Synthesis of Substituted 3,4-Dialkyl-2,6-Diaryl-Piperidin-4-ol Derivatives and Their Conformational Study

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Abstract: The synthesis of series of 3,4-dialkyl-2,6-diaryl-piperidin-4-ol derivatives (**7-12**) by reduction of *cis*-3-alkyl-2,6-diaryl-piperidin-4-one (**1-6**) using Grignard reagent has been reported. The synthesized heterocycles have been characterized on basis of spectroscopic data and their conformation has also been discussed.

Keywords: Piperidine, Grignard Reagent, Conformation, Spectra.

Introduction

2,6-disubstituted-piperidine derivatives are regarded as an important building block of many alkaloid natural products, therapeutic drugs and they serve a role as key intermediates for synthesis of various organic compounds including thiazolidones, oxirane, thiazine, etc [1-4]. The substituted piperidine derivatives are found to possess of various antimicrobial activities including anti-inflammatory, anti-tuberculosis, antipyretic, antibacterial, antifungal, etc [5, 6]. The antimicrobial activities are improved or declined when the conformation of piperidine is swapped due to substitution on different position. Hence, analyzing the conformation of compound has become important in recent years. Accordingly, Our recent investigation has demonstrated that reduction of keto functional group at C(4) of piperidine moiety incorporated with phenyl, *p*-chlorophenyl and *p*-methoxyphenyl substituents and they exerts noteworthy conformational changes.

Experimental

General details

Melting point of synthesised compounds was determined in open glass capillaries and was uncorrected. IR spectra were recorded on Perkin-Elmer 577 IR spectrophotometer using KBr pellets. ^1H spectra (500 MHz) and ^{13}C spectra (125 MHz) were recorded on Bruker AVANCE III 500 MHz NMR Spectrometer in CDCl_3 with tetramethyl silane as the internal standard and the chemical shifts were reported in ppm scale. Mass spectra were studied using JEOL GCMATE II mass spectrometer. The purity of the compounds was checked by thin layer chromatography on silica gel 60 F₂₅₄ (Merck) and spots were developed using iodine vapour or ultraviolet light.

General synthesis of 4-hydroxy-piperidine derivative (7-12)

Grignard reagent (0.01 mol) was added slowly to a solution of appropriate piperidin-4-one (0.005 mol) in sodium dried ether and the mixture was refluxed until the completion of reaction. The reaction mixture was allowed to cool and poured into the mixture of crushed ice (125 g), 100 ml of water and 10-20 ml of Conc. HCl contained in a 500 ml beaker. The hydrochloride thus obtained was filtered and dried at the pump. The dried hydrochloride was pasted with 2 or 3 drops of acetone and neutralized with aqueous ammonia followed by the addition of water. The tertiary alcohols obtained were chromatographed from benzene-chloroform (3:1) mixture.

Synthesis of (3R,4R)-3-ethyl-4-(propan-2-yl)-2,6-bisphenylpiperidin-4-ol (7)

Reaction Time: 18 Hours; Yield: 74 %; *R_f* value = 0.34 (CHCl_3 -Benzene = 9:1); Pale yellow viscous oil; IR (KBr, ν_{max} , cm^{-1}): 3404.13 and 3309.62 (NH and OH), 3061 (ArCH), 1279 and 1026 (C-O str); ^1H NMR (500 MHz, CDCl_3): δ 7.18-7.48 (m, 10H, ArH), 4.05-4.08 (dd, 1H, 6- H_a), 3.93-3.97 (d, 1H, 2- H_a), 2.66-2.73 (m, 1H, 5- H_a), 2.62-2.65 (dd, 1H, 5- H_c), 2.58-2.60 (m, 1H, 3- H_a), 1.69 (br, 2H, NH and OH), 1.05-1.09 (m, 1H, 4-CH), 0.94 (t, 3H, 4- CH_3), 0.75 (m, 2H, 3- CH_2), 0.44 (t, 3H, 3- CH_3); ^{13}C NMR (125 MHz, CDCl_3): δ 126.05-132.44, 68.15, 64.06, 62.01, 56.14, 47.99, 38.68, 18.05, 16.13, 10.99; HRMS: 323.46 (M^+) (Calcd. for $\text{C}_{22}\text{H}_{29}\text{NO}$: 323.47).

Synthesis of (3R,4R)-3-ethyl-4-(propan-2-yl)-2,6-bis(4-chloro)phenylpiperidin-4-ol (8)

Reaction Time: 21 Hours; Yield: 74.9 %; *R_f* Value 0.31 (CHCl_3 -Benzene = 9:1); Pale yellow viscous oil; IR (KBr, ν_{max} , cm^{-1}): 3350 (NH and OH), 2960 (ArCH), 1292 and 1015 (C-O str), 765 (ArCl); ^1H NMR (500 MHz, CDCl_3): δ 7.26-7.44 (m, 8H, ArH), 4.03-4.06 (dd, 1H, 6- H_a), 3.69-3.72 (d, 1H, 2- H_a), 2.62-2.69 (m, 5- H_a), 2.55-2.59 (dd, 1H, 5- H_c), 2.49-2.54 (m, 1H, 3- H_a), 1.65 (br, 2H, NH and OH), 0.78-0.95 (m, 7H, 4-alkyl), 0.75 (m, 2H, 3- CH_2), 0.45 (t, 3H, 3- CH_3); ^{13}C NMR (125 MHz, CDCl_3): δ 127.84-130.86, 68.16, 66.00, 63.07, 58.44, 51.45, 38.91, 18.05, 16.08, 14.05, 10.95; HRMS: 392.54 (M^+) (Calcd. for $\text{C}_{22}\text{H}_{27}\text{Cl}_2\text{NO}$: 392.36).

