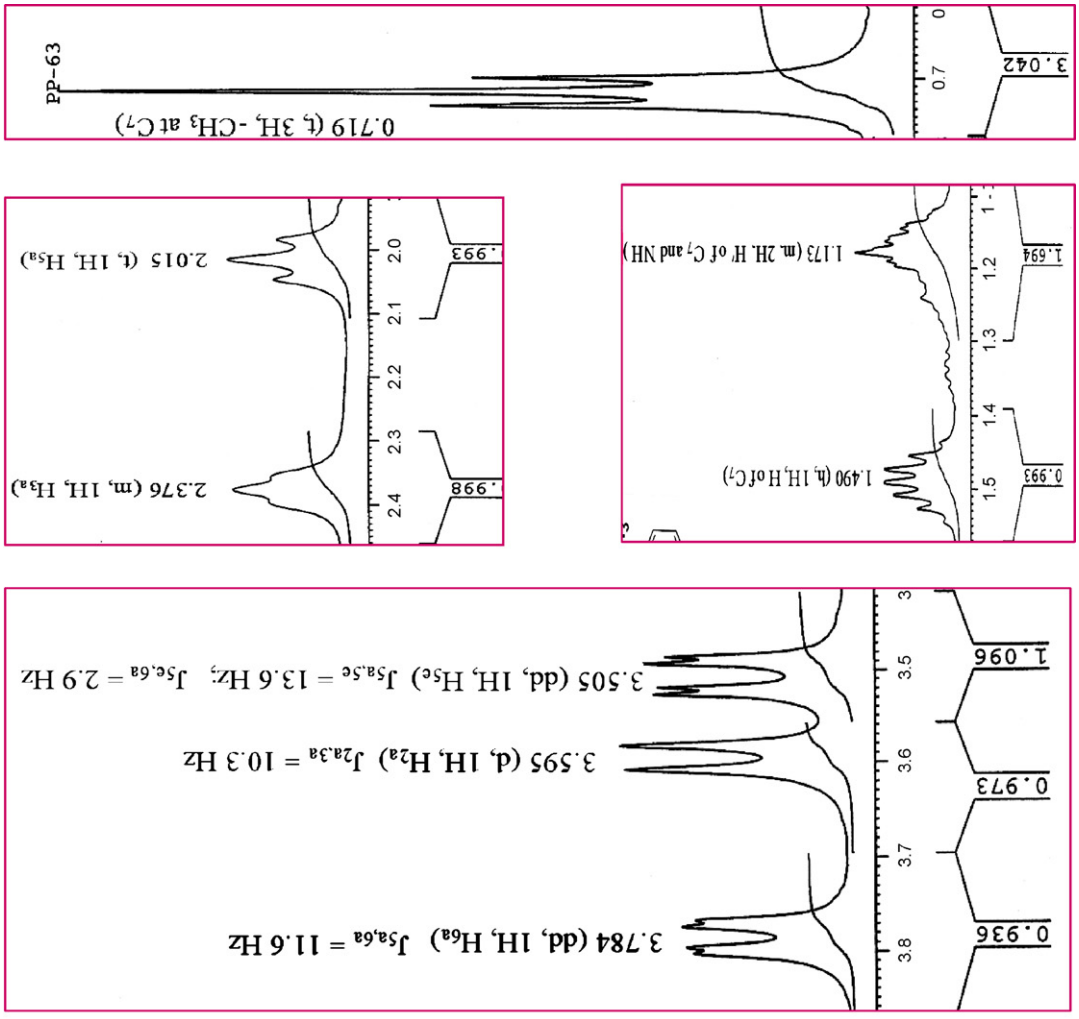

Fig. 7. ^{1}H NMR spectrum of compound **13**.

