

Synthesis of 5-Methyl-1,2,3,4,5,6-hexahydrocyclopenta[g]carbazole-1,7-diones and Crotonyl-2-isopropyl-1-oxo-1,2,3,4-tetrahydrocarbazoles from 1-Oxo-1,2,3,4-tetrahydrocarbazoles by Friedel-Crafts Reaction

Isravel A. Danish and Karnam J. R. Prasad

Department of Chemistry, Bharathiar University, Coimbatore-641 046, India

Reprint requests to Dr. K. J. R. Prasad. E-mail: prasad_125@yahoo.com

Z. Naturforsch. **59b**, 711 – 715 (2004); received January 2, 2004

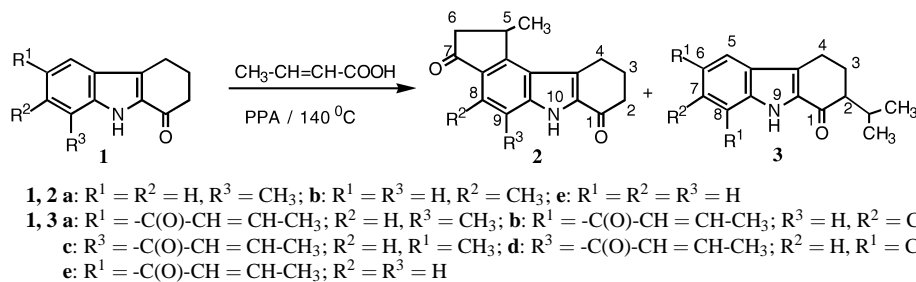
The reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles (**1**) with crotonic acid in polyphosphoric acid afforded hitherto unknown 5-methyl-1,2,3,4,5,6-hexahydrocyclopenta[g]carbazole-1,7-diones (**2**) and 6-crotonyl-2-isopropyl-1-oxo-1,2,3,4-tetrahydrocarbazoles (**3**) in a single step. A plausible mechanism for the formation of the title compounds has been proposed, and all new compounds were characterized by IR, NMR, mass spectral methods and elemental analysis.

Key words: 1-Oxo-1,2,3,4-tetrahydrocarbazoles, Crotonic Acid, Polyphosphoric Acid, 1,2,3,4,5,6-Hexahydrocyclopenta[g]carbazole-1,7-diones, Friedel-Crafts Reaction

Development of new methods for the synthesis of functionalized carbazoles is currently attracting organic chemists due to the discovery of many carbazole alkaloids with diverse biological properties such as anti-inflammatory, bactericidal, analgesic antibiotic, fungicidal, anticonvulsant, trypanocidal and neuroleptic [1 – 8]. Tetrahydrocarbazole and its derivatives are evaluated in human beings as an antidepressant drug [9]. In particular, pyrido[4,3-*b*]carbazoles were reported to possess anti-cancer and anti-HIV properties [11 – 14]. Moreover among the oxygenated carbazole derivatives grimbine (pyrano[2,3-*a*]carbazoles) and carbazomycins are of much importance due to their antibiotic properties [9, 10]. The importance of pyranocarbazoles and the lack of reports on their preparation from the easily accessible 1-oxo-1,2,3,4-tetrahydrocarbazoles, had induced us to derive an elegant synthetic route to prepare pyrano[2,3-*a*]carbazoles. Until now the preparation of pyrano[2,3-*a*]carbazoles has been reported only from 1-hydroxycarbazoles [10, 15, 16].

