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Synthesis and stereochemistry of *cis*-2,6-diphenyl-1-alkylpiperidines

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ABSTRACT

Facile and efficient synthesis of *N*-alkyl-2,6-diphenylpiperidines (NADPPs) was achieved by reductive amination cyclization (RAC) reaction on 1,5-diketones using alkylammonium formate. The reaction is a useful extension of classical Leuckart reductive amination. The RAC reaction is convenient and product isolation is simple when conducted under microwave (MW) irradiation in polyethylene glycol-200 (PEG-200) medium. The N(1) alkyl groups in NADPPs prefer equatorial position in both solid and liquid states possibly due to favorable CH–π-interactions to evade unfavorable 1,3-diaxial interactions. Incisive analysis of ^{1}H NMR spectra of NADPPs showed that anisotropic effects of C(2) and C(6) phenyl rings are maximum on C(3)H of the alkyl chain.

Introduction

Studies on the chemistry of piperidine and its derivatives have continuously attracted attention of organic chemists from the days of early developments of the field of Organic Chemistry.[1] Their importance is primarily due to profound biological activity and wide representation in nature as structural motifs on natural products.[2] In contrast to their counterpart cyclohexanes, piperidines exhibit unique and dynamic stereochemistry.[3] In continuation of our interest in synthesis and stereochemistry of piperidines,[4] particularly after total synthesis of anatalline a tobacco natural product,[5] we became interested in the synthesis, characterization, and stereochemistry of 1-alkyl-2,6-diphenylpiperidines (NADPPs) **1**. A few examples of piperidine natural products with substitution on C(2) and C(6) position are dihydropinidine **2**,[6] isosolenopsine A **3**,[7] and deoxoprosopinine **4** (Fig. 1).[8] Many piperidine alkaloids are active against central nervous system (CNS). Indeed, some 2, 6-disubsttuted piperidines, for example, isosolenopsine A isolated from fire ant venom have shown to possess necrotic activity.[9] In addition, some 2,6-disubstituted piperidine alkaloids have been used as tranquilizers and for inducing hypotensive activity.[10] *N*-Methylanabasine **5** is a CNS active tobacco alkaloid that has substitution on N(1) and C(2) positions of the central piperidine core.[11] In addition to being medicinally important natural products, many non-natural piperidines found applications as drugs,[12] for example, few oral anesthetics and narcotic analgesics have the piperidine ring in their pharmacopore.[13] Generally 1-alkyl *cis*-2,6-diphenylpiperdines **1**, for example, *cis*-2,6-diphenyl-*N*-methylpiperidine **1a** are synthesized by initial *N*-alkylation of 2,6-diphenylpyridine with alkyl *p*-toluenesulfonates, reduction of the resulting quaternary ammonium salt with $NaBH_4$, and finally by catalytic hydrogenation over Pd/C.[14] Reductive amination of 1,5-diphenylpentane-1,5-dione **6** with an alkyl amine to produce 1-alkyl *cis*-2,6-diphenylpiperdines **1** is an alternate method but the hydrogenation run on 5% Ru/C catalyst provides two products namely *cis*-2,6-diphenyl-1-methylpiperidine and *trans*-2,6-diphenyl-1-methylpyridine.[15] We have now discovered new and environmentally benign reductive amination cyclization (RAC) of 1,5-diphenylpentane-1,5-dione **6** with different alkylammonium formates for the synthesis of a series of 1-alkyl *cis*-2,6-diphenylpiperdines **1** (Scheme 1) which we present herein. This is the first Letter of reductive amination of diketones with alkylammonium formates and is a useful extension to classical Leuckart reaction.[16] To carry out RAC reaction we have employed food-compatible and non-toxic polyethyleneglycol-200 (PEG-200) and microwave (MW) irradiation. Furthermore, we evaluated stereochemistry of the N(1)-alkyl group and anisotropic effect of the C(2) and C(6)-phenyl rings on it.

Results and discussion

Synthesis of NADPPs **1** started with 1,5-diphenylpentane-1,5-dione **6** that is readily available from microwave irradiation of an intimate mixture of corresponding Mannich salt, acetophenone, and five-fold excess of PEG-200.[17] The reaction of 1,5-diphenylpentane-1,5-dione **6** to produce 1-methyl-2,6-diphenylpiperidine **1a** was selected as a test case to arrive at optimal reaction condition

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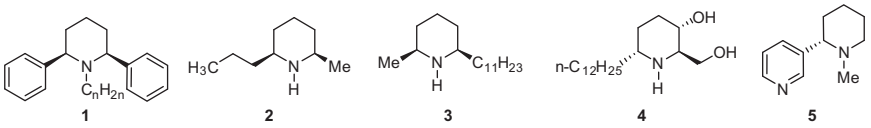
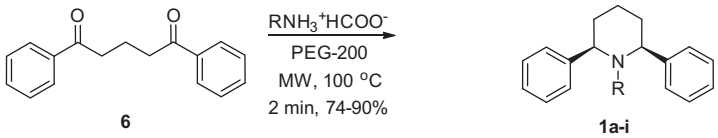


Figure 1. Structures of 1-alkyl-2,6-diphenylpiperidine **1**, dihydropinidine **2**, isosolenopsine A **3**, deoxoprosopinine **4**, and *N*-methylanabasine **5**.