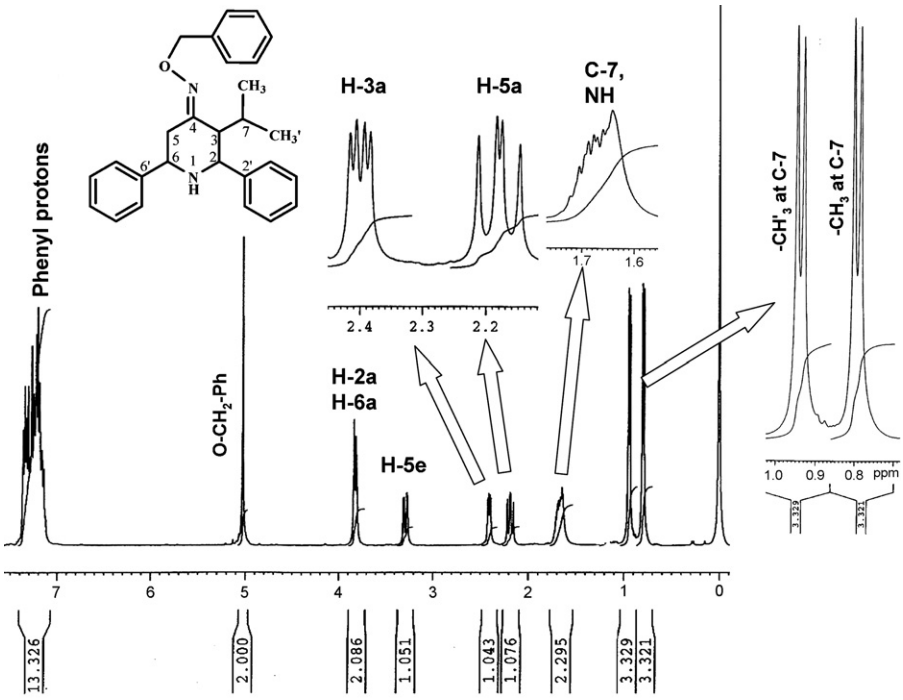

Fig. 8. ^{1}H NMR spectrum of compound **14**.

$J_{3a,7}$ = 3.9 Hz suggest that this value is probably due to only *gauche* coupling. From this, we inferred that the preferred conformation of the isopropyl group is as depicted in Fig. 13. This also supported by the earlier observations of 3-isopropyl-2,6-diarylpiperidin-4-one [28].

On the basis of the observed vicinal coupling constants, we inferred that the compounds **9**–**13** adopt normal chair conformation (Fig. 9) with equatorial disposition of all the substituents at C-2, C-6 and also at C-3 while **14** contributes significant boat conformation (Fig. 11) along with the predominant chair conformation.

2.4. ^{13}C NMR spectral analysis of 2,6-diphenylpiperidin-4-one O-benzyloxime (8)

In the ^{13}C NMR spectrum of compound **8** displayed in Fig. 14, there are four low intense signals at 157.78, 143.61, 143.53 and 137.99 ppm and high intense signals at 128.54–126.61 ppm observed in the aryl region. There are five intense signals in the aliphatic region at 75.40, 61.98, 60.67, 40.41 and 34.20 ppm.

Of these five signals in the upfield region, 75.40 ppm shows cross peak only with the *O*-benzyl moiety methylene protons singlet at 5.10 ppm in HSQC spectrum (Fig. 15). The 61.98 and 60.67 ppm signals also having cross peaks only with, respectively, H-2a and H-6a protons indicate these carbon signals are, respectively, due to C-2 and C-6 of the piperidone ring. From the methylenic protons correlation in HSQC, 40.41 and 34.20 ppm are, respectively, assigned to the methylenic carbons C-3 and C-5.

The signals from 128.54–126.61 ppm show cross peak with the aryl protons signal in HSQC, consequently these intense aryl carbon signals are assigned to the phenyl ring carbon at C-2 and C-6 and also in *O*-benzyl group. The absence of correlation beyond 128.54 ppm in HSQC predicts those are quartenery carbons. From the help of HMBC spectra (Fig. 16), the 157.78 and 137.99 ppm resonances are assigned to the C-4 (C=N) and *O*-benzyl *ipso* carbon, respectively, without ambiguity. Obviously the other two signals at 143.61 and 143.55 ppm are due to the *ipso* carbons C-2′ and C-6′. The

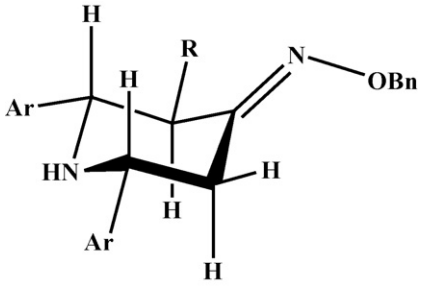

Fig. 9. Chair conformation.

