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Note

Indolization of 4-piperidones : Synthesis of 1,3-diphenyl-1,2,3,4-tetrahydro-γ-carbolines

M Murugesan* & K Kaniappan

Department of Chemistry, PSG College of Arts & Science, Coimbatore 641 014, India

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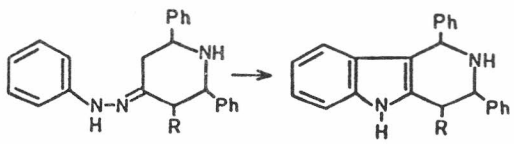
Several 1,3-diphenyl-1,2,3,4-tetrahydro-γ-carbolines (**2**) have been synthesized from the corresponding 2,6-diphenylpiperidin-4-ones by using formic acid as a solvent as well as cyclizing agent. A one-step synthesis of γ-carboline from 2,6-diphenylpiperidin-4-ones using formic acid and glacial acetic acid respectively is also reported.

The phenylhydrazone derivatives of acyclic ketones are readily cyclized to indoles in the presence of zinc chloride. Borsche showed that the phenylhydrazone of cyclohexanone undergoes a similar reaction to yield 1,2,3,4-tetrahydrocarbazole[1]. Glacial acetic acid is used in this case as the solvent and also as the cyclizing agent[2]. This reaction is also applicable for the six membered heterocyclic compounds having nitrogen, oxygen or sulphur in the ring[3]. These are extensions of the well known Fischer-indole synthesis. Indolization of phenylhydrazones using formic acid with sulphuric acid or hydrochloric acid as cyclizing agent is known for a long time. Saleha and Khan[4] used formic acid only for the cyclization of phenylhydrazones of fenchylaldehyde, 2-carboethoxyacetanilide, 4-methoxyphenylpyruvic acid and 2-hydroxyphenylacetaldehyde.

Recently, 2-benzyl-1,2,3,4-tetrahydro-γ-carboline has been prepared by treating the corresponding phenylhydrazone with acetic acid and hydrogen chloride mixture[5]. γ-Carboline itself was first prepared by Robinson and Thornley[6] by a three step synthesis using 4-chloropyridine and ortho-phenylene diamine but this method can be readily extended only to the symmetrical ortho-diamines.

In this investigation the phenylhydrazone derivatives of 2,6-diphenylpiperidin-4-ones have been cyclized in the presence of formic acid, leading to the formation of 1,3-diphenyl-1,2,3,4-tetrahydro-γ-carbolines (**2**). Here formic acid acts as a solvent as well as the cyclizing agent. Acetic acid can also be used for the cyclization of piperidone hydrazones. The resulting compounds and their spectral data have been analysed.



1a	R = H	2a	R = H
1b	R = CH_3	2b	R = CH_3
1c	R = C_2H_5	2c	R = C_2H_5
1d	R = i-Pr	2d	R = i-Pr

Phenylhydrazone derivatives of cyclic ketones undergoes cyclization in presence of acidic reagents. The presence of α-carbon atom facilitates indolization of the phenylhydrazone. 2,6-Diphenyl-4-piperidones contain the α-carbon atom (α-methylene groups), which facilitates cyclization. It has been found that the acidic reagents convert the piperidone hydrazone into the tetrahydro-γ-carboline derivatives. This fact has been confirmed by the spectral studies and elemental analysis.

The ^1H NMR spectrum of the new compound **2c** indicated that the presence of two proton signals at δ 3.7 and the presence of 14 phenyl protons in a complex multiplet. The indole NH peak appears at δ 9.2 and the proton concentration mark indicated that hydrogen of carboline NH has merged with aromatic protons to give a multiplet in the region δ 6.4-7.6. The first and third position hydrogens appeared δ 9.2 and 8.1 respectively. Collectively, these data in addition to the elemental analysis, led us to assign the structure of new compound **2c** as 4-ethyl-1,3-diphenyl-1,2,3,4-tetrahydro-γ-carboline.

In addition to the providing evidence for the structure of these compounds, unusual chemical shifts of certain protons can be observed. The 9-position hydrogen of γ-carboline consistently appears at lower field than the other hydrogens of the benzo ring. This is due to its close proximity to the first position phenyl group of the piperidone ring where it lies in the deshielding region of that group. Other benzo ring protons appear within the relatively narrow range of chemical shifts, although, 6-H would seen generally to be the most deshielded.

A comparison of the chemical shift values of the 4-ethyl-1,3-diphenyl-1,2,3,4-tetrahydro-γ-carboline with those of corresponding 3-ethyl-2,6-diphenylpiperidin-4-one reveals several striking features. In the ^{1}H NMR spectrum of **2c**, the methylene protons of the ethyl group gave two well separated multiplets. There was a geminal coupling between the methylene protons. Each of them underwent vicinal coupling with the methyl protons and with the methine proton at C-4. This proves that the geometry of the starting material has been retained in carboline. The doubling of signals due to phenyl substituents and the ring protons further confirm this conclusion.

Experimental Section

All the m.ps are uncorrected. IR spectra were recorded on a Perkin-Elmer 337 spectrometer, and ^{1}H NMR on a varian VXR-300 spectrometer at 90 MHz using TMS as internal reference.

2,6-Diphenylpiperidin-4-ones were prepared according to the procedure of Noller and Baliah[7].

General procedure for the preparation of phenylhydrazone derivatives. The 2,6-diphenylpiperidin-4-ones (1 mole) and phenylhydrazine (1 mole) were refluxed in ethanol for 1 hr. Slow addition of water gave a 75% yield of crude product, m.p. 67-70°C. These phenylhydrazones are not stable, decomposes in a few days to sticky, brown mass.

