Asian Journal of Chemistry Vol. 19, No. 1 (2007), 34–38

Synthesis and Characterization of N-(N-Methylene-3H/alkyl-2,6-diphenyl piperiden-4-ol)dibenzyl amines

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Various 2,6-diphenyl-4-piperidones (**1a–d**) prepared through Mannich reaction by the condensation of benzaldehyde with different appropriate ketones and dry ammonium acetate, on addition of formaldehyde and dibenzylamine in the presence of ammonium chloride, afford the novel Mannich bases of N-(N-methylene-2,6-diphenyl-3-H/alkyl piperiden-4-ol)dibenzyl amines (**2a–d**). The structures of all the compounds have been confirmed on the basis of their analytical, IR, ^{1}H NMR and mass spectral data.

Key Words: Synthesis, N-(N-Methylene-3H/alkyl-2,6-diphenyl piperiden-4-ol)dibenzyl amines.

INTRODUCTION

In general, different Mannich bases are prepared by condensing formaldehyde with different types of secondary amines or with compounds containing active hydrogen atom[1–3]. In most cases, enough concentrated hydrochloric acid is added at the beginning of the reaction to make the mixture to acidic pH. In other instances, the mixture is acidified at the end of the reaction in order to depolymerise the unreacted formaldehyde and bring it into solution[4]. Among the various types of amines used in Mannich base condensation reactions, secondary amines are found to give better yields[5]. If the ketone component used in the condensation reaction is a liquid, an excess of it may be used as a solvent[6].

The essential feature of the reaction is the replacement of active hydrogen atom by a dialkylaminomethyl group. Variety of Mannich bases such as diethylaminomethyl benzimidazole[7], dimethylaminomethyltipyrine[8], etc., have been reported earlier. The synthesis of Mannich bases from 6-methoxy-α-tetralone with formaldehyde and secondary amines in the presence of a catalytic amount of chlorotrimethylsilane (CTMS)[10] and β-aminoketones[11] by reaction of pyrrolidene/piperidine / piperazine / 4-methylpiperidine/morpholine with 6-methoxy-tetralone / 5-methoxy-1-indanone / 6-ketoestradiol-17-β-acetate-3-methyl ether have also been reported. The analgesic properties of demerol, amidone and esters of 4-phenyl-4-piperidinols are also well known[12]. In view of this the major focal point of the present work has been concerned with the synthesis of Mannich bases

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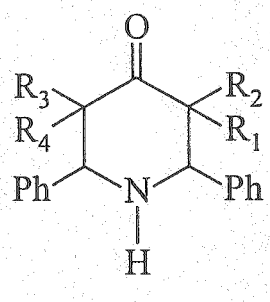
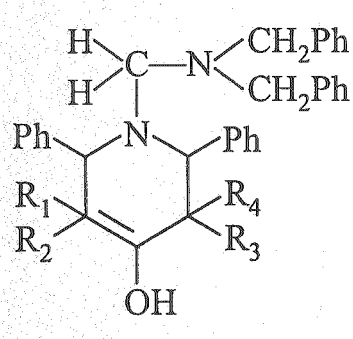
of N-(N-methylene-3H/alkyl-2,6-diphenyl-piperidin-4-ol)dibenzyl amines using different piperidin-4-ones as precursor.

RESULTS AND DISCUSSION

Various piperidin-4-ones used for synthesis of Mannish bases are as follows **(1a–d)** and **(2a–d)**:





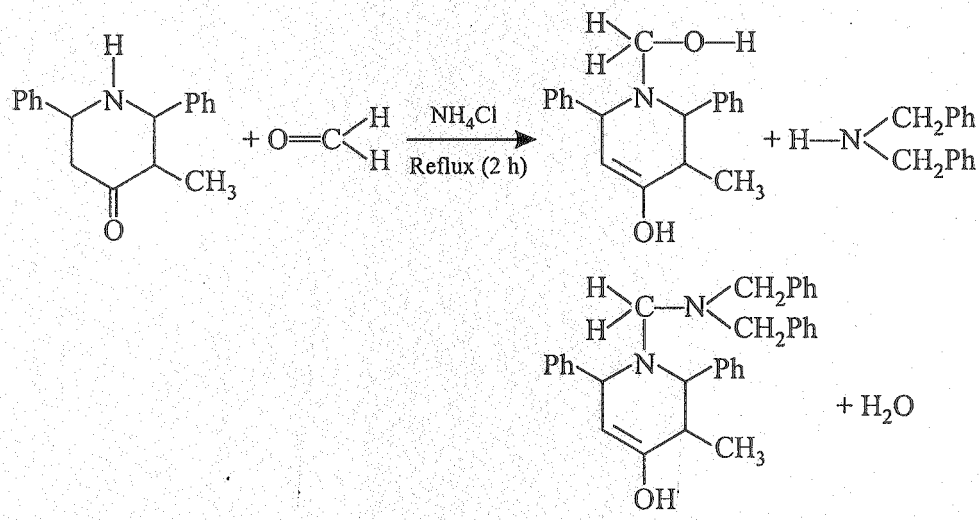
Compd.	R_1	R_2	R_3	R_4	Compd.	R_1	R_2	R_3	R_4
(1a)	H	H	H	H	**(2a)**	H	H	H	H
(1b)	CH_3	H	H	H	**(2b)**	CH_3	H	H	H
(1c)	CH_3	CH_3	H	H	**(2c)**	CH_3	CH_3	H	H
(1d)	CH_3	H	CH_3	H	**(2d)**	CH_3	H	CH_3	H

