A study on the reactivity of 3-methyl-2,6-diphenyl-4-piperidone

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The reactivity of 3-methyl-cis-2,6-diphenyl-4-piperidone 1 has been explored to develop a variety of heterocyclic compounds viz., diazepinone 3, oxazepinone 4, thiadiazole 8, γ-carboline 13, isoxazolyl and pyrazolyl tetrahydropyridines 16 and 17 and various spiro heterocycles 18,19 and 21 by the functionalization of carbonyl and active methylene centres.

The main objective of this paper is to explore the potentialities and possible ways of synthetically viable intermediates in the development of interesting heterocycles. The design and synthesis of conformationally restricted molecules is an important approach towards improving the potency, selectivity etc. One such class of compounds constitute 4-piperidones and their derivatives, whose syntheses and stereodynamics are well investigated1. Indeed, 2,6-disubstituted-4-piperidines are the constituents of a number of alkaloids which possess broad spectrum of biological activity2. Inspite of the extensive studies on structure-activity relationship, still there is a scope to explore the utility of 4-piperidones as synths in the development of newer heterocycles. As part of our research programme, the reactivity of 3-methyl-cis-2,6-diphenyl-4-piperidone 1 is investigated. The latter has two reactive sites carbonyl and active methylene groups apart from NH, which proved to be a versatile intermediate in different types of reactions. This paved the way to synthesize some heterocyclic compounds such as diazepinone, oxazepinone, thiadiazole, isoxazolyl and pyrazolyl tetrahydropyridines, γ-carboline, various spiro-heterocycles etc.

The ring expansion reaction of 1 has been studied. The Beckmann reaction of 3-methyl-2,6-diphenyl-4-piperidinnoxime 2 on treatment with SOCl₂ and conc. H₂SO₄ results in the formation of 3-methyl-cis-2,7-diphenylhexahydro-1,4-diazepinone 3. On the other hand 1 on Bayer-Villiger reaction with m-chloroperbenzoic acid (m-CPBA) afforded 3-methyl-cis-2,7-diphenylhexahydro-4-oxa-1-azepinone 4 (Scheme 1). Under the conditions of the reaction, usually N-oxides would be expected to avoid this, the 1 was taken in the form of its hydrochloride and kept at lab temperature for week days. The 3 and 4 in their ¹H NMR spectra showed two doublets (δ, 5.20, J = 11.0 Hz, C₂-Hax; 5.76, J = 9.5 Hz, C₇-H eq for benzylic protons. The coupling constants JH₂-H₃ (–10 Hz) and JH₇-H₆AX (–10 Hz) observed in these systems led to presume that they prefer chair conformation with equatorial substituents as in 1. Furthermore, the vicinal coupling constants observed for C₇-Hax and C₆-Heq is 0 Hz which indicates that the dihedral angle between them is 90° (ref.4).

Not only the oxime derivative but also the hydrazones of 1 seems to be the versatile precursors for various heterocycles. In view of this the reactivity of

Reagents and conditions : i. NH₂OH.HCl, TEA, 40 min; ii. SOCl₂, conc. H₂SO₄, 3h NaOH; iii. mCPBA, 7 days; Na₂SO₄, Na₂CO₃