In this regard, the reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles **1** [17] with crotonic acid in PPA under Friedel-Crafts conditions yielded interestingly hitherto unknown compounds namely, 5-methyl-1,2,3,4,5,6-hexahydrocyclopenta[g]carbazole-1,7-diones **2** and 6-crotonyl-2-isopropyl-1-oxo-1,2,3,4-tetrahydrocarbazoles **3** in a single step. The reaction of 8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole **1a** with

crotonic acid in the presence of PPA at 140 °C afforded a mixture of two products. The product obtained from the first chromatographic fraction of petroleum ether and ethyl acetate, in its IR spectrum showed strong absorptions at 1697 cm⁻¹ and 1655 cm⁻¹ corresponding to the two C=O groups. The intense band at 3282 cm⁻¹ was due to the NH group stretching vibrations. The ¹H NMR showed a doublet of three proton intensity at δ = 1.49 with *J* = 6.4 Hz which was due the methyl protons at C-5. The methylene protons at C-2, C-3, C-4 and C-6 resonated as four multiplets between δ = 2.35 – 2.44, δ = 2.68 – 2.76, δ = 2.97 – 3.05 and δ = 3.20 – 3.29, respectively. The 9-CH₃ protons appeared as a singlet at δ = 2.52. The benzylic proton at 5-H appeared as a multiplet in the region δ = 3.79 – 3.86. A sharp singlet at δ = 7.49 was due to the C-8 proton. The carbazole NH proton appeared as a broad singlet at δ = 9.33. The ¹³C NMR spectrum showed two sharp singlets at δ = 157.92 and δ = 191.27 corresponding to the two carbonyl groups at C-7 and C-1, respectively. Based on the spectral data and elemental analysis the structure of the compound obtained was found to be 5,9-dimethyl-1,2,3,4,5,6-hexahydrocyclopenta[g]carbazole-1,7-dione (**2a**). Similarly 5,8-dimethyl-1,2,3,4,5,6-hexahydrocyclopenta[g]carbazole-1,7-dione (**2b**) was obtained from **1b** and 5-methyl-1,2,3,4,5,6-hexahydrocyclopenta[g]carbazole-1,7-dione (**2c**), from **1e** (Scheme 1).



Scheme 1. Synthesis of 5-methyl-1,2,3,4-tetrahydrocyclopenta[g]carbazole-1,7-diones and crotonyl-2-isopropyl-1-oxo-1,2,3,4-tetrahydrocarbazoles.