Synthesis of (3R,4R)-3-ethyl-4-(propan-2-yl)-2,6-bis(4-methoxy)phenyl-piperidin-4-ol (9)

Reaction Time: 20 Hours; Yield: 79.2 %; *R_f* Value 0.58 (CHCl₃-Benzene = 9:1); Pale yellow viscous oil; IR (KBr, ν_{max} , cm⁻¹): 3345 (NH and OH), 3059 (ArCH), 1300 and 1034 (C-O str); ¹H NMR (500 MHz, CDCl₃): δ 7.39-7.43 and 6.90-6.95 (m, 8H, ArH), 4.06-4.09 (dd, 1H, 6-H_a), 3.86, 3.83 (s, 6H, Ar-OCH₃), 3.71 (d, 1H, 2-H_a), 2.58-2.78 (m, 3H, 5-H_a, 5H_e and 3-H_a), 1.59 (br, 2H, NH and OH), 0.94-1.10 (m, 7H, 4-alkyl), 0.79 (t, 1H, 3-CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 114.52-123.42, 73.82, 64.27, 55.42, 51.35, 42.42, 31.87, 18.94, 10.66; HRMS: 383.25 (M⁺) (Calcd. for C₂₄H₃₃NO₃: 383.52).

Synthesis of (3R,4R)-3,4-diethyl-2,6-bisphenylpiperidin-4-ol (10)

Reaction Time: 20 Hours; Yield: 73.4 %; *R_f* value = 0.58 (CHCl₃-Benzene = 9:1); Pale yellow viscous oil; IR (KBr, ν_{max} , cm⁻¹): 3352 (NH and OH), 3058 (ArCH), 1284 and 1029 (C-O str); ¹H NMR (500 MHz, CDCl₃): δ 7.47-7.53 and 7.24-7.35 (m, 10H, ArH), 4.25-4.28 (dd, 1H, 6-H_a), 3.95-3.97 (d, 1H, 2-H_a), 2.19 (br, 2H, NH and OH), 1.75-1.78 (dd, 1H, 5-H_e), 1.81-1.82 (m, 1H, 3-H_a), 1.64-1.68 (m, 1H, 5-H_a), 1.05-1.13 (m, 4H, 3 and 4-CH₂), 0.96 (t, 3H, 4-CH₃), 0.49 (t, 3H, 3-CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 126.84-128.65, 74.60, 63.82, 56.87, 50.13, 44.72, 33.63, 19.00, 14.26, 7.94; HRMS: 309.24 (M⁺) (Calcd. for C₂₁H₂₇NO: 309.44).

Synthesis of (3R,4R)-3,4-diethyl-2,6-bis(4-chloro)phenylpiperidin-4-ol (11)

Reaction Time: 20 Hours; Yield: 82.1 %; *R_f* Value 0.4 (CHCl₃-Benzene = 9:1); Pale yellow viscous oil; IR (KBr, ν_{max} , cm⁻¹): 3394 (NH and OH), 3031 (ArCH), 1288 and 1010 (C-O str), 723 (ArCl); ¹H NMR (500 MHz, CDCl₃): δ 7.38-7.47 and 7.27-7.31 (m, 8H, ArH), 4.21-4.24 (dd, 1H, 6-H_a), 3.92-3.94 (d, 1H, 2-H_a), 1.75-1.78 (dd, 1H, 5-H_e), 1.70-1.73 (m, 1H, 5-H_a), 1.62-1.67 (m, 1H, 3-H_a), 1.47-1.50 (br, 2H, NH and OH), 1.05-1.07 (m, 2H, 4-CH₂), 0.94 (t, 3H, 4-CH₃), 0.80 (m, 2H, 4-CH₂), 0.48 (t, 3H, 3-CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 128.06-130.48, 74.40, 62.93, 56.14, 50.20, 44.72, 33.58, 18.90, 14.61, 7.92; HRMS: 378.24 (M⁺) (Calcd. for C₂₁H₂₅Cl₂NO: 378.34).