Scheme 1
hydrazones of 1 was studied in detail. Compound 1 on treatment with hydrazine / phenyl hydrazine / tosyl hydrazine in the presence of triethylamine furnished the respective hydrazones 5, 6 and 7. However, in case of 5, a dimerized product 5a was also formed in minor proportion contrary to the earlier reports. When 5, 6 and 7 were subjected to cyclocondensation with SOCl₂ in dichloromethane, tetrahydropyridino-1,2,3-thiadiazole 8 was obtained in case of 5 and 7 but not with 6. Similarly, all hydrazones were treated with iodine in benzene in presence of base. Oxidation took place only in 5 resulting in the formation of 4-ido-5-methyl-2,6-diphenyl-1,2,5,6-tetrahydropyridine 9 by merged elimination - substitution process. This obviously indicates that the reaction proceeds with unsubstituted hydrazones only. However, 5, 6 and 7 when subjected to oxidation with anhyd K₂CO₃ or 50% NaOH under PTC conditions, highly substituted olefin 10 was formed only with 5 and 7, which is contrary to Shapiro reaction. Thus it is obvious, the 6 is not responding to any of the above mentioned reactions. On the other hand, when 6 was treated with benzyl bromide under phase transfer conditions (TBAI/50%NaOH/CH₂Cl₂) N-benzyl-N-phenyl-hydrazone 11 was obtained. The nitroso derivative of 6, (12) on cyclocondensation with PPA led to iso Harman type of alkaloid derivative, γ-carboline 13 (Scheme II). The structures of 9 and 10 were confirmed by ¹H NMR spectra. A multiplet and three doublets were observed in 9 for the ring protons at C-2, C-3, C-5 and C-6 (δ, 4.93, d, J = 5.4 Hz; δ, 5.64, d, J = 6.1 Hz; δ, 2.51 - 2.53, m; δ, 4.41, d, J = 12.1 Hz), respectively, whereas in 10 a singlet, two double doublets and a multiplet were observed for the ring protons at C-2, C-4, C-5 and C-6 (δ, 5.61, s; δ, 5.45, dd, J = 3.8 & 12.4 Hz; δ, 2.70 - 2.90 m; δ, 3.62 - 3.80 m).

Scheme II

Reagents and conditions : i. NH₂NH₂·H₂O, TEA, 45 min / PhNHNH₂, TEA, 1 hr / TsNHNH₂, TEA; 1 hr / ii. SOCl₂, 0-25°C, 1 hr; iii. I₂, C₆H₅₂, TEA, 10°C, 1 hr; iv. aq K₂CO₃, 3 hr or 50 % aq NaOH, TBAI, 4 hr; v. PhCH₂Br, TBAI, 50% aq NaOH, 6 hr; vi. NaN₃, HCl, 3 hr; vii. PPA, room temp. - 50°C, 30 min.
4.84, dd, $J = 3.4$ & 12.1 Hz), respectively. This shows that a powerful oxidizing agent (12) orients the double bond towards less substituted carbon stereospecifically.

The N-acetyl derivative of 1, (14) on enamination with morpholine gave N-acetyl-4-morpholinotetrahydropyridine 15. Since, these enamino derivatives resembles olefins in many of their reactions, 15 has been utilized as a potential source to build five membered heterocycles. Thus, isoxazolyl and pyrazolyl tetrahydropyridines 16 and 17 have been obtained by the reaction of 15 with nitrile oxides and nitrile imines generated in situ from benzaldoxime and benzaldehyde phenylhydrazone in the presence of chloramine-T (CAT) (Scheme III). Generally, such reactions with olefins furnish 2-oxazolines and 2-pyrazolines only.8

Contrary to this, one pot synthesis of 5-acetyl-7-methyl-3, 4, 6-triphenyl-4, 5, 6, 7-tetrahydropyridinol-[3,4-d] isoxazole 16 and 5-acetyl-7-methyl-1,3,4,6-tetraphenyl-4,5,6,7-tetrahydropyridinol-[3,4-d] pyrazole 17 has been achieved by this process.

The in-built spiro systems in a heterocyclic ring generally increases the biological potency and more so with such systems having smaller rings. In fact, heteroatoms in small rings affect bond angles, bond lengths and bond strengths through a combination of factors including their intrinsic hybridization, magnitude of covalent radii, angle-bending constants, non bonded interactions and long range electronic effects. The functionalization of carbonyl moiety in 4-piperidone has become yet another source to develop various three membered ring series viz., cyclopropane, oxirane, thirane etc. However, attempts to synthesize aziranes met with no success (Scheme IV).