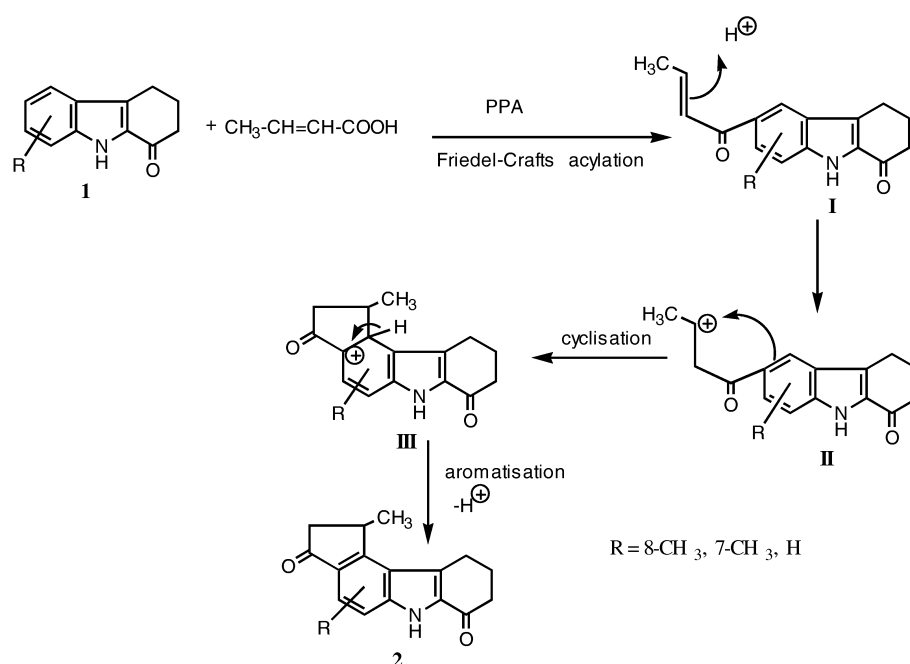
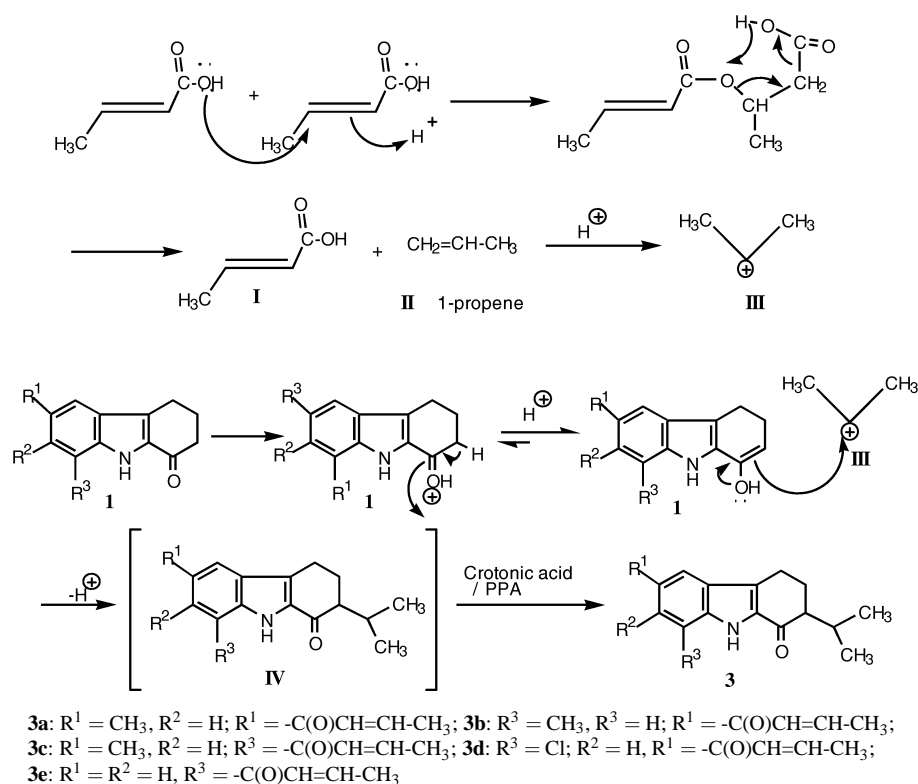
The interesting observation made in this reaction is that a similar series of products were obtained only from the 8-methyl-, 7-methyl- and the unsubstituted 1-oxo-1,2,3,4-tetrahydrocarbazoles (**1a**, **1b** and **1e**) as **2a**, **2b** and **2e**, respectively. It is pertinent to mention here that earlier findings [18] have revealed that the order of preference of the 1-oxo-1,2,3,4-tetrahydrocarbazoles for an electrophile is $C-6 > C-8 > C-5 > C-7$. The sixth position is more susceptible for electrophilic substitution, and analogous products were not obtained from **1c** and **1d** since C-6 was occupied by a methyl or a chloro substituent.

The second chromatographic fraction, obtained by elution with petroleum ether:ethyl acetate (80:20), on removal of solvent gave a red crystalline powder which decomposed at 300 °C. The IR spectrum of the product clearly indicated the presence of the two carbonyl groups by intense bands at 1680 and 1654 cm^{-1} . The NH stretching vibration was inferred from the strong band at 3295 cm^{-1} . The ^1H NMR spectrum showed a doublet at $\delta = 0.86$ with $J = 6.6$ Hz for the geminal dimethyl group. A multiplet between $\delta = 1.49 - 1.63$ with four proton intensity was due to the $\text{CH}(\text{Me})_2$ and the methyl protons of the crotonyl group. Another unresolved multiplet between $\delta = 2.19 - 2.57$ of two proton intensity is due to the methylene protons at C-3. The C-8 methyl protons resonated as a sharp singlet at $\delta = 2.61$. The methylene protons at C-4 appeared as a multiplet between $\delta = 3.03 - 3.13$. An unresolved multiplet between $\delta = 4.02 - 4.06$ was due to 2-H. The olefinic protons of the crotonyl group ($\text{CH}=\text{CHMe}$ and $\text{CH}=\text{CHMe}$) appeared as a multiplet of two proton intensity in the region $\delta = 7.53 - 7.90$. The aromatic protons at 5-H and 7-H appeared as two singlets at $\delta = 7.67$ and $\delta = 8.45$, respectively. The carbazole NH proton appeared as a broad singlet at $\delta = 8.79$. The mass spectrum showed its molecular