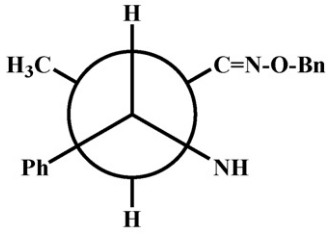

Fig. 10. Flattening about C(2)–C(3) bond.

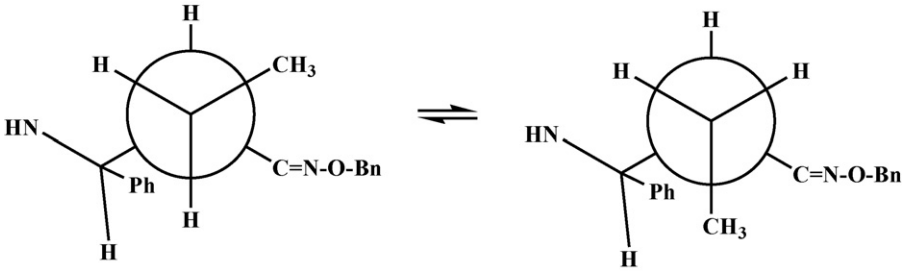

Fig. 11. Ethyl group conformation in compound **13**.

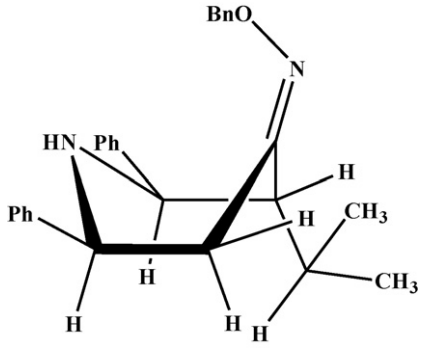

Fig. 12. Boat conformation.

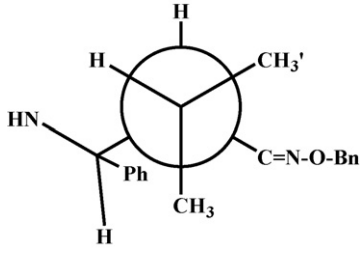

Fig. 13. Isopropyl group conformation in compound **14**.

^{1}H–^{13}C one and multiple bond correlations are represented in Table 7.

2.5. ^{13}C NMR spectral study of 3-alkyl-2,6-diarylpiperidin-4-one O-benzyloximes (**9**–**14**)

The ^{13}C NMR spectrum of compound **9** is reproduced in Fig. 17, which shows similar kind of resonances beyond the aliphatic region and are assigned as like that of **8**.

Moreover, the intensed signal at 75.65 ppm also assigned to the *O*-benzyl methylene carbon as in the case of **8**.

By considering the β-effect of the methyl sustituent at C-3, the signal resonating at 69.50 ppm can be assigned to the benzylic carbon C-2. Generally introduction of an equatorial methyl substituent at C-3 of the piperidone moiety causes a large β-effect (≈7 ppm) at C-2 benzylic carbon [38]. Indeed, the ^{13}C resonance at 69.50 ppm is assigned to the C-2 benzylic carbon. Obviously the other higher frequency signal is designated to the C-6 benzylic carbon.

