SUMMARY

Piperidine is a fundamental heterocycle. Its structural motif is found in a large number of alkaloids. The investigations on the synthesis of piperidines and concomitant stereochemical studies are, therefore, essential for the development of heterocyclic chemistry. Keeping this in mind, we have synthesized several N-aryl / N-alkyl substituted piperidines via a convenient microwave (MW) mediated reductive-amination-cyclization (RAC) method from corresponding 1,5-dicarbonyl compounds. We have now investigated the stereochemical behavior of the resulting N-substituted piperidines using NMR spectroscopic techniques and theoretical methods. Furthermore, we have extended the newly developed protocol of RAC for the synthesis of some piperidine based chiral ligands and 6-azasteroid fragments.

1. Synthesis and stereochemistry of cis-N-alkyl-2,6-diphenylpiperidines

In the stable conformation of cis-N-alkyl-2,6-diphenylpiperidine, two equatorial phenyl rings could lock the piperidine ring in the chair conformation. Then, the N-alkyl group can have two orientations, namely, equatorial and axial. These two orientations are inter-convertible through nitrogen inversion. The two-phenyl rings sandwich the N-alkyl group if it is in the equatorial orientation and in the process, it could experience their steric / electronic effects. On the other hand, if the N-alkyl group is in the axial orientation, it could experience steric interaction due to 3,5-syn-diaxial hydrogens. To understand stereo-chemical behavior of the N-alkyl piperidines, we have synthesized a series of homologous derivatives of cis-N-alkyl-2,6-diphenylpiperidines 3a-k starting from 1,5-diphenyl-1,5-pentanedione 2 which in turn was prepared from glutaric acid 1 and benzene (Scheme 1). In the synthesis of various piperidines 3b-k, the N-alkyl
groups were systematically changed along the homologous series from methyl in 3b to n-heptyl in 3h. Similarly, to understand the limits of steric / electronic influence of the phenyl rings, 2,6-diphenylpiperidines having N-isopropyl 3i, N-isobutyl 3j and N-cyclohexyl 3k groups were synthesized.

![Chemical structure diagram](image)

Reagents and conditions: i. Ac₂O, reflux, 1 h, 86%; ii. C₆H₆, anhyd. AlCl₃, rt, 40 min, 40%; iii. RNH₂·HCOO⁻, PEG-200, MW (370 W), 2 min, 67-90%.

Scheme 1

Analysis of the 'H NMR spectra of 3a-k showed that hydrogens present on C-3 of the N-alkyl groups were subjected to maximum shielding effect by the C2- and C6-phenyl rings. This effect was in the order of 0.5 ppm in CDCl₃ (Figure 2). Based on this observation, it was concluded that in piperidine 3 the N-alkyl groups occupy equatorial position in spite of possible steric hindrance, perhaps due to favorable CH-π interactions with the C2- and C6-phenyl rings. Such favorable interactions were possible because...
both the phenyl rings stay nearly orthogonal to the piperidine ring in the minimum energy conformation.

B. Experimental data; C. Computational data

Graph 1: $^1$H NMR chemical shift value of terminal methyl group vs chain length in NADPPs 3b-h.

The DFT calculations were carried out to substantiate the observations made from the $^1$H NMR spectral studies. The energy minimized structures revealed that, the hydrogens on C-3 of the alkyl groups indeed occur in the shielding zone of the 2,6-diphenyl rings. Such conformations are in the order of 2 - 3 kcal / mol lower in energy, compared to next unfavorable conformations.
The $^1$H NMR spectra of 3a-k were recorded again by protonating the nitrogen with CF$_3$COOH to evaluate the aromatic anisotropic shielding effects in resulting quaternary ammonium salts. The spectra reveal that R groups occupy equatorial position with piperidine ring taking twisted chair conformation. The anisotropic shielding effects of C2- and C6-phenyl rings on N-alkyl group were observed in the salts also.

Next, the $^1$H NMR spectra of 2,6-diphenylpiperidines with branched alkyl chains, namely isopropyl 3i and isobutyl 3j (Chart 1) were studied to probe into shielding effects of 2,6-diphenyl rings on the N-alkyl substituent. The chemical shift values of methyl
groups in 3a, 3l (δ ~ 0.6 ppm) and 3d, 3j (δ ~ 0.3 ppm) suggest that the alkyl groups are equatorial and prefer to reside in shielding zone of the C2- and C6-phenyl rings.