ion peak, at $m/z = 309$ (4%) and the base peak at 267 (100%) indicating that the crotonyl group is free and uncyclised. The elemental analysis agreed well with the proposed molecular formula $\text{C}_{20}\text{H}_{23}\text{NO}_2$. The spectral data and the elemental analysis suggest the structure of the product to be 6-crotonyl-2-isopropyl-8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**3a**). A similar series of compounds were realized as **3b**, **3c**, **3d** and **3e** from **1b**, **1c**, **1d** and **1e** (Scheme 1).

The formation of products **3a–e** showed that when C-6 position of **1** was blocked with either a methyl (**1c**) or chloro substituent (**1d**), the electrophilic attack by the crotonyl group occurred at C-8 (**3c** and **3d**). When the C-8 or C-7 (**1a** and **1b**) was blocked by a methyl group, the crotonyl group reacted at C-6 (**3a** and **3e**), and similarly in the unsubstituted compound. So it can be concluded that C-6 position is more susceptible towards an electrophile compared to other positions. This regioselectivity is supported by para-relationship between C-6 and the ring nitrogen atom. The deactivating effect of the chloro substituent may account for the poor yield, when C-6 is substituted.

A plausible mechanism for the formation of products **2** and **3** might be the following. The conversion of **1** to **2** can be interpreted as occurring *via* the Friedel-Crafts acylation of **1** with crotonic acid followed by internal electrophilic substitution followed by cyclisation and aromatisation (Scheme 2). For the formation of **3** the chemical components of the above reaction suggest that crotonic acid is the source for both the acyl group and the isopropyl group. A propene molecule (**II**) may be formed from two molecules of crotonic acid. Then the enolic form of 1-oxo-1,2,3,4-tetrahydrocarbazole (**1**) under acidic conditions reacts with the 2-propyl cation (**III**) formed from 1-propene (**II**) and successively the resulting intermediate **IV** was

Scheme 2. Mechanism for the formation of **2**.Scheme 3. Mechanism for the formation of **3**.

acylated with **1** in presence of polyphosphoric acid to yield **3** (Scheme 3).

Experimental Section

General: Thin layer chromatography was used to access the purity of the products. Melting points were determined by using a Mettler FP 51 melting point apparatus and are uncorrected. IR spectra were recorded using KBr discs on a Shimadzu FTIR-8201 PC Infrared Spectrophotometer and ^1H NMR on a Varian AMX 400 FT-NMR spectrometer and ^{13}C NMR on a Bruker DRX-300 spectrometer using TMS as internal reference in CDCl_3 . The chemical shifts are quoted in ppm. Mass spectra were recorded on a Joel JMS-D 300 mass spectrometer. Microanalyses were obtained with Perkin Elmer Model 240 CHN analyzer.