Cycloaddition of dimethylsulfoxonium methylicle9 to carbonyl moiety of 1 in the presence of K BuO' in dry DMSO affords piperidinoxiranes 18. The two isomers formed, one with equatorial oxygen 18a (54%) and another with axial oxygen 18b (24%) were separated by column chromatography (Figure 1). The downfield absorption of methyl protons in 18b compared to that in 18a confirms that the methyl group and oxygen in the former are in the same plane and also in close proximity with each other. These spiro epoxides are active synthons in many reactions10. In fact, 18a on reaction with ammonium thiocyanate in acetonitrile in presence of Ce (IV) salt affords the corresponding spiro-thiirane 19 in good yield. Similarly 18a on treatment with triethylphosphonoacetate in presence of K BuO' in dry DMSO results spirocyclopropane derivative 21 with retention of configuration as per Denny's mechanism11. On the other hand, the Wadsworth-Emmon's reaction of 1 with triethylphosphonoacetate gives the corresponding carbethoxy methylidine derivative 20 which on treatment with dimethylsulfoxonium methylicle in presence of K BuO' also affords 21.
We conclude that the synthetic methodology described in this communication is useful for obtaining different heterocycles. In all the cases cis-geometry of the aryl substituents in the parent molecule is retained in the products formed. Thus, it is worth noting that 4-piperidones are potentially useful synthons.

Experimental Section

General. Melting points were taken on Tempo Mel-Temp apparatus and are uncorrected. Elemental analyses were performed at Regional Sophisticated Instrumentation Centre, Punjab University, Chandigarh, India. IR spectra were recorded on a Perkin Elmer Grating IR Spectrometer in KBr pellets. 1H NMR and 13C NMR spectra were measured at 200 and 50 MHz respectively in CDCl₃ or DMSO-d₆, with TMS as an internal standard and all chemical shifts are reported in δ units. TLC's were developed on silica-gel H(BDH) in ethyl acetate: hexane as moving phase. Column chromatography were performed on 60-120 mesh silica-gel (Qualigens). Except the compounds noted in the experimental section, all other starting materials were purchased from Aldrich, Glaxo, SD fine chemical companies.

3-Methyl-cis-2,6-diphenyl-4-piperidone 1. It was prepared as per the literature procedure.

3-Methyl-cis-2,6-diphenyl-4-piperidonoxime 2. Dry powdered 1 (0.1 g, 0.35 mmole), hydroxylamine hydrochloride (0.08 g, 1.15 mmole) and triethylamine (0.4 mL, 2.86 mmole) were taken in ethanol (30 mL) and refluxed for 40 min, concentrated and cooled. The product separated was filtered and dried. The fine colourless needles formed were collected, yield 79%, m.p. 161-162°C. Anal. Caled for C₁₈H₁₈N₂O: C, 77.21; H, 7.19; N, 9.99. Found: C, 77.01; H, 7.05; N, 10.07%.

3-Methyl-cis-2, 7-diphenyl-1, 2, 3, 4, 6, 7-hexahydro-1,4-diazepin -5-one 3. To an ice-cold solution of 2 (0.1 g, 0.35 mmole) in 25 mL of dry benzene, 0.5 mL of thionyl chloride in 15 mL of 1,4-dioxane was added portion wise and stirred well. To this, 2 mL of conc. H₂SO₄ was added dropwise and the contents were stirred for another 3 hr and poured onto crushed ice. The pH of the solution was maintained at 7-8 by the addition of cold 10% NaOH solution. The solid separated was purified by column chromatography (2:3 ethyl acetate: hexane) to get pure 3, yield 75%, m.p. 194-96°C. Anal. Caled for C₁₈H₁₈N₂O : C, 77.11; H, 7.13; N, 9.99. Found: C, 76.92; H, 7.01; N, 9.83%. IR (KBr): 3300 (CONH), 1690 (CO); 1H NMR (200 MHz; CDCl₃): 1.01 (3H, d, J = 6.0 Hz, CH₃), 2.60 (1H, bs, amine NH), 3.23 (1H, d, J = 12.5 Hz, H-6₉), 3.60 (1H, dd, J = 9.5 and 12.8 Hz, H-6₈), 4.20 - 4.38 (1H, m, H-7₆), 5.20 (1H, d, J = 11.0 Hz, H-2₆), 5.76 (1H, d, J = 9.5 Hz, H-7₉); 13C NMR (50 MHz; CDCl₃): 15.9 (CH₃), 38.5 (C-6), 56.0 (C-3), 66.0 (C-2), 74.0 (C-7), 143.0 & 144.2 (Ar ipso-C), 174.2 (carbonyl carbon).

