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REGULAR ARTICLE

An efficient one-pot synthesis of carbazole fused benzoquinolines and pyridocarbazoles

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Abstract. A one-pot, solvent-free protocol for the synthesis of chloro-substituted benzoquinoline-carbazole derivatives *via* a modified Friedländer hetero-annulation reaction between 2, 3, 4, 9-tetrahydrocarbazol-1-one and 3-amino-2-naphthoic acid in the presence of $POCl_3$ is described. In addition, the direct pseudo multicomponent transformation of 2, 3, 4, 9-tetrahydrocarbazol-1-one, malononitrile and 9-ethyl-3-carbazolecarboxaldehyde results in the formation of a multifunctionalized carbazole through a Knoevenagel–Michael addition-cyclization reaction has also been reported. All the newly synthesized molecules were deduced by spectral and analytical methods.

Keywords. Modified Friedländer reaction; benzoquinoline-carbazoles; pseudo multicomponent reaction; carbazole substituted pyridocarbazole.

1. Introduction

The structural diversity and biological importance of nitrogen containing heterocycles such as carbazole and quinoline derivatives have made them attractive targets in both medicinal and organic chemistry. The heteroaryl-carbazole derivatives have been found to display a diverse array of important functions and are abundant in bioactive natural products.[1–4] For example, the pyridocarbazole type alkaloids, ellipticine(extracted from the leaves of *Ochrosia elliptica*) and Olivacine (isolated from *Aspidosperma olivaceum*) exhibit a wide spectrum of biological and medicinal activities.[5–9] The benzoquinoline core structure is also found in a wide variety of biologically active natural products and pharmaceuticals with anti-Parkinson, antipsychotic, antibacterial, UDP (Uridine diphosphate)-glucuronosyl transferase, antimalarial, agonistic and antipsychotic activities.[10–14] Kantevari *et al.,* reported that the coupling of 9-methyl-9H-carbazole to tetrahydroquinoline nucleus could deliver a new scaffold with better antimycobacterial activity than its individual reactants.[15] Recently our research group reported carbazole and quinoline-based hybrid moieties for its pharmacological interest.[16]

As an extension to our efforts in developing heterocycles of biological interest and also considering the significant role of carbazoles and benzoquinolines in biological applications, we were inspired to synthesize a new series of benzoquinoline-carbazole and carbazole dimer from 2,3,4,9-tetrahydro-1*H*-carbazol-1-one as the precursor *via* a one-pot protocol.

2. Experimental

2.1 *General*

All the chemicals were bought from Sigma-Aldrich and Merck and were utilized for the process without further purification. Melting points (M.p.) were determined on a Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and are uncorrected. They are expressed in degree centigrade (°C). FT-IR spectra were recorded on Avatar Model FT-IR (4000−400 cm^{-1}) spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on an Agilent- 400 MHz

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(^{1}H) and 100 MHz (^{13}C) spectrometers respectively in $CDCl_3$ using TMS (tetramethylsilane) as internal reference; chemical shifts are expressed in parts per million (ppm); coupling constants (J) are reported in hertz (Hz) and the terms J_o and J_m refer to ortho coupling constant and meta coupling constant. The signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), bs (broad singlet) and dd (doublet of doublet). Microanalyses were carried out using Vario EL III model CHNS analyzer (Vario, Germany). Absorption spectral measurements were carried out using JASCO V-630 UV–Visible spectrophotometer. Quartz cuvettes of path length 1cm were used to record the absorption spectra. The emission spectral studies were performed with JASCO FP-6600 spectrofluorometer equipped with a 1 cm quartz cuvette at the Department of Chemistry, Bharathiar University. When known compounds had to be prepared according to literature procedures pertinent references are given. The purity of the products was tested by TLC plates coated with silica gel-G using petroleum ether and ethyl acetate in the ratio of 1:1 as developing solvents.

2.2 *General procedure for the synthesis of 7-chloro-benzo[6′,7′-a′]quino[2′,3′-a]-5,6-dihydrocarbazole* ***3***

A mixture of 2,3,4,9-tetrahydrocarbazol-1-one **1** (1.0 mmol) and 3-amino-2-naphthoic acid **2** (1.0 mmol) was refluxed with phosphorus oxychloride (5 mL) for 5 h at 120 °C. The completeness of the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice water and extracted with ethyl acetate. Combined organic layers were dried over anhydrous magnesium sulphate. It was then purified on a silica-gel column chromatography (eluent: petroleum ether/ethyl acetate, 99:1).