Of the three signals in the lower frequency region, the most upfield signal at 11.91 ppm is ascribed to the methyl carbon at C-3. In the remaining two signals, one appeared at 34.77 ppm as like that of C-5 methylenic carbon of **8** is conveniently assigned to C-5 of **9**. Obviously the other signal at 43.37 ppm is designated to the C-3 methylenic carbon, which is 2.97 ppm deshielded than the C-3 of **8**. Indeed, this is obviously due to the α-effect of the methyl substituent at C-3. Similar kind of β-effect of the methyl group at C-3 on C-2 benzylic carbon of 1-hetera-2,6-diaryl-3-methyl-4-cyclohexanones is also noted [39].

The ^{13}C NMR spectra of **10**–**12** are also analysed and assigned similarly in **9**. Further in **10**–**12**, two pair *ipso* carbons are observed due to the *p*-substituents in the phenyl rings at C-2 and C-6. In **10** and **11** the substituent bearing *ipso* carbons (C-2‴′ and C-6‴′) are appeared in the upfield region than C-2′ and C-6′ *ipso* carbons, where as in **12** the methoxy bearing *ipso* carbons are appeared in the most downfield region.

The methyl carbons present at C-2‴′ and C-6‴′ of **11** are observed in the deshielding region compared to methyl group at C-3 (21.01 and 21.05 ppm) due to ring current effect. The methoxy carbons substituted at C-2‴′ and C-6‴′ of **12** are observed at 55.09 ppm.

Table 7
Correlations in the HSQC and HMBC spectra of compound **8** (δ, ppm)

Signal	Correlations in the HSQC spectrum	Correlations in the HMBC spectrum
7.46–7.48 [*ortho* protons (i.e., H-2″ and H-6″)]	126.61, 126.74	126.74, 126.61
7.25–7.36 (remaining aryl protons)	127.65, 127.96, 128.31, 128.54	143.61, 143.55, 128.54–127.65
5.10 (–O–CH_2–Ph)	75.40	137.99, 128.54–127.65
3.93 (H-2a)	61.98	126.74, 126.61
3.85 (H-6a)	60.67	126.74, 126.61
3.52 (H-5e)	34.20	157.78, 40.41
2.58 (H-3e)	40.41	157.78, 34.20
2.34 (H-3a)	40.41	157.78, 143.61, 61.98
2.01 (H-5a)	34.20	157.78, 143.55, 60.67

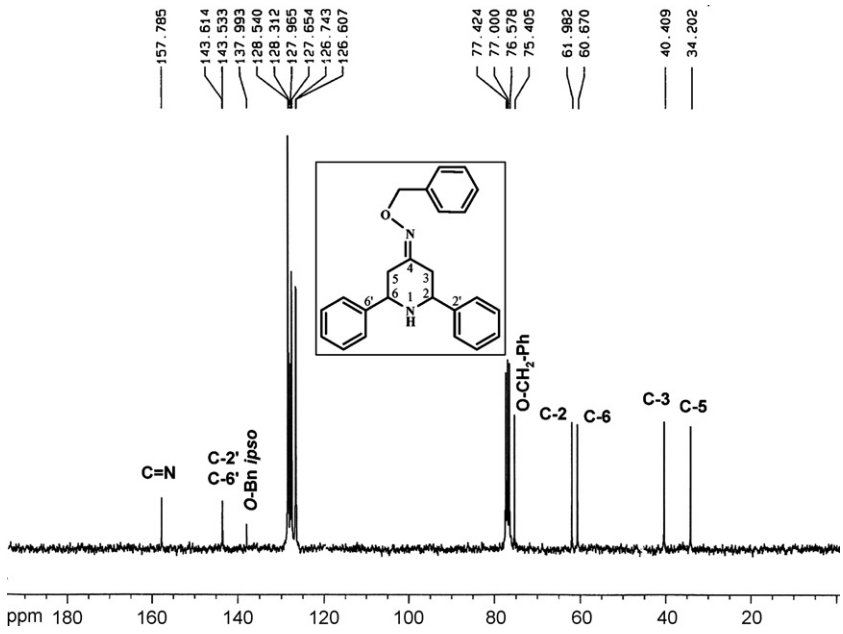

Fig. 14. ^{13}C NMR spectrum of compound **8**.