3-Methyl-cis-2, 7-diphenyl-1, 2, 3, 4, 6, 7-hexahydro-4-oxa-1-azepin -5-one 4. A mixture of hydrochloride of 1 (0.1 g, 0.33 mmole) in conc. H₂SO₄ and m-CBBA (0.3 g, 1.9 mmole) in 15 mL of dry CH₂Cl₂ was taken in a flask which was protected from light and kept in a dark place for a weak days. After completion of the reaction, the contents were washed with 10% aq. Na₂SO₄ solution, saturated Na.CO₃ solution followed by water. It was dried over anhyd Na₂SO₄ and evaporated in vacuo to get 4, yield, 64% which was purified by column chromatography (2:3 ethyl acetate : hexane), m.p. 68-69°C. Anal. Caled for C₁₈H₁₈N₂O : C, 76.84; H, 6.81; N, 4.97. Found: C, 76.71; H, 6.67; N, 4.83%. IR (KBr): 3340 (NH), 1700 (CO), 1210 (COC); 1H NMR (200 MHz; CDCl₃):
MHz; CDCl₃): 1.12 (3H, d, J = 6.7 Hz, CH₃), 2.16 (1H, bs, NH), 2.54 (1H, d, J = 14.3 Hz, H-6₆), 3.19 (1H, dd, J = 9.6 & 14.3 Hz, H-6₅), 3.80 (1H, m, H-3₆), 4.16 (1H, d, J = 8.3 Hz, H-2₆), 4.28 (1H, d, J = 10.4 Hz, H-7₆); ¹³C NMR (50 MHz; CDCl₃): 20.4 (CH₃), 46.4 (C-6), 56.1 (C-3), 140.0 & 144.1 (Ar ipso-C), 176.8 (carbonyl carbon).

3-Methyl-cis-2,6-diphenyl-4-piperidino hydrazone 5/phenylhydrazone 6/p-tosylhydrazone 7. The hydrazones were prepared by heating 1 (0.1 g, 0.38 mmole), and hydrazine hydrate / phenylhydrazine / p-toluensulfonyl hydrazide 6.24; N, 9.61. Found: C, 57.49; H, 4.71; N, 3.62%. IR (KBr): 1655 (C=C); 1380-39°C. Anal. Calcd for C₂₄H₂₁N₃O₂S: C, 69.26; H, 6.29; N, 9.43. Found: C, 69.08; H, 6.11; N, 9.72%.

4-Methyl-5,7-diphenyl-4, 5, 6, 7-tetrahydropryridino [3,4-d] [1,2,3]thiadiazole 8. Compound 5/7 (0.2 mmole) was added portionwise to an excess of thionylchloride (2 mL) at 0°C and the contents were allowed to attain room temperature. After 1hr, it was extracted with CH₂Cl₂ (10-15 mL) washed with saturated Na₂CO₃ solution and water and dried over anhyd. Na₂SO₄. Removal of the solvent in vacuo gave the crude product which was subjected to column chromatography (2:3 ethyl acetate : hexane) to get pure 8, yield 71%, m.p. 122-23°C (lit. m.p. 122°C).

4-Iodo-5-methyl-2, 6-diphenyl-l, 2, 5, 6-tetrahydropyridine 9. Into a solution of iodine (0.12 g, 0.43 mmole) in 15 mL of benzene, and a catalytic amount of triethylamine, 5 mmole) was added portionwise to an excess of benzyl-N-phenylhydrazono )-3-methyl-2, 6-diphenyl-4-piperidine 11. It was prepared by stirring 6 (0.5 g, 1.5 mmole), benzylbromide (0.18 mL, 1.8 mmole), TBAI (0.2 g, 0.6 mmole), 50% aq NaOH (25.5mL) and CH₂Cl₂ (10 mL) at 40°C for 6hr. The mixture was diluted with water and extracted with little excess of CH₂Cl₂. The organic layer was washed with saturated NaHCO₃ solution, brine and water. The solvent was evaporated to get 11, yield 64%, which was purified by column chromatography (3:2 ethyl acetate:hexane), m.p. 155-56°C. Anal. Calcd for C₁₈H₁₉N₂O: C, 81.56; H, 7.13; N, 9.32%. 4-(N-Benzyl-N-phenylhydrazono)-3-methyl-2, 6-diphenyl-4-piperidine 11. The nitrosation was carried out for 6 as per the literature procedure, yield 64%, m.p. 165-66°C. Anal. Calcd for C₂₄H₂₁N₄O: C, 74.77; H, 6.29; N, 14.47. Found: C, 74.91; H, 6.21; N, 14.56%.