For the purpose of comparison of chemical shift values of the alkyl hydrogens in NADPPs 3, 2-phenyl-N-propylpiperidine 7 was synthesized according to the Scheme 2. The 1,5-ketoester 5, prepared by Friedel-Craft acylation of benzene with glutaric anhydride 4, was treated with n-propylammonium formate in PEG-200 under microwave irradiation to furnish the corresponding amide 6. Further, LAH reduction of the amide 6, yielded 2-phenyl-1-propylpiperidine 7.

![Scheme 2](image)

Reagents and conditions: i. C6H5, anhyd. AlCl3, rt, 40 min., 40%; ii. MeOH, H2SO4, reflux, 6 h, 76%; iii. CH3CH2CH2NH2·HCOO', PEG-200, MW (100 W), 2 min, 48%; iv. LAH, THF, rt, 2 h, 62%.

When comparison was made with the chemical shift values of the methyl group in N,N-dimethyl-1-propylamine, 1-propylpiperidine, 2-phenyl-1-propylpiperidine 7 and NADPP 3d it was noted that there was a progressive up-field shift in the case of 7 and 3d, with the introduction of adjacent phenyl rings and this phenomena can be attributed to phenyl ring anisotropic effects.

To evaluate shielding effect of the C2- and C6-phenyl rings on alkyl groups with a heteroatom in place of a carbon in the alkyl chain, few oxygen incorporated alkyl derivatives of 2,6-diphenylpiperidines 31-o were synthesized as given in Scheme 3. The NMR spectra of NADPPs 31-o exhibited anisotropic effects of the phenyl rings similar to
those found in alkyl derivatives, specifically on hydrogens present on C-3 / C-2. The X-ray crystal structure and DFT computations on NADPP 3I showed that hydrogen bonding interactions stabilize the conformation of N-2-hydroxyethyl group.

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\begin{align*}
&\text{O} & \text{O} & \text{i} & \text{N} \\
&\text{2} & & & \text{3I-o}
\end{align*}
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**Reagents and conditions:** i. RNH₃⁺HCOO', PEG-200, MW (370 W), 2 min, 68-79%.

**Scheme 3**

In continuation, we became interested to study the stereochemistry of 1,2,6-triarylpyridines 3p-s. The substrates were synthesized from 1,5-diketone 2 according to Scheme 4. From the ¹H NMR spectra, it became clear that in 3p-s the hydrogens on C3 of the N-aryl ring experience shielding by the anisotropic effect of 2,6-diphenyl groups. The computational structures show that in the minimum energy conformation, the three aryl rings, namely, two on C2, C6 and the one on nitrogen arrange parallels.
Reagents and conditions: i. RNH₂"HCOO", PEG-200, MW (370 W), 2 min, 66-75%.

Scheme 4

Next, we addressed the question: what is the effect of 2,6-phenyl rings in 3 on N-arylalkyl chain. We have synthesized piperidines 3t-w having benzyl, phenethyl, 4-methoxyphenethyl and phenylpropyl substituents (Scheme 5). The ¹H NMR spectra clearly show that in these cases also, the substituent on nitrogen reside in the equatorial position. Structural features of arylalkylamines are present in several alkaloids.

Reagents and conditions: i. RNH₂"HCOO", PEG-200, MW (370 W), 2 min, 56-77%.

Scheme 5
2. Synthesis of ethanolamine based chiral ligands

In the previous chapter, we described a convenient microwave mediated reductive-amination-cyclization protocol for easy synthesis of \(\text{N-alkyl-2,6-diphenylpipendines}\). In continuation of this study, we contemplated the synthesis and structural studies on ethanolamine based chiral auxiliaries of the type 9. We reasoned that with single chiral centre, the ethanolamine 9 could be resolved into enantiomers and could be used for chiral induction in reactions involving prochiral centers. Several attempts were made to resolve 9 into its enantiomers using chiral carboxylic acids like camphorsulfonic acid, tartaric acid, lactic acid, ascorbic acid, etc. Nevertheless, these attempts were unsuccessful. Therefore, reductive-amination-cyclization on 1,5-ketoester 5 with phenyl alaninol and formic acid under microwave irradiation was attempted. However, this reaction also did not give required amide.