1a: R = CH_3 (83%);
1b: R = CH_2CH_3 (81%);
1c: R = $CH_2CH_2CH_3$ (79%);
1d: R = $CH_2CH_2CH_2CH_3$ (90%);
1e: R = $CH_2CH_2CH_2CH_2CH_3$ (75%);
1f: R = $CH_2CH_2CH_2CH_2CH_2CH_3$ (74%);
1g: R = $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ (81%);
1h: R = $CH(CH_3)_2$ (76%);
1i: R = $CH_2CH(CH_3)_2$ (83%).

Scheme 1. Synthesis of 1-alkyl-2,6-diphenylpiperidines **1a–i** by reductive amination cyclization reaction on 1,5-diketone **6**.

for RAC. Instead of using methylamine and subsequent reduction with a reducing agent we selected to employ methylammonium formate for RAC reaction to be carried out under MW irradiation. We reasoned that the methylammonium formate will decompose under MW irradiation to provide methylamine and formic acid.[18] Released amine will then be utilized for imine formation and formic acid will provide necessary acidic conditions for this transformation. Subsequently, formic acid will be utilized for reduction of the imine intermediate by transfer hydrogenation. Resulting amine will undergo cyclization to generate cyclic imine and formic acid once again will be involved in the reduction of the intermediate to generate NADPP **1a**.[19] We employed PEG-200 as the medium to absorb and transfer MW energy to the reactants and facilitate to cross energy barriers encountered during the multi-step transformation.[20] PEG-200 is a mixture of oligomeric ethylene glycols with average molecular weight of 200.[21] The mixture is dominated by tetraethylene glycol. PEG-200 has several desirable characteristics like being liquid at room temperature, good solvent for organic compounds, water solubility, capacity to respond to microwaves of 2.45 GHz frequency, non-toxic and safe because of its high boiling point (above 230 °C).[22] The reaction of the diketone **6** and methylammonium formate conducted in mono-mode microwave oven at 100 °C provided RAC product 1-methyl-*cis*-2,6-diphenylpipeeridiene **1a** in 90% yield as a single diastereomer. There was no contamination with corresponding comparatively less stable *trans*-isomer, possibly because of the thermodynamic control in the rate determining step.[23] The MW reaction conducted at higher temperature (125 °C) leads to charring consequently lower yield (41%). At lower temperature (60 °C) the reaction was sluggish (10 min). Reaction under direct heating took 6 h for completion and yield was lower (60%) for formation of **1a**.[24] The reaction conducted in higher boiling PEG-400 provided the product **1a** in lower yield (45%) possibly because of viscous nature of the solvent. The MW mediated RAC reaction took place in ethanol or in ethylene glycol but required sealed 30 bar resistant glass vials. Reaction under solvent-less conditions but under microwave irradiation provided the product in low yield (15%) with considerable charring. Workup of the reaction conducted in PEG-200 was very facile as simple dilution with water separated the product which was extracted with ethyl acetate. Alternatively, in one run, we could isolate the product by washing the reaction mixture with ten-fold excess of *tert*-butyl methyl ether

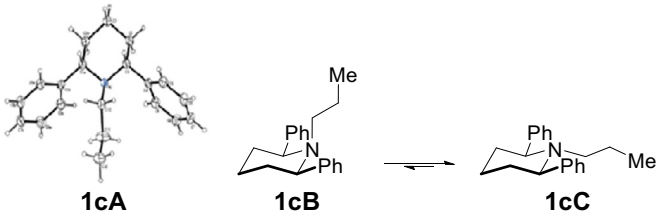
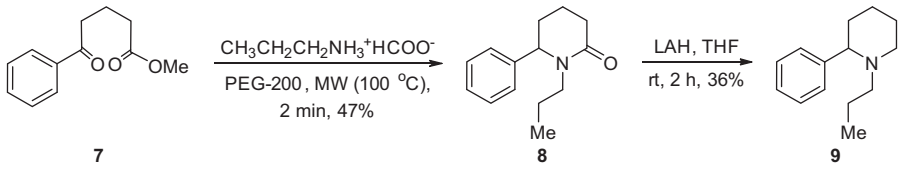


Figure 2. Single crystal XRD structure of *N*-propyl-2,6-diphenylpiperidine **1cA** and solution phase equilibrium between two conformations of **1c** with the propyl group axially oriented **1cB** and equatorially oriented **1cC**.

as the product **1a** but not PEG-200 dissolved in the solvent. Recovered PEG-200 could be used for second run. Structure of **1a** was assigned on the basis of spectral (IR, ^1H, ^{13}C, DEPT-135 NMR) and analytical data. The ^{13}C NMR spectrum of **1a** displayed 8 signals which confirmed C_2 symmetric nature of the compound. The C(2) H and C(6)H appeared as double doublet with J = 9.0, 3.0 Hz which indicated their axial disposition. Consequently sterically bulky C(2) and C(6) phenyl groups occupy equatorial positions and they have *cis* stereochemistry.