General procedure: Reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles (1**) with crotonic acid**

1-Oxo-1,2,3,4-tetrahydrocarbazole (**1**, 0.003 mol) was mixed thoroughly with 10 g of polyphosphoric acid (prepared from 8 g of P_2O_5 and 2 ml of orthophosphoric acid), crotonic acid (0.006 mol) was added and heated on an oil bath at 140°C for six hours. Then, the reaction mixture was poured into crushed ice. It was neutralised with 10% NaOH solution and extracted with ethyl acetate (3×50 ml). The combined organic layers were thoroughly washed with water and dried over anhydrous sodium sulfate. On removal of the solvent a red coloured crude mixture was obtained which was purified by column chromatography over silica gel. Elution with a petroleum ether-ethyl acetate (85:15) mixture afforded a yellow crystalline powder of product **2**, and elution with the above solvent mixture (75:25) yielded a red crystalline powder of product **3**.

5,9-Dimethyl-1,2,3,4,5,6-hexahydrocyclopenta[g]carbazole-1,7-dione (2a**)**

M. p. 258°C . – IR (KBr): $\nu = 3282$ (NH), 1697 (C=O), 1655 (C=O), 1593 , 1537 , 1480 , 1238 , 1173 cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): $\delta = 1.49$ (d, $J = 6.4$ Hz, 3 H, 5-Me), 2.35 – 2.44 (m, 2 H, 2- H^2), 2.52 (s, 3 H, 9-Me), 2.68 – 2.76 (m, 2 H, 3- H^2), 2.97 – 3.05 (m, 2 H, 4- H^2), 3.20 – 3.29 (m, 2 H, 6- H^2), 3.79 – 3.86 (m, 1 H, 5-H), 7.49 (s, 1 H, 8-H), 9.33 (b s, 1 H, carbazole NH). – $^{13}\text{C}\{^1\text{H}\}$ NMR (300 MHz, CDCl_3): $\delta = 17.30$ (9-Me), 24.44 (5-Me), 25.89 (C-3), 30.38 (C-4), 32.97 (C-2), 38.59 (C-5), 46.29 (C-6), 121.99 (C-4a, C-9a), 122.61 (C-7a), 122.95 (C-8), 130.76 (C-9), 130.97 (C-4b), 132.80 (C-10a), 141.94 (C-4c), 157.92 (C=O), 191.27 (C=O). – MS (EI, 70 eV): m/z (%) = 267 (100) [M^+]. – $\text{C}_{17}\text{H}_{17}\text{NO}_2$ (267.17): calcd. C 76.42, H 6.36, N 5.24; found C 76.38, H 6.40, N 5.27.

5,8-Dimethyl-1,2,3,4,5,6-hexahydrocyclopenta[g]carbazole-1,7-dione (2b**)**

M. p. 210°C . – IR (KBr): $\nu = 3236$ (NH), 1684 (C=O), 1653 (C=O), 1560 , 1532 , 1458 , 1267 , 1167 cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): $\delta = 1.45$ (d, $J = 7.0$ Hz, 3 H, 5-Me), 2.22 – 2.43 (m, 2 H, 2- H^2), 2.61 – 2.68 (m, 2 H, 3- H^2), 2.71 (s, 3 H, 8-Me), 2.94 – 3.05 (m, 2 H, 4- H^2), 3.17 – 3.24 (m, 2 H, 6- H^2), 3.75 – 3.79 (m, 1 H, 5-H), 7.09 (s, 1 H, 9-H), 9.26 (b s, 1 H, carbazole NH). MS (EI, 70 eV): m/z (%) = 267 (100) [M^+]. – $\text{C}_{17}\text{H}_{17}\text{NO}_2$ (267.17): calcd. C 76.42, H 6.36, N 5.24; found C 76.47, H 6.40, N 5.19.