Cyclization of 2,6-diphenyl-4-piperidone phenylhydrazone. A mixture of freshly prepared 2,6-diphenyl-4-piperidone phenylhydrazone (10 g) and 50% formic acid (60 mL) in ethanol (60 mL) was heated under reflux for 1 hr. The mixture was cooled to 0°C. The crystals which formed were collected by filteration and recrystallised from ethanol in yellow shining crystals. Yield of pure 1,3-diphenyl-1,2,3,4-tetrahydro-γ-carboline (**2a**) was 6.2 g (60%), m.p. 189-91°C. (Found : C, 84.6; H, 6.9; N, 8.23. $C_{23}H_{20}N_2$ requires C, 85.1; H, 6.17; N, 8.64%); IR (KBr): 3275 (NH), 3175 (indole NH), 3050-3000 (Ar C-H stretching), 1620 (Ar C=C), 840 cm^{-1} (indole 1,2-disubstitution); ^{1}H NMR (DMSO-d_6): δ 3.15 (4H), 6.6-7.5 (m, Ar-H), 8.1 (t, 3H), 9.0 (d, 4H and/or 1H), 9.5 (s, indole NH).

Cyclization of 3-methyl-2,6-diphenyl-4-piperidone phenylhydrazone. A mixture of freshly prepared 3-methyl-2,6-diphenyl-4-piperidone phenylhydrazone (12 g) and 50% formic acid (60 mL) in ethanol (60 mL) was heated under reflux for 2.5 hr. The mixture was cooled to 0°C. The crystals which formed were collected by filteration and recrystallised from ethanol to give **2b**, yield 6.2 g (50%), m.p. 122-24°C. (Found : C, 85.46; H, 5.89; N, 8.54. $C_{24}H_{22}N_2$ requires C, 85.2; H, 6.5; N, 8.28%); IR (KBr): 3275 (NH), 3190 (indole NH), 3020 (Ar C-H stretching), 1610 (Ar C=C), 1480 (CH_3 stretching), 850 cm^{-1} (indole 1,2-disubstitution); ^{1}H NMR (DMSO-d_6): δ 3.35 (d, CH-CH_3), 6.6-7.6 (m, Ar-H), 8.1 (t, 3H), 9.2 (d, 4H and/or 1H), 9.5 (s, indole NH).

Cyclization of 3-ethyl-2,6-diphenyl-4-piperidone phenylhydrazone. A mixture of freshly prepared 3-ethyl-2,6-diphenyl-4-piperidone hydrazone (15 g) and 50% formic acid (75 mL) in ethanol (75 mL) was heated under reflux for 3 hr. The mixture was cooled to 0°C. The crystals which formed were collected by filteration and recrystallized from ethanol to yield pure 4-ethyl-1,3-diphenyl-1,2,3,4-tetrahydro-γ-carboline (**2c**), 7 g (47%), m.p. 158°C (Found : N, 7.47. $C_{25}H_{24}N_2$ requires N, 7.95%); IR (KBr): 3300 (NH), 3200 (indole NH), 3000 (Ar C-H stretching), 1600 (Ar C=C), 1500 (CH_3 stretching), 840 cm^{-1} (indole 1,2-disubstitution); ^{1}H NMR (DMSO-d_6): δ 1.3 (t, CH_3), 3.7 (q, $-CH_2-$), 6.4-7.6 (m, Ar-H), 8.1 (t, 3H), 9.2 (d, 4H and/or 1H), 9.7 (s, indole NH).

Cyclization of 3-isopropyl-2,6-diphenyl-4-piperidone phenylhydrazone. A mixture of freshly prepared 3-isopropyl-2,6-diphenyl-4-piperidone hydrazone (10 g) and 50% formic acid (60 mL) in ethanol (60 mL) was heated under reflux for 10 hr. Refluxing time is very important in this case because isopropyl group produce steric hinderence. The mixture was cooled to 0°C. The crystals which formed were collected by filteration and recrystallised from ethanol to yield pure 4-isopropyl-1, 3-diphenyl-1, 2, 3, 4-tetrahydro-γ-carboline (**2d**), 4 g (40%), m.p. 152°C (Found : N, 7.9. $C_{26}H_{26}N_2$ requires N, 7.65%); IR (KBr): 3300 (NH), 3175 (indole NH), 3000 (Ar C-H stretching), 1600 (Ar C=C), 1400 (isopropyl group), 820 cm^{-1} (indole 1,2-disubstitution); ^{1}H NMR (DMSO-d_6): δ 1.2 (q, isopropyl), 6.6-7.6 (m, Ar-H), 8.1 (t, 3H), 9.2 (d, 4H and/or 1H), 9.5 (s, indole NH).

One-step synthesis of 1,3-diphenyl-1,2,3,4-tetrahydro-γ-carboline : General procedure : Method-I . A mixture of 2,6-diphenylpiperidin-4-ones (2g, 0.008 mole), 50% formic acid (20 mL) in ethanol (20 mL) and phenylhydrazine (3.5 g, 0.032 mole) was refluxed for 1 hr. The solution was cooled to room temp or sometimes below room temp. The crystals which formed were collected by filteration and recrystallised from ethanol, yield 75%. Melting points and spectral data of the resulting compounds are the same as that

of the compounds obtained by the previous method.

Method-II. A solution of phenylhydrazine (2.5 g, 0.023 mole) and 2,6-diphenylpiperidin-4-ones (2.5 g, 0.01 mole) in glacial acetic acid (15 mL) was refluxed for 1 hr and the resulting solution was cooled under tap water. The crystals which formed were collected by filteration and recrystallised from ethanol, yield 25%. Melting points and spectral data of the resulting compounds are the same as that of the compounds obtained by the previous method.

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