Synthesis of (3R,4R)-3,4-diethyl-2,6-bis(4-methoxy)phenylpiperidin-4-ol (12)

Reaction Time: 22 Hours; Yield: 76.3 %; *R_f* Value 0.32 (CHCl₃-Benzene = 9:1); Pale yellow viscous oil; IR (KBr, ν_{max} , cm⁻¹): 3529 (NH and OH), 2962 (ArCH), 1299 and 1033 (C-O str); ¹H NMR (500 MHz, CDCl₃): δ 7.36-7.60 and 6.85-7.01 (m, 8H, ArH), 4.16-4.19 (dd, 1H, 6-H_a), 3.865, 3.833 (s, 6H, Ar-OCH₃), 3.67-3.69 (d, 1H, 2-H_a), 1.77-1.79 (dd, 1H, 5-H_e), 1.68-1.76 (m, 1H, 5-H_a), 1.62-1.67 (m, 1H, 3-H_a), 1.472-1.51 (br, 2H, NH and OH), 0.934-1.10 (m, 4H, 3 and 4-CH₂), 0.949 (t, 3H, 4-CH₃), 0.508 (t, 1H, 3-CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 113.40-114.36, 127.63-131.08, 74.66, 63.16, 56.20, 50.35, 44.84, 33.67, 19.04, 14.67, 7.96; HRMS: 369.29 (M⁺) (Calcd. for C₂₃H₃₁NO₃: 369.49).

Results and Discussion

The synthesis of target 3,4-dialkyl-2,6-diaryl-piperidin-4-ol derivatives (**7-12**) was accomplished by a Mannich reaction followed by reduction using Grignard reagent as shown in scheme 1. The parent compound, *cis*-2,6-diaryl-piperidin-4-one derivatives (**1-6**) were synthesized by double mannich reaction using ketone, arylaldehyde and ammonium acetate in a stoichiometry of 1:2:1 ratio [7, 8]. The product obtained was subjected to column chromatography using benzene-chloroform (3:1) eluent.

Scheme 1. Synthesis of 3,4-dialkyl-2,6-diaryl-piperidin-4-ol (7-12).

Among the two isomeric alcohols as shown in figure 1, the axial hydroxyl isomer was obtained as major isomer. Several attempts to obtain the equatorial hydroxyl isomer (minor product) with various eluting agents in various proportions were unsuccessful.

Figure 1. Isomeric forms of compounds 7-12.

IR spectra reveal that the absence of absorption around $1700\text{--}1710\text{ cm}^{-1}$ corresponding to C=O group and broad absorption around $1300\text{--}1400\text{ cm}^{-1}$ corresponding to –NH and –OH group clearly indicates the formation tertiary alcohol at C(4).

In $^1\text{H-NMR}$, the aromatic protons are observed around 7 ppm. The H(2) and H(6) protons are resonated at 3.6–3.9 ppm (d) and 4.1–4.2 ppm (dd) respectively. As shown in table 1, the observation of large coupling constant ($\sim 10\text{ Hz}$) and small coupling constant $\sim 2\text{--}3\text{ Hz}$ about C(5)–C(6) bond reveals equatorial orientations of aryl rings at C(2) and C(6). Similarly, the observation of large coupling constant ($\sim 10\text{ Hz}$) about C(2)–C(3) bond indicates the equatorial orientations of alkyl group at C(3). Hence, all the synthesized compounds exist in normal chair conformation with equatorial orientation of all the substituents.

Table 1. Coupling constant of Compounds 7 – 12.

Compound	Coupling constant (In Hz)			
	$^3J_{6a,5a}$	$^3J_{6a,5e}$	$^2J_{5a,5e}$	$^3J_{2a,3a}$
7	11.6	2.8	13.2	10.6
8	12.8	3.2	12.8	10.4
9	12.8	3.2	12.8	10.4
10	10.25	2.25	12.75	10.0
11	11.5	3.25	13.5	10.5
12	10.5	3.0	13.0	10.5

The alkyl group at C(3) experiences severe *gauche* interaction with aryl group at C(2) and to avoid it, the ring flattened about C(2)–C(3) bond. Hence, The coupling constant about C(2)–C(3) bond ($^3J_{2a,3a}$) are considerably lower than the *trans* coupling constant about C(5)–C(6) bond ($^3J_{6a,5a}$). The introduction of isopropyl group at C(4) instead of ethyl substituents increases $^3J_{6a,5a}$ due to ring puckering about C(5)–C(6) bond.

Figure 2. Conformation of C(4) substituent of 10–12.

The compound **10-12** can exist in three possible conformation for the equatorial alkyl group and axial hydroxyl group at C(4) as shown in figure 2. The conformation 2a is destabilized due to severe gauche interaction. Hence it has been suggested that compound **10-12** exists as an equilibrium mixture of conformation 2a and 2c. However, *syn*-1,3-diaxial interaction among methyl group of isopropyl substituent at C(4) and adjacent benzylic proton, downfield signals were observed for C(3) and C(5) protons.

In ^{13}C -NMR, the signals at 62.9-66.0 ppm and 56.2-62.0 were assigned to C(2) and C(6). The downfield absorption with low intensities at 68.1-74.4 ppm were assigned to quaternary carbon, C(4). Also, introduction of isopropyl group shields C(4) carbon considerably due to electron donating nature. Also, the mass spectral data is consistent with the structure of compounds **7-12** as expected. It can be concluded that the substituents on C(4) position and substituted phenyl moiety were considerably influences the structural orientation.

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