5-Methyl-1,2,3,4,5,6-hexahydrocyclopenta[g]carbazole-1,7-dione (2e**)**

M. p. 170°C . – IR (KBr): $\nu = 3231$ (NH), 1690 (C=O), 1655 (C=O), 1578 , 1535 , 1470 , 1238 , 1146 cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): $\delta = 1.49$ (d, $J = 6.9$ Hz, 3 H, 5-Me), 2.25 – 2.53 (m, 4 H, 2- H^2 , 3- H^2), 2.69 – 2.73 (m, 2 H, 4- H^2), 3.16 – 3.29 (m, 2 H, 6- H^2), 3.82 – 3.86 (m, 1 H, 5-H), 7.41 (d, $J = 8.7$ Hz, 1 H, 8-H), 7.70 (d, $J = 8.7$ Hz, 1 H, 9-H), 9.54 (b s, 1 H, carbazole NH). MS (EI, 70 eV): m/z (%) = 253 (100) [M]. – $\text{C}_{16}\text{H}_{15}\text{NO}_2$ (253.16): calcd. C 75.90, H 5.93, N 5.53; found C 75.92, H 5.87, N 5.58.

6-Crotonyl-2-isopropyl-8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (3a**)**

M. p. 300°C (dec.). – IR (KBr): $\nu = 3295$ (NH), 1680 (C=O), 1654 (C=O), 1583 , 1458 , 1252 , 1182 cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): $\delta = 0.86$ (d, $J = 6.6$ Hz, 6 H, 2- $\text{CH}(\text{Me})_2$), 1.49 – 1.63 (m, 4 H, $\text{CH}(\text{Me})_2$, $\text{CH}=\text{CHMe}$), 2.19 – 2.57 (m, 2 H, 3- H^2), 2.61 (s, 3 H, 8-Me), 3.03 – 3.13 (m, 2 H, 4- H^2), 4.02 – 4.06 (m, 1 H, 2-H), 7.53 – 7.90 (m, 2 H, $\text{CH}=\text{CHMe}$ and $\text{CH}=\text{CHMe}$), 7.67 (s, 1 H, C_5 -H), 8.45 (s, 1 H, 7-H), 8.79 (b s, 1 H, carbazole NH). – MS (EI, 70 eV): m/z (%) = 309 (4) [M^+], 267 (100) [$\text{M}^+ - i\text{Pr}$]. – $\text{C}_{20}\text{H}_{23}\text{NO}_2$ (309.20): calcd. C 77.68, H 7.44, N 4.53; found C 77.71, H 7.48, N 4.49.

6-Crotonyl-2-isopropyl-7-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (3b**)**

M. p. 200°C . – IR (KBr): $\nu = 3422$ (NH), 1690 (C=O), 1640 (C=O), 1560 , 1458 , 1244 cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): $\delta = 0.96$ (d, $J = 6.5$ Hz, 6 H, 2- $\text{CH}(\text{Me})_2$), 1.42 – 1.59 (m, 4H, $\text{CH}(\text{Me})_2$, $\text{CH}=\text{CHMe}$), 2.17 – 2.50 (m, 2 H, 3- H^2), 2.79 (s, 3 H, 7-Me), 2.93 – 3.35 (m, 2 H, 4- H^2), 3.99 – 4.02 (m, 1 H, 2-H), 7.01 – 7.16 (m, 1H, $\text{CH}=\text{CH-Me}$), 7.34 (d, $J = 7.7$ Hz, 1 H, $\text{CH}=\text{CHMe}$), 7.48 (s, 1 H, C_5 -H), 8.40 (s, 1 H, 8-H), 8.61 (b s, 1 H, carbazole NH). – MS (EI, 70 eV): m/z (%) = 309 (4) [M^+], 267 (100) [$\text{M}^+ - i\text{Pr}$]. – $\text{C}_{20}\text{H}_{23}\text{NO}_2$ (309.20): calcd. C 77.68, H 7.44, N 4.53; found C 77.60, H 7.39, N 4.58.