Table 8
Chemical shift difference between piperidone (**1**–**7**) and oxime ether (**8**–**14**) ($\delta_{\text{piperidone}} - \delta_{\text{oxime ether}}$) ($\Delta\delta$, ppm)

Compound	C-2	C-3	C-4	C-5	C-6	C-2′	C-6′	$\underline{C}H_3$ at C-3
8	−0.98	9.79	50.02	16.00	0.33	−1.01	0.95	–
9	−1.00	8.23	49.35	16.13	0.56	−1.04	1.20	−1.81
10	−1.01	8.21	49.30	16.15	0.65	−1.01	1.20	−1.81
11	−0.98	8.17	49.29	16.19	0.61	−0.97	1.21	−1.85
12	−0.91	8.41	49.61	16.33	0.80	−0.83	−1.00	−1.69
13	−0.65	8.95	51.17	17.24	1.07	−0.23	−0.38	−1.05 ($\underline{C}H_2$), −0.47 ($\underline{C}H_3$)
14	−0.26	8.00	51.02	17.41	1.56	−1.71	−1.21	−1.91($\underline{C}H$), −0.23 ($\underline{C}H_3$, $\underline{C}H'_3$)

+: shielding; −: deshielding.

In compounds **13** and **14**, due to the replacement of methyl by ethyl or isopropyl substituents, respectively, at C-3 causes an increase in α-effect on the C-3 methylenic carbon and decrease in β-effect on C-2 benzylic carbons, Other signals are assigned similar to that of **9** and their chemical shift values are furnished in Table 3.

2.6. Effect of oximination

Generally in six-membered heterocycles, decrease in electronegativity of a particular group in the ring skeleton shield the α-carbons and deshields the β- and γ-carbons [40]. Inspite of the less polar nature of the C=N than C=O bond, the electronegativity of the C=N–O–Bn group must be less than that of C=O group. All the $\Delta\delta$ ($\delta_{\text{piperidone}} - \delta_{\text{oxime ether}}$) values for the piperidone ring carbons of the synthesized compounds **8**–**14** are represented in Table 8. A perusal of the data in Table 8, the $\Delta\delta$ values of **14** are significantly deviate from other compounds. This is due to the bulkier isopropyl group at C-3 of the oxime ether **14** and conformational preference.

Generally in ketoximes, the *syn* α-carbon is shielded than the *anti* α-carbon, probably the chemical shift difference between

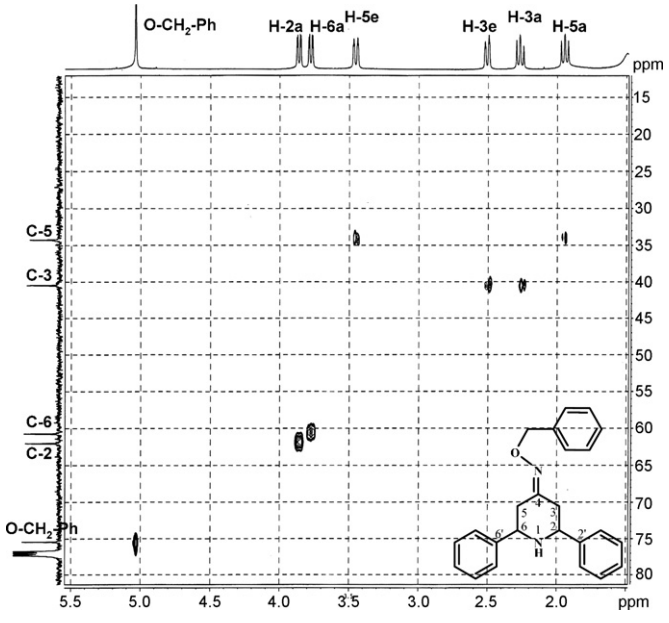

Fig. 15. HSQC spectrum of compound **8**.