Subsequent to achieving facile synthesis of 2,6-diphenyl-1-methylpiperidine **1a**, we extended the study for the synthesis of homologous series of hitherto unknown *N*-alkyl *cis*-2,6-diphenylpiperidines **1b–g** (Scheme 1). In each case the RAC reaction provided diastereoselective *cis*-isomer. Spectral data of **1b–g** compared well with the parent **1a**. Further, the structure of *N*-propyl-*cis*-2,6-diphenylpiperidine **1c** was confirmed by single crystal XRD analysis (structure **1cA** in Fig. 2).[25] The solid state structure displayed a flattened chair for the piperidine ring with equatorial orientation for the two phenyl rings and for the *N*-propyl group. Two phenyl rings were orthogonal to the mean plane of the piperidine ring.

The solution phase stereochemistry of *N*-alkyl 2,6-diphenyl-1-methylpiperidines 1 is interesting as the N(1) alkyl groups could occupy axial orientation to avoid steric interactions with C(2) and C(6) phenyl rings **1cB** (Fig. 2) or occupy equatorial orientation to have favorable CH–π interactions with electron rich aromatic rings **1cC** and also avoid unfavorable 1,3-diaxial interactions with $C(3)H_{ax}$ and $C(5)H_{ax}$. The conformational isomers **1cB** and **1cC**



Scheme 2. Two-step synthesis of 2-phenyl-1-propylpiperidine **9**.

are inter-convertible through Walden inversion at nitrogen. We have taken *cis*-2,6-diphenyl-*N*-propylpiperidine **1c** as a representative example to evaluate solution phase stereochemistry of NADPPs **1a**–**g**, particularly since the solid state structure of **1c** is available. The ^{1}H NMR spectrum of the $CDCl_3$ solution of **1c** exhibited triplet for methyl in the propyl group at δ 0.31 ppm. When this value is compared with the chemical shift of δ 0.96 ppm for the methyl group in *N*-propylpiperidine,[26] it is up-field shifted by δ 0.65 ppm. This observation indicates that the propyl group prefers equatorial orientation so that the terminal methyl group gets into the shielding zone of the C(2) and C(6) phenyl rings. To evaluate chemical shift value of terminal methyl of the *N*-propyl group that is flanked by one phenyl ring, we have synthesized 2-phenyl-1-propylpiperidine **9** from methyl 5-oxo-5-phenylpentanoate[27] **7** by following two-step protocol (Scheme 2). The MW mediated RAC reaction on **7** with propylammonium formate provided lactam **8**. Reduction of the lactam **8** with lithium aluminum hydride furnished piperidine **9** in moderate yield. The terminal methyl group in **9** appeared at δ 0.70 ppm in its ^{1}H NMR spectrum indicating that it is under anisotropic shielding influence of the C(2) phenyl ring. Careful study of ^{1}H NMR spectra of NADPPs **1d**–**g** indicated that C(3) methylene of the *N*-alkyl group gets maximum shielding influence of C(2) and C(6) phenyl rings.[28]

Since the straight-chain alkyl groups in **1a**–**g** displayed residency at equatorial position in preference to axial position, in continuation, we evaluated the stereochemistry of branched alkyl chains. For this purpose we synthesized NADPPs with N(1) isopropyl **1h** and N(1) isobutyl **1i** groups. The MW mediated RAC reaction with isopropylammonium formate or isobutylammonium formate and the 1,5-diketone **6** provided corresponding piperidine derivatives **1h**–**i** in good yield (Scheme 1). In each case spectral and analytical data confirmed the assigned structure and they compared well with the parent **1a**. The chemical shift value of terminal methyl of *N*-isopropyl (δ 0.60 ppm) in **1h** compared well with that of the *N*-ethyl (δ 0.59 ppm) group in **1b**. Similarly the chemical shift value of terminal methyl of *N*-isobutyl (δ 0.35 ppm) in **1i** compared well with that of methyl in *N*-propyl (δ 0.31 ppm) in **1c**. Anticipated up-field shift of methyl groups in **1h**–**i** indicated preference of the N(1) alkyl groups to occupy equatorial position. Overall, the ^{1}H NMR spectral data indicated that similar to that of its solid state structure, the piperidine ring **1** adopts chair conformation and the N(1) alkyl groups occupy equatorial position. Preference for equatorial position for the alkyl groups could be due to favorable CH–π interactions and avoidance of unfavorable 1,3-diaxial interactions.

Conclusion

In summary, we have demonstrated facile synthesis of *N*-alkyl-2,6-diphenylpiperidines by RAC reaction on 1,5-diketones using alkylammonium formates. The RAC reaction works well when conducted in PEG-200 medium under the influence of MWs. Incisive analysis of ^{1}H NMR spectra showed that N(1) alkyl groups occupy equatorial position. The anisotropic effect of C(2) and C(6) phenyl rings are maximum on C(3)H of the alkyl chain.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.085.

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