The unsubstituted and 3-alkyl substituted 2,6-diphenyl-4-piperidones **(1a–d)** were prepared as per literature[13, 14]. The piperidin-4-ones have two active hydrogen centres, one at N-atom and the other at 3- and 5-positions. The condensation of **(1)** with formaldehyde in the presence of ammonium chloride afforded the corresponding alcohols **(2a–d)**. The alcohols further condensed with dibenzyl amine to yield the Mannich bases **(3a–d)** **(Scheme-1)**.

The IR spectra of the piperidin-4-ones gave a sharp peak at 1701 cm^{-1} corresponding to a carbonyl stretch present in the heterocyclic ring. On the other hand, the absence of carbonyl stretching frequency at 1701 cm^{-1} and appearance of a sharp peak at 2719 cm^{-1} for the alcoholic group in the IR spectrum of the product confirms the formation of Mannich bases. The presence of a sharp peak at 1580 cm^{-1} for C=C olefinic group in the IR spectrum of Mannich bases confirms the enolisation of carbonyl functional group. The absence of a broad peak in between 3250–3050 cm^{-1} indicates that the enolic group is not involved in hydrogen bonding.

The electron releasing inductive effect of the alkyl substituent at C-3 reduces the acidity of an α-hydrogen[8, 9] and thus the enol formation is mainly the shifting of proton from C-5 position. On the other hand, in the case of N-(N-methyl-2-6-diphenyl piperidin-4-ol) dibenzyl amine the enolisation is due to the shifting of proton either from C-3 or C-5 position. The conversion of carbonyl to alcoholic group in the Mannich bases may be due to transannnular effect of the lone pair in N atom of heterocycle. The absence of a sharp band at 3297 cm^{-1} in the IR spectra of Mannich bases as compared to that of peperidin-4-ones confirms the

attachment of dibenzylaminomethyl group only at N—H centre, not at C-3 or C-5 position. This may be due to the more acidic nature of proton attached to sp^2 hybridized N-atom as compared to the proton attached to sp^3 hybridised carbon at C-3 or C-5 position.



Scheme-1

The singlet signals at δ 3.85, 4.40 and 7.26 ppm of the Mannich bases assigned to four benzyl methylene, two (N—CH_2—N) methylene and alcoholic protons, respectively. The absence of the corresponding signals in the ^{1}H NMR spectra of the precursor piperidin-4-ones is also taken as a strong evidence for the formation of Mannich bases. The non-formation of Mannich bases in the absence of anhydrous ammonium chloride proves its catalytic importance in synthesis.

EXPERIMENTAL

Melting points were determined on a Zenith apparatus and are unconnected. IR spectra were recorded by KBr pellet technique at room temperature in the region 4000–500 cm^{-1} on a Bruker IFS 66V FT-IR spectrometer. ^{1}H spectra were recorded in $CDCl_3$ using TMS as in internal standard on a Jeol GSX 400 NMR spectrometer. Elemental analyses were carried out on a CEST 1106 instrument. Mass spectra were recorded on a Jeol DX 3031 HF spectrometer with a JMA DA 5000 data system. All the chemicals used were of AnalaR grade. Dibenzyl amine and formaldehyde were purchased from Aldrich.

General procedure for the synthesis of mannich bases[15]

To a solution of unsubstituted and 3-alkyl substituted 2,6-diphenyl piperidin-4-ones (0.01 mol) in ethanol (20 mL), aqueous formaldehyde (0.3 mL, 0.01 mol), dibenzyl amine (1.98 mL, 0.01 mol) and anhydrous ammonium chloride (0.5 g, 0.01 mol) were added It was refluxed for 90 min. Hot water was added to incipient turbidity and the mixture was chilled and filtered. The filtrate was concentrated to about 10 mL. Hot water was again added to a faint turbidity and the mixture was chilled overnight. The resulting crude product was purified by column chromatography (hexane/ethyl acetate, 9 : 1) and crystallized from 95% ethanol.