4-Methyl-2-nitroso-1, 3-diphenyl-3,4-trihydrocarboline 13. The reaction was accomplished by adding 12 (0.05 g, 0.12 mmole) portionwise to 2 mL of PPA at rt. When the contents were brought to 50°C, the solution turned to red colour, then cooled and diluted with water. The product formed was extracted with CH₂Cl₂, washed with saturated Na₂CO₃ and water. Evaporation of the solvent gave 13, yield 52%, which was purified by column chromatography (3:1 ethyl acetate:hexane), m.p. 91°C (dec). Anal. Calcd for C₂₅H₂₅N₂O: C, 78.45; H, 5.76; N, 11.43.
1. Acetyl-3-methyl-2,6-diphenyl-4-piperidone 14. This was prepared as per the literature procedure, yield 75%, m.p. 113-114°C.

2. 4-Acrylyl-7-methyl-1,3,4,6-tetraphenyl-4,5,6,7-tetrahydropyridino [3,4-d] isoxazole 16. A solution of 15 (0.04 g, 0.15 mmole) and benzaldoxime (0.015 mL, 0.12 mmole), in 15 mL of absolute ethanol and a catalytic amount of chloramine T was refluxed almost in the same regions as in 18a. The remaining protons showed signals almost in the same regions as in 18a.

3. Acetyl-7-methyl-3,4,6-triphenyl-4,5,6,7-tetrahydropyridino [3,4-d] isoxazole 16. A solution of 15 (0.04 g, 0.15 mmole) and benzaldoxime (0.015 mL, 0.12 mmole), in 15 mL of absolute ethanol and a catalytic amount of chloramine T (CAT) was refluxed for 4 hr. The reaction mixture was extracted with ether, washed with dil. NaOH, brine and water. Evaporation of the solvent in vacuo gave a semi-solid which was purified by column chromatography, yield 60%, (1:2 ethyl acetate: hexane) m.p. 90°C (dec). Anal. Calcd for C19H21NO: C, 77.38; H, 7.01; N, 6.86. Found: C, 76.71; H, 7.39; N, 7.61%.

4. Acetyl-7-Methyl-3, 4, 6-triphenyl-4,5,6,7-tetrahydropyridino [3,4-d] pyrazole 17. The above procedure was followed with benzaldehyde phenylhydrazine instead of benzaldoxime to get 17, yield 55%, m.p. 69-70°C. Anal. Calcd for C19H21NO: C, 81.96; H, 6.04; N, 8.69. Found: C, 81.80; H, 6.12; N, 8.59%. IR (KBr): 1715 (C=O), 1620 (C=C), 1502 (C=N); 1H NMR (200 MHz; CDCl3-DMSO-d6): 1.17 (3H, d, J=6.0 Hz, CH3), 2.56 (3H, s, CH3, amide), 2.95-3.12 (1H, m, H-7), 4.66 (1H, d, J=11.45 Hz, H-6), 4.91 (1H, s, H-4).