2.3 *The spectral and analytical data of all the compounds* ***3(a–d)***

2.3a *7-Chloro-benzo[6′,7′-a′]quino[2′,3′-a]-5,6-dihydrocarbazole (**3a**)*: White solid; yield: 283 mg (80%); M.p. 201−203 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3436(NH), 1592 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.47 (br s, 1H, NH), 8.66 (s, 1H, ArH), 8.52 (s, 1H, ArH), 8.04–7.98 (m, 2H, ArH), 7.62 (d, 1H, ArH, J_o = 7.60 Hz), 7.52–7.47 (m, 2H, ArH), 7.39 (d, 1H, ArH, J_o = 8.40 Hz), 7.29–7.27 (m, 1H, ArH), 7.13 (t, 1H, ArH, J_o = 7.20 Hz), 3.51–3.48 (m, 2H, CH_2), 3.21–3.17 (m, 2H, CH_2); ^{13}C NMR(100 MHz, $CDCl_3$) (ppm) δ_C: 149.2, 148.4, 143.8, 138.6, 138.1, 134.0, 132.4, 131.6, 128.5, 127.9, 126.8, 126.6, 126.0, 124.7, 124.5, 123.5, 120.0, 119.8, 111.8, 26.7, 19.0; Anal. calcd. for $C_{23}H_{15}ClN_2$: C, 77.85; H, 4.26; N, 7.89; found: C, 77.94; H, 4.22; N, 7.83 %.

2.3b *7-Chloro-3-methyl-benzo[6′,7′-a′]quino[2′,3′-a]-5,6-dihydrocarbazole (**3b**)*: White solid; yield: 253 mg (69%); M.p. 198−200 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3462 (NH), 1592 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.34 (br s, 1H, NH), 8.64 (s, 1H, ArH), 8.49 (s, 1H, ArH), 8.03–7.97 (m, 2H, ArH), 7.51–7.46 (m, 2H, ArH), 7.38 (s, 1H, ArH), 7.25 (d, 1H, ArH, J_o = 8.80 Hz), 7.08 (d, 1H, ArH, J_o = 8.80 Hz), 3.49–3.45 (m, 2H, CH_2), 3.17–3.13 (m, 2H, CH_2), 2.45 (s, 3H, CH_3); ^{13}C NMR(100 MHz, $CDCl_3$) (ppm) δ_C: 148.5, 143.9, 138.4, 136.5, 134.0, 132.7, 131.6, 129.3, 128.5, 127.9, 127.0, 126.5, 126.1, 125.9, 124.5, 123.5, 119.3, 111.4, 26.7, 21.4, 19.0 (CH_3); Anal. calcd. for $C_{24}H_{17}ClN_2$: C, 78.15; H, 4.65; N, 7.59; Found: C, 78.24; H, 4.63; N, 7.65%.

2.3c *7-Chloro-1-methyl-benzo[6′,7′-a′]quino[2′,3′-a]-5,6-dihydrocarbazole (**3c**)*: White solid; yield: 246 mg (67%); M.p. 199−201 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3281 (NH), 1590 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.13 (br s, 1H, NH), 8.68 (s, 1H, ArH), 8.55 (s, 1H, ArH), 8.05–8.12 (m, 2H, ArH), 7.54–7.47 (m, 3H, ArH), 7.12–7.05 (m, 2H, ArH), 3.52–3.49 (m, 2H, CH_2), 3.22–3.19 (m, 2H, CH_2), 2.59 (s, 3H, CH_3); Anal. calcd. for $C_{24}H_{17}ClN_2$: C, 78.15; H, 4.65; N, 7.59; Found: C, 78.22; H, 4.69; N, 7.63%.

2.3d *3,7-Dichloro-benzo[6′,7′-a′]quino[2′,3′-a]-5,6-dihydrocarbazole (**3d**)*: White solid; yield: 213 mg (55%); M.p. 195−197 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3263 (NH), 1549 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.69 (br s, 1H, NH), 8.60 (s, 1H, ArH), 8.06–8.01 (m, 2H, ArH), 7.58 (m, 1H, ArH), 7.55–7.53 (m, 2H, ArH), 7.39 (d, 2H, ArH, J_o = 8.40 Hz), 7.25 (s, 1H, ArH), 3.53–3.49 (m, 2H, CH_2), 3.19–3.15 (m, 2H, CH_2), Anal. calcd. for $C_{23}H_{14}Cl_2N_2$: C, 70.96; H, 3.62; N, 7.20; Found: C, 70.87; H, 3.66; N, 7.27%.