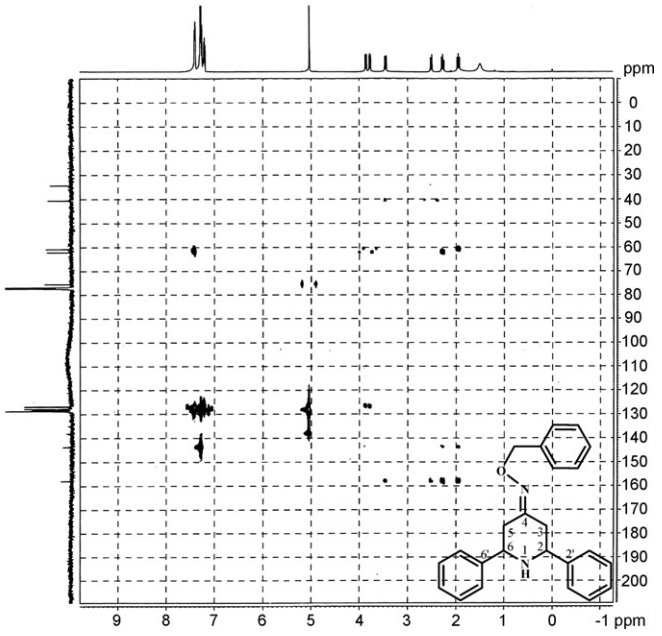

Fig. 16. HMBC spectrum of compound **8**.

the α-carbons ($\Delta\delta_\alpha$) varying from 2.0 to 7.5 ppm, depending on the structure of the oximes [26,41–43]. The difference in the chemical shift increases with a decrease in the dihedral angle between the C=N and C–α-H bonds. If the α-hydrogen lies in the NOC-α plane, the dihedral angle between them is zero. For such oximes the $\Delta\delta_\alpha$ value is around 7 ppm [42]. The $\Delta\delta_\alpha$ values of the synthesized compounds **8–14** are furnished in Table 9. The $\Delta\delta_\alpha$ values of **8–12** are not much deviated from 7.0 ppm while compound **13** exhibits a slight variation only, which suggest there may be no appreciable possibility for the boat conformation. For **14**, the deviation is appreciable and suggests that there may be a possibility for the significant contribution to the boat form in addition to the predominant chair form.

2.6.1. α-Effect

The α-effect can be studied by comparing the chemical shifts of the α-carbon C-3 and C-5 of the oxime ether with the corresponding piperidones. In oxime ethers, the C=N group shields the α-carbon due to its decreased electronegativity than C=O. So shielding of α-carbon is in accord with the expected electronegativity effect. However shielding of *syn* α-carbon is more pronounced than that of *anti* α-carbon. This is due to 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) gets slight positive charge and the C-5 carbon gets slight negative charge, consequently the proton is deshielded and the carbon is shielded significantly.

Table 9
Chemical shift difference between the α-carbons ($\Delta\delta_\alpha$) in oxime ethers (**8–14**) and piperidones (**1–7**)

Oxime ether	Piperidone	$\delta_{anti} - \delta_{syn}$ (ppm)		
		Oxime ether	Piperidone	Oxime ether-piperidone
8	**1**	6.21	0	6.21
9	**2**	8.60	0.70	7.90
10	**3**	8.61	0.72	7.89
11	**4**	8.52	0.68	7.84
12	**5**	8.62	0.70	7.92
13	**6**	15.09	6.80	8.29
14	**7**	18.61	7.05	11.56

Totally the shielding magnitude on *syn* α-carbon is around 16–17 ppm for **8–14** whereas the shielding magnitude on *anti* α-carbon is only about 8–10 ppm. In the former (*syn* α-effect), the magnitude is increased from 16.00 ppm (for **8**) to 17.24 ppm (for **14**) whereas in the latter (*anti* α-effect) is decreased from 9.79 ppm (for **8**) to 8.00 ppm (for **14**). This variation is only due to the effect of the alkyl sustituent at the *anti* α-carbon (C-3).

Due 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 slight negative charge. Inspite of 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) shielded by the negative charge on the *syn* α-carbon. The difference between the H-5e and H-5a is about 1.5 ppm in **8–13** whereas the difference is considerably decreased in **14** probably due to its conformational preference. The difference between the H-5e and H-5a is about 0.01 ppm in 3-methyl-2,6-diaryl piperidin-4-one [44].