3-Methyl-cis-2,6-diphenyl spiro piperidino-4,2'-oxirane 18. To a solution of 1 (0.1 g, 0.38 mmole) in 25 mL of dry DMSO, trimethylsulfonium iodide (TMSI) (0.2 g, 1.0 mmole) and KBrO (0.1 g, 1.0 mmole) in 10 mL of dry DMSO was added dropwise while stirring during 45 min. The solution was stirred for further 4 hr and diluted with water and continued stirring till a solid product separated out. It was filtered, dried and recrystallized from ethanol. The isomers were separated by column chromatography (2:3 ethyl acetate: hexane), 18a, yield 54%, m.p. 92-93°C. Anal. Calcd for C19H21NO: C, 81.68; H, 7.57; N, 5.03. Found: C, 81.49; H, 7.46; N, 5.12%. IR (KBr): 3302 (NH), 1204 (COC); 1H NMR (200 MHz; CDCl3-DMSO-d6): 0.55 (3H, d, J=6.1 Hz, CH3), 2.44 (1H, dd, J=1.6 & 12.1 Hz, H-5a), 2.35 (1H, dd, J=1.32 & 12.4 Hz, H-5b), 2.30-2.32 (1H, m, H-5a), 2.98 (1H, d, J=13.5 Hz, H-2'), 2.59 (1H, d, J=13.2 Hz, H-2), 3.75 (1H, d, J=10.6 Hz, H-4a), 4.35 (1H, dd, J=3.4 & 12.9 Hz, H-6b); 13C NMR (50 MHz; CDCl3-DMSO-d6): 21.2 (CH3), 27.4 (C-5), 29.4 (C-3), 40.6 (C-2'), 45.2 (C-4), 49.1 (C-2) 54.0 (C-6) 141 & 143.1 (Ar ipso-C); 18b, yield 24%, m.p. 98-100°C; 1H NMR (200 MHz; CDCl3-DMSO-d6): 1.2 (3H, d, J = 6.45 Hz, CH3). The remaining protons showed signals almost in the same regions as in 18a.
1.0 mmole) was added slowly and stirring was continued for 9-10 hr maintaining the temperature at 60-70°C. The solution was cooled, poured on to cold water and extracted with dichloromethane, evaporation of the solvent affords a semi-solid, which was solidified on treatment with pet. ether (40-60) (36%), m.p. 58-60°C. Anal. Calcd for C_{23}H_{27}N_{2}O_{2}: C, 79.05; H, 7.78; N, 4.10%. Found: C, 79.21; H, 7.64; N, 4.10%. IR (KBr): 3300, 3200, 2920, 1770, 1610, 1440, 1300, 1130, 700 cm\(^{-1}\).

Ethyl-3-methyl-cis-2,6-diphenyl spiro piperidino-4,2'-cyclopropane-1'-carboxylate 21. Method A. Triethylphosphonoacetate (0.1 mL, 0.55 mmole) was added dropwise with stirring to a slurry of KBuO (1g) in dry DMSO (25 mL) and stirred well till the evolution of gas ceases. To this 18a (0.5 g, 0.18 mmole) was added slowly and the stirring was continued for 10-12 hr maintaining the temperature at 60°C. The solution was cooled and poured onto crushed ice. The solid separated was filtered and recrystallized from alcohol, yield 75%, m.p. 81°C (dec). Anal. Calcd for C_{23}H_{27}N_{2}O_{2}: C, 79.05; H, 7.78; N, 4.10%. Found: C, 79.21; H, 7.64; N, 4.10%. IR (KBr): 3300 (NH), 1710 (C=O), 1340 (COC), \(^1\)H NMR (200 MHz; CDCl\(_3\)-DMSO-d\(_6\)): 1.16 (3H, d, J = 6.45 Hz, CH\(_3\), at C-3), 1.64 (3H, t, CH\(_3\), ester), 1.79 (1H, dd, J = 8.25 & 12.1 Hz, H-3\(^{\alpha}\)), 1.85 (1H, dd, J=11.05 & 12.1 Hz, C-3\(^{\alpha}\)), 2.15 (1H, dd, J = 1.6 & 11.95 Hz, H-5\(^{\alpha}\)), 2.34 (1H, dd, J=1.35 & 12.0 Hz, H-3\(^{\alpha}\)), 2.45 (1H, dd, J = 8.25 & 11.95 Hz, H-1\(^{\prime}\)), 2.78-2.86 (1H, m, H-3), 4.02-4.20 (2H, q, J=6.3 Hz, CH\(_2\), ester), 4.32 (1H, d, J=11.1 Hz, H-2\(^{\alpha}\)), 4.48 (1H, dd, J=2.9 & 12.0 Hz, H-6\(^{\alpha}\)).

Method B. 21 was also obtained from 20 by treatment of the latter with TMSOI and KBUO in dry DMSO for 4 hr, yield 65%, which had identical physical and spectroscopic properties to those described above.

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