2.4 *General procedure for the preparation of carbazole substituted pyrido[2,3-a]carbazoles* ***6*** *and* ***7***

A mixture of 2,3,4,9-tetrahydrocarbazol-1-one **1** (1.0 mmol), malononitrile **4**, (1.0 mmol), 9-ethyl-3-carbazole carboxaldehyde **5** (1.0 mmol) and lithium ethoxide (3 equiv.) in 15 mL of ethanol\methanol was heated to reflux for 3 h. The reaction was monitored by TLC which indicated the formation of the product. The excess of solvent was removed by distillation and the mixture was poured into ice-water. The reaction mixture was then neutralized with 5N HCl and extracted with ethyl acetate. The organic layer was thoroughly washed with water and dried over anhydrous Na_2SO_4. Upon removal of the solvent, a brown crude mixture was obtained. It was purified by column chromatography over silica gel using petroleum ether: ethyl acetate (97:3) mixture as eluent to afford the corresponding product, 2-ethoxy/methoxy-4-aryl/heteroaryl-5,6-dihydro-11*H*-pyrido[2,3-*a*]carbazole-3-carbonitrile **6** & **7**.

2.5 *The spectral and analytical data of all the compounds* ***6*** *&* ***7***

2.5a *2-Ethoxy-4-(9′-ethyl-9H-carbazol-3′-yl)-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile (**6a**)*: Yellow solid; yield: 351 mg (73%); M.p. 272−274 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3259 (NH), 2216 (CN), 1544 (C=N);

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.81 (br s, 1H, NH), 8.10 (d, 1H, ArH, J = 8.00 Hz), 8.06 (s, 1H, ArH), 7.58–7.44 (m, 6H, ArH), 7.29–7.27 (m, 1H, ArH), 7.15–7.11 (m, 2H, ArH), 4.64 (q, 2H, C_2-OC**H**$_2$CH$_3$, J = 7.20 Hz), 4.42 (q, 2H, N_9'-C**H**$_2$CH$_3$, J = 7.20 Hz), 2.97–2.94 (m, 4H, CH_2), 1.54–1.48 (m, 6H, C_2-OCH$_2$C**H**$_3$ & N_9'-CH$_2$C**H**$_3$); ^{13}C NMR(100 MHz, $CDCl_3$) (ppm) δ_C: 163.5, 155.4, 148.4, 140.4, 140.0, 137.8, 132.4, 126.8, 126.1, 126.0, 125.8, 124.4, 122.9, 122.7, 121.9, 120.7, 120.6, 120.2, 119.8, 119.2, 118.6 (CN), 116.1, 111.7, 108.7, 108.6, 93.9, 63.1 (C_2-O**C**H$_2$CH$_3$), 37.7 (N_9'-**C**H$_2$CH$_3$), 25.4, 19.4, 14.6 (C_2-OCH$_2$**C**H$_3$), 13.8 (N_9'-CH$_2$**C**H$_3$); Anal. calcd. for $C_{32}H_{26}N_4O$: C, 79.64; H, 5.43; N, 11.61; Found: C, 79.74; H, 5.47; N, 11.57%.

2.5b *2-Ethoxy-4-(9′-ethyl-9H-carbazol-3′-yl)-10-methyl-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile (**6b**)*: Yellow solid; yield: 347 mg (70%); M.p. 271−273 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3449 (NH), 2217 (CN), 1551 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.62 (br s, 1H, NH), 8.10 (d, 1H, ArH, J = 8.00 Hz), 8.06 (s, 1H, ArH), 7.54–7.41 (m, 5H, ArH), 7.26–7.25 (m, 1H, ArH), 7.07 (d, 2H, ArH, J = 8.00 Hz), 4.66 (q, 2H, C_2-OC**H**$_2$CH$_3$, J = 7.20 Hz), 4.42 (q, 2H, N_9'-C**H**$_2$CH$_3$, J = 6.80 Hz), 2.94–2.93 (m, 4H, CH_2), 2.59 (s, 3H, CH_3), 1.54–1.47 (m, 6H, C_2-OCH$_2$C**H**$_3$ & N_9'-CH$_2$C**H**$_3$); ^{13}C NMR(100 MHz, $CDCl_3$) (ppm) δ_C: 163.5, 155.4, 148.5, 140.4, 140.0, 137.4, 132.1, 126.1, 126.1, 126.0, 125.9, 125.0, 122.9, 122.7, 121.9, 120.8, 120.7, 120.6, 120.4, 119.3, 119.2, 117.5 (CN), 116.2, 108.7, 108.6, 93.9, 62.9 (C_2-O**C**H$_2$CH$_3$), 37.7 (N_9'-**C**H$_2$CH$_3$), 25.5, 19.5, 16.7 (CH$_3$), 14.6 (C_2-OCH$_2$**C**H$_3$), 13.8 (N_9'-CH$_2$**C**H$_3$); Anal. calcd. for $C_{33}H_{28}N_4O$: C, 79.81; H, 5.68; N, 11.28; Found: C, 79.90; H, 5.64; N, 11.21%.