The *anti* α-protons (H-3a and H-3e) are shielded according to the decrease in electronegativity at C-4. In **8–14**, except H-5e, all the remaining α-protons are shielded than the parent piperidone. The chemical shifts are decreased in the order H-5e > H-3e > H-3a > H-5a in **8**. Similarly for the 3-alkyl compounds **9–14**, the chemical shift of the α-protons are in the order H-5e > H-3a > H-5a. The differences between all the α-proton are shown in Table 10.

2.6.2. β-Effect

The β-effect can be studied by comparing the chemical shifts of the β-carbon C-2 and C-6 of the piperidone oxime ether with corresponding piperidones. In six membered heterocycles, decrease in electronegativity of a group in the ring deshield β-carbons and shield β-protons [25].

The deshielding of *anti* β-carbon is in accordance with the expected electronegativity effect. The magnitude of deshielding is about 1 ppm for compounds **8–12**, but **13** and **14** were deshielded, respectively, by 0.65 and 0.26 ppm. This is due to the replacement of methyl by bulkier ethyl and isopropyl group, respectively, in **13** and **14**. But the *syn* β-carbons are shielded. Moreover, the shielding magnitude is increased from compounds **8–14**. The reason for the shielding is due to the negative charge on the *syn* α-carbon, which is transmitted to small extent on the *syn* β-carbon. Thus the shielding produced on the *syn* β-carbon by the transmittance of the negative charge overcomes the deshielding produced by the electronegativity effect.

The β-protons are shielded according to electronegativity effect. Shielding of *syn* β-proton is pronounced (about 0.1 ppm) than the *anti* β-proton due to the negative charge on the *syn* β-

Table 10
Chemical shift differences between piperidone ring protons of compounds **8–14** (δ, ppm)

Compound	H(5e)–H(5a)	H(3e)–H(3a)	H(5e)–H(3a)	H(3a)–H(5a)	H(2a)–H(6a)
8	1.51	0.24	1.10	0.33	0.08
9	1.58	–	1.11	0.47	−0.33
10	1.62	–	1.15	0.47	−0.32
11	1.53	–	1.07	0.46	−0.33
12	1.57	–	1.13	0.45	−0.33
13	1.49	–	1.12	0.37	−0.19
14	1.10	–	0.88	0.22	0.01

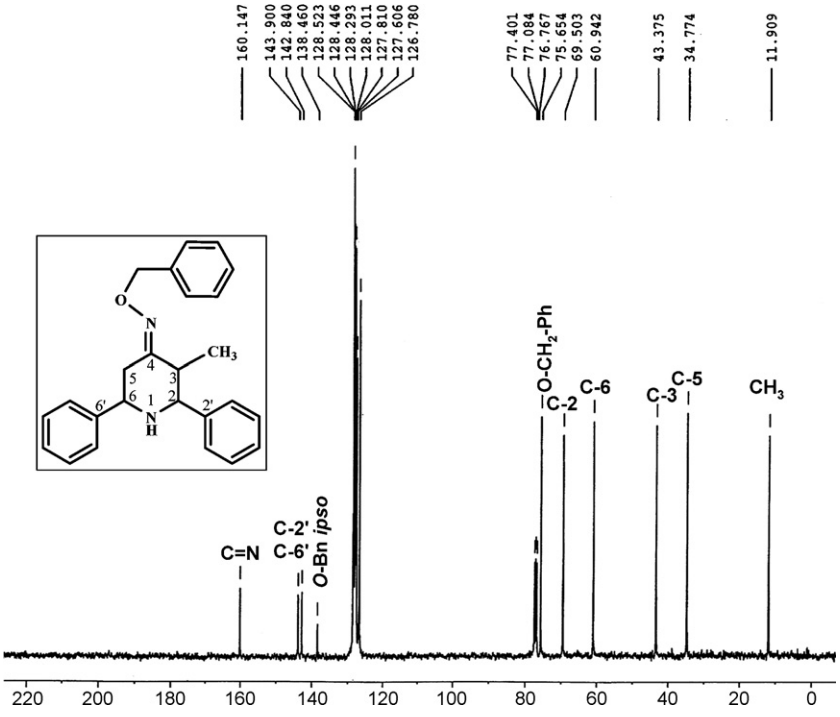

Fig. 17. ^{13}C NMR spectrum of compound **9**.

carbon and is more (0.3 ppm) for **14** due to its conformational preference. The chemical shift difference between the benzylic protons is presented in Table 10.