8-Crotonyl-2-isopropyl-6-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (3c)

M.p. 155 °C. – IR (KBr): ν = 3420 (NH), 1695 (C=O), 1638 (C=O), 1541, 1458, 1246, 1173 cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): δ = 0.97 (d, J = 6.5 Hz, 6 H, 2-CH(Me) $_2$), 1.43–1.61 (m, 4H, CH(Me) $_2$, CH=CHMe), 2.28–2.56 (m, 2 H, 3-H 2), 2.59 (s, 3 H, 6-Me), 2.70–3.27 (m, 2 H, 4-H 2), 3.99–4.10 (m, 1 H, 2-H), 6.23 (s, 1 H, 5-H), 7.42 (d, J = 8.1 Hz, 1 H, CH=CHMe), 7.50–7.63 (m, 1 H, CH=CHMe), 7.79 (s, 1 H, 7-H), 8.18 (b s, 1 H, carbazole NH). – MS (EI, 70 eV): m/z (%) = 309 (4) [M^+], 267 (100) [$\text{M}^+ - \text{iPr}$]. – $\text{C}_{20}\text{H}_{23}\text{NO}_2$ (309.20): calcd. C 77.68, H 7.44, N 4.53; found C 77.65, H 7.41, N 4.61.

6-Chloro-8-crotonyl-2-isopropyl-1-oxo-1,2,3,4-tetrahydrocarbazole (3d)

M.p. 143 °C. – IR: ν = 3450 (NH), 1680 (C=O), 1638 (C=O), 1560, 1450, 1290, 1175 cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): δ = 0.96 (d, J = 6.5 Hz, 6 H, 2-CH(Me) $_2$), 1.38–1.67 (m, 4H, CH(Me) $_2$, CH=CHMe), 2.03–3.08 (m, 4 H, 3-H 2 , 4-H 2), 3.48–3.85 (m, 1 H, 2-H), 6.79–6.99 (m, 1H, CH=CHMe), 7.65 (d, J = 7.6 Hz, 1 H, CH=CHMe), 7.93 (s, 1H, 5-H), 8.19 (s, 1H, 7-H), 9.09 (b s, 1 H, carbazole NH). –

MS (EI, 70 eV): m/z (%) = 329 (4) [M^+], 287 (100) [$\text{M}^+ - \text{iPr}$]. – $\text{C}_{19}\text{H}_{20}\text{NO}_2\text{Cl}$ (329.64): calcd. C 69.22, H 6.07, N 4.25; found C 69.27, H 6.01, N 4.19.

6-Crotonyl-2-isopropyl-1-oxo-1,2,3,4-tetrahydrocarbazole (3e)

M.p. 205 °C. – IR: ν = 3410 (NH), 1684 (C=O), 1636 (C=O), 1583, 1458, 1252, 1182 cm^{-1} . – ^1H NMR (400 MHz, CDCl_3): δ = 0.94 (d, J = 6.6 Hz, 6 H, 2-CH(Me) $_2$), 1.38–1.64 (m, 4 H, CH(Me) $_2$, CH=CHMe), 2.52–2.69 (m, 2 H, 3-H 2), 2.84–3.15 (m, 2 H, 4-H 2), 4.06–4.10 (m, 1 H, 2-H), 7.35 (d, J = 8.5 Hz, 1 H, CH=CHMe), 7.45 (d, J = 8.3 Hz, 1 H, 7-H), 7.53–7.62 (m, 1H, CH=CHMe), 7.86 (d, J = 8.3 Hz, 1 H, 8-H), 8.46 (s, 1H, C $_5$ -H), 8.71 (b s, 1 H, carbazole NH). – MS (EI, 70 eV): m/z (%) = 295 (4) [M^+], 253 (100) [$\text{M}^+ - \text{iPr}$]. – $\text{C}_{19}\text{H}_{21}\text{NO}_2$ (295.19): calcd. C 77.30, H 7.11, N 4.79; found C 77.34, H 7.06, N 4.75.

Acknowledgements

The authors thank SIF, IISc, Bangalore for the ^1H NMR spectral analysis and the Head, RSIC, CDRI, Lucknow for the mass spectral data and elemental analysis. We also acknowledge the help for recording ^{13}C NMR spectrum by Dr. R. Balamurali, POSTECH, Pohang, South Korea.

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