N-(N-Methylene-2,6-diphenyl piperiden-4-ol)dibenzyl amine (3a): 32%, m.p. 264°C; Anal.(%), Calcd. for $C_{32}H_{32}N_2O$: C, 82.48; H, 6.96; N, 6.09; O, 3.48%; Found: C, 83.48; H, 6.89; N, 6.01; O, 3.42%. IR (KBr, cm^{-1}): 2780 ν(N—CH_2), 2719 ν(OH), 1581 ν(C=C); ^{1}H NMR: δ 2.74 (d, H at C-2), 4.05 (d, H at C-3), 2.62 (d, 2 H at C-5), 2.74 (t, H at C-6), 4.40 (s, 2H for CH_2 in N—CH_2—N), 3.84 (s, 4 H for CH_2 in Ph—CH_2), 7.26 (s, alcoholic H), 7.35 (m, 10 H for C_6H_5— at C-6) and 7.48 (m, 10 H for C_6H_5 in benzyl); MS: m/z 460 (M^+).

N-(N-Methylene-2,6-diphenyl-3-methyl piperiden-4-ol)dibenzyl amine (3b): 30%, m.p. 225°C; Anal.(%), Calcd. for $C_{33}H_{34}N_2O$: C, 83.54; H, 7.17; N, 5.91; O, 338%; Found: C, 83.49; H, 7.15; N, 5.86; O, 3.34%. IR (KBr, cm^{-1}): 2941 ν(CH_3 asymmetric), 2885 ν(CH_3 symmetric), 2780 ν(N—CH_2), 2720, ν(OH), 1580 ν(C=C); ^{1}H NMR: δ 0.87 (d, 3 H for CH_3), 2.66 (m, H at C-3), 2.72 (d, H at C-2), 3.63 (d, H at C-6),3.85 (s, 4 H for CH_2 in 2-Ph—CH_2), 4.10 (d, H at C-5), 4.40 (s, 2 H for CH_2 in N—CH_2—N), 7.26 (s, alcoholic H), 7.35 (m, 10 H for C_6H_5— at C-2 and C-6), 7.48 (m, 10 H for C_6H_5— at C-2 and C-6), 7.48 (m, 10 H for C_6H_5— in benzyl); MS: m/z 474 (M^+).

N-(N-Methylene-2,6-diphenyl-3-ethyl piperiden-4-ol)dibenzyl amine (3c): 34%, m.p. 258°C; Anal.(%), Calcd. for $C_{34}H_{36}N_2O$: C, 83.61; H, 5.74; O, 3.28%; Found: C, 83,54; H, 7.34; N, 5.69; O, 3.25%. IR (KBr cm^{-1}): 2940 ν(CH_3 asymmetric), 2883 ν(CH_3 symmetric), 2916 ν(CH_2 asymmetric), 2845 ν(CH_2 symmetric), 2780 ν(N—CH_2), 2720 ν(OH), 1580 ν(C=C); ^{1}H NMR: δ 0.92 (t, 3 H for CH_3 in C_2H_5), 1.28 (m, 2 H for CH_2 in C_2H_5), 2.65 (m, H at C-3) , 2.70 (d, H at C-5), 3.62 (d, H at C-6), 3.85 (s, 4 H for CH_2 in two Ph—CH_2), 4.11 (d, H at C-5), 4.42 (s, 2 H for CH_2 in N—CH_2—N), 7.25 (s, alcoholic H), 7.36 (m, 10H for C_6H_5 at C-2 and C-6), 7.49 (m, 10H for C_6H_5— in benzyl); MS: m/z 488 (M^+).

N-(N-Methylene-2,6-diphenyl-3-isopropyl piperiden-4-ol)dibenzyl amine (3d): 32%, m.p. 270°C; Anal.(%), Calcd. for $C_{35}H_{38}N_2O$: C, 83.67; H, 7.57; N, 5.58; O, 3.19%; Found: C, 83.64; H, 7.52; N, 5.5; O, 3.16%. IR (KBr, cm^{-1}): 2945 ν(CH_3 asymmetric), 2880 ν(CH_3 symmetric), 2895 ν(C—H isolated), 2780 ν(N—CH_2), 2720 ν(OH) 1581 ν(C=C); ^{1}H NMR: δ 0.98 (d_6, H for two CH_3), 1.65 (m, H for C=H in isopropyl), 2.62 (dd, H at C-3), 2.72 (d, H at C-3) 3.60 (d, H at C-6), 3.84 (s, 4H for CH_2 in two Ph—CH_2), 4.12 (d, H at C-5), 4.43 (s, 2H for CH_2 in N—CH_2—N), 7.24 (s, alcoholic H), 7.35 (m, 10 H for C_6H_5— at C-2 and C-6), 7.48 (m, 10 H for C_6H_5 in benzyl); MS: m/z 502 (M^+).

ACKNOWLEDGEMENTS

The authors thank Dr. Sheela Ramachandran, Principal and Dr. B. Sambath Kumar, Secretary, PSG College of Arts and Science, Coimbatore-14 and Thiru V. Rajan, Managing Trustee, PSG & Son's Charities for continuous support and for facilities provided. Thanks are also due to Dr. K. Selvaraj, Head, Department of Chemistry, PSG College of Arts and Science, for his valuable suggestions and help. One of the authors (Dr. M. Jambulingam) is thankful to UGC, New Delhi for financial assistance to carry out the work.

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(*Received*: 16 March 2005; *Accepted*: 9 May 2006) AJC-4904