2.6.3. γ-Effect

The γ-effect is studied by comparing the chemical shifts of the *ipso* carbons (C-2′ and C-6′) in piperidones with oxime ethers.

In all compounds the *ipso* carbons are deshielded in accordance with the electronegativity effect. The γ-effect magnitude is about 1 ppm for **8–12** and is decreased for **13** whereas highly increased for **14** due to their substituent nature at C-3. All the values are reported in Table 8.

2.6.4. Oximino group effect on alkyl group

In accordance with the electronegativity effect, the β-effect on methyl carbon is about 1.8 ppm (deshielding) for **9–12** and methylene and methine carbon (C-7) of **13** and **14** are 1.05 and 1.91 ppm, respectively. The γ-effect also observed on the alkyl group in **13** (CH_3 group of the CH_2CH_3 substituent at C-3) and **14** (CH_3 groups of the $CH(CH_3)_2$ at C-3) and its deshielding magnitude is about 0.47 and 0.23 ppm, respectively.

3. Conclusion

All the synthesized 2,6-diarylpiperidin-4-one *O*-benzyloximes (**8–14**) were characterized by their IR, Mass and NMR spectra. All the spectral data support and confirm the formation of the target compounds. Well-pronounced oximination effect is observed on the piperidone ring carbons and the associated protons. The oximination effect is extended up to *ipso* carbons and alkyl substituents at C-3.

From the observed chemical shifts and coupling constants, the conformation of the synthesized compounds is proposed and conformational preference of the alkyl substituent at C-3 also established. The compounds **8–13** adopt normal chair conformation with equatorial disposition of substituents at C-2, C-6 and C-3 while the compound **14** contribute significant boat con-

formation along with the predominant chair conformation in solution.

4. Experimental

All the reported melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in AVATAR-330 FT-IR spectrophotometer (Thermo Nicolet) and only noteworthy absorption levels (reciprocal centimeters) are listed. ^{1}H NMR spectra were recorded at 400 MHz on BRUKER AMX 400 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard and ^{13}C NMR spectra were recorded at 100 MHz on BRUKER AMX 400 MHz spectrometer in $CDCl_3$. ^{1}H–^{1}H COSY, phase-sensitive NOESY, one-bond and multiple bond ^{1}H–^{13}C correlations spectra were recorded on BRUKER DRX 500 MHz NMR spectrometer using standard parameters. 0.05 M solutions of the sample prepared in $CDCl_3$ were used for recording 2D NMR spectra. The tubes used for recording NMR spectra are of 5 mm diameter. Electron impact mass spectra were recorded on mass engine HP 5989 series while ESMS was recorded on an API 3000 series mass spectrometer and microanalyses were performed on Heraeus Carlo Erba 1108 CHN analyzer. Unless otherwise stated, all the reagents and solvents used were of high grade and purchased from Lancaster and Merck. All the solvents were distilled prior to use.

All the parent 2,6-diarylpiperidin-4-ones were prepared by the literature precedent of Noller and Baliah [3].

4.1. Synthesis of 2,6-diarylpiperidin-4-one O-benzyloximes

A mixture of 2,6-diarylpiperidin-4-one **1** (0.1 mol), *O*-benzylhydroxylamine hydrochloride (0.1 mol) and sodium acetate trihydrate (0.3 mol) in methanol was refluxed till completion of the reaction. After completion of the reaction water was added and extracted with ether, dried with anhydrous sodium sulphate and evaporated. The residue was triturated with solvent ether to get solid product **8**. The compounds **9**–**14** were also synthesized similarly.

Acknowledgements

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