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Alternatively, the ketoester 5 was heated in toluene reflux with phenylalaninol to yield \((3S,8aS)-3\text{-benzyl-8a-phenylperhydropyrido[2,1-b][1,3]oxazol-5-one} 11 \left(\left[\alpha\right]^{25}_D = -11.1^\circ\right)\) and methyl 5-\((1S)-1\text{-benzyl-2-hydroxyethyl}l\text{rmino-5-phenylpentanoate} 10\). The reduction of oxazolone 11 furnished ethanolamine based chiral auxiliary \((2S)-3\text{-phenyl-2-[(2S)-2-phenylhexahydro-1-pyrindinyl]propan-1-ol} 12 \left(\left[\alpha\right]^{25}_D = 38.5^\circ\right)\) as a single enantiomer (Scheme 6)
In continuation of this study, we synthesized ethanolamine based chiral ligand 15, where two chiral centers were located on the pyrrolidine platform. In this effort the starting material was 1,4-ketoester 13. The 1,4-ketoester 13 on reaction with phenylalaninol furnished (3S,7aS)-3-benzyl-7a-phenylper hydropyrrolo[2,1-b][1,3]oxazol-5-one 14 ([α]_{D}^{25} = -8°), which on reduction with LAH in dry THF provided chiral (2S)-3-phenyl-2-[(2S)-2-phenyltetrahydro-1H-1-pyrrolyl]propan-1-ol 15 ([α]_{D}^{25} = 58°, Scheme 7).
3 Synthetic studies towards 8-azasteroids

The azasteroids form a distinct class in the group of steroids. In 8-azasteroids, nitrogen takes the place of a carbon atom in the steroidal framework. There is a continuous interest in the synthesis and biological evaluation of azasteroids and azasteroid like molecules as they exhibit highly potent bio-action. We were interested in the synthesis of 8-azasteroids from simple low-cost starting materials such as aryl vinyl ketone and cyclic ketones. In this route to 8-azasteroids, we planned to follow AD → ACD → ABCD-ring motif construction. Towards this goal we have used MW mediated intramolecular Leukart-Wallach RAC reaction for facile and convenient construction of advanced intermediates for 8-azasteroids having ACD rings.

Reagents and conditions: i. PEG-200, MW (370 W), 2 min, 63 – 78%.

Scheme 8

The precursors required for the RAC reactions were 1,5-diketones 18 which were synthesized conveniently from Mannich salts 16 and cyclic ketones 17 under microwave irradiation. Some of the diketones prepared in this study fit well into steroid structure.
Reagents and conditions: i. NH₄⁺HCOO⁻, PEG-200, MW (370 W), 2 min, 12%.

Scheme 10

Some of the advanced intermediates incorporating ACD rings of the 8-azasteroids, for example, (2RS,4aSR,8aSR)-4a-methyl-2-phenylperhydroquinoline 19 was prepared by RAC reaction on the 1,5-diketones 18c using ammonium formate. The structure and the stereochemistry of the decahydroquinoline 19 was confirmed on the basis of spectral data, particularly on the basis of ¹³C NMR spectral data reported for similar compounds.

Reagents and conditions: i. HOCH₂CH₂NH₂⁺HCOO⁻, PEG-200, MW (370 W), 2 min, 72%; ii. NaBH₄, CH₃COOH, THF, reflux, 2 h, 65%; iii. Ac₂O, py, reflux, 2 h, 68%.

Scheme 11

The precursor for 8-azasteroid, 2-[(2RS,4aSR,8aRS)-2-phenylperhydro-1-quinolinyloxy]-1-ethanol 21 was prepared from 2-(3-oxo-3-phenylpropyl)-1-cyclohexanone 18b by RAC reaction. The reaction of 1,5-diketone 18b with ethanolammonium formate
under microwave irradiation gave 2-[(2RS,4aSR,8aRS)-2-phenylperhydro-1-quinoliny]-1-ethanol 21 and 2-[(2RS,4aSR,8aSR)-2-phenylperhydro-1-quinoliny]-1-ethanol 22 along with (3aSR,5aSR,9aRS)-3a-phenylperhydro[1,3]oxazolo[3,2-a]quinoline 20 in good yield (Scheme 11) The oxazolo-quinoline 20 was converted to the perhydroquinoline 21 with sodium borohydride The stereochemistry of perhydroquinolines 21 and 22 were finalized based on 13C NMR spectra

In this chapter we described a facile microwave mediated synthesis of several diketones, which fit into steroid skeleton were prepared by MW mediated Michael addition of cyclic ketones to in situ generated phenyl vinyl ketones The MW mediated RAC reaction on the 1,5-diketones furnished secondary / tertiary amines which form A, B and C rings of 8-azasteroids