2.5c *2-Ethoxy-4-phenyl-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile (**6c**)*: Yellow solid; yield: 292 mg (80%); M.p. 261−263 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3331 (NH), 2216 (CN), 1552 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.80 (br s, 1H, NH), 7.57 (d, 1H, ArH, J_o = 8.00 Hz), 7.53–7.47 (m, 3H, ArH), 7.44 (d, 1H, ArH, J_o = 8.00 Hz), 7.34 (d d, 2H, ArH, J_m = 1.80 Hz & J_o = 7.80 Hz), 7.28 (t, 1H, ArH, J = 7.40 Hz), 7.14 (t, 1H, ArH, J = 7.40 Hz), 4.62 (q, 2H, C_2-OC**H**$_2$CH$_3$, J = 7.20 Hz), 2.96–2.92 (m, 2H, CH_2), 2.87–2.83 (m, 2H, CH_2), 1.51 (t, 3H, C_2-OCH$_2$C**H**$_3$, J = 7.20 Hz); ^{13}C NMR(100 MHz, $CDCl_3$) (ppm) δ_C: 163.4, 154.2, 148.6, 137.8, 135.5, 132.2, 129.2, 129.0, 128.7, 128.4, 126.9, 126.7, 124.6, 121.3, 120.2, 119.9, 118.8 (CN), 115.7, 111.7, 93.2, 63.0 (O**C**H$_2$CH$_3$), 25.2, 19.4, 14.5 (OCH$_2$**C**H$_3$); Anal. calcd. for $C_{24}H_{19}N_3O$: C, 78.88; H, 5.24; N, 11.50; Found: C, 78.79; H, 5.28; N, 11.57%.

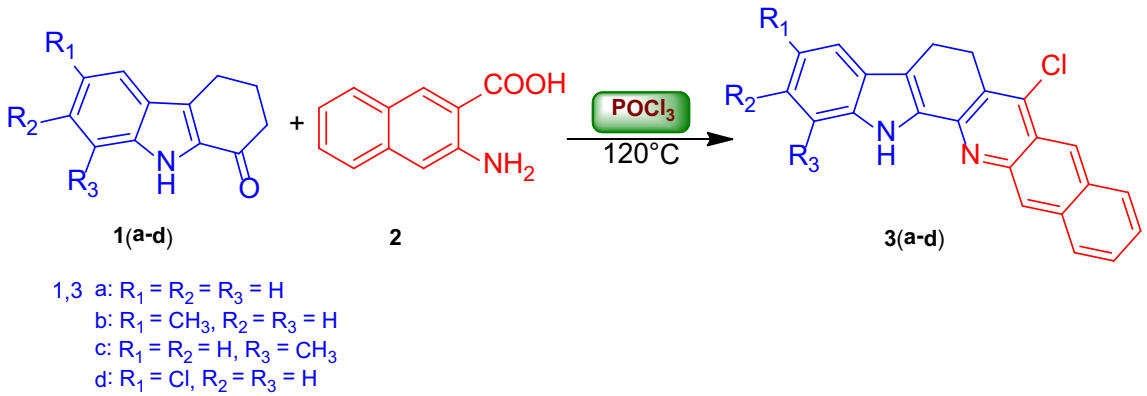
2.5d *2-Ethoxy-10-methyl-4-phenyl-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile (**6d**)*: Yellow solid; yield: 299 mg (79%); M.p. 259−261 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3345 (NH), 2218 (CN), 1553 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.59 (br s, 1H, NH), 7.54–7.47 (m, 3H, ArH), 7.42 (d, 1H, ArH, J_o = 6.80 Hz), 7.35 (d d, 2H, ArH, J_m = 1.60 Hz & J_o = 6.40 Hz), 7.10–7.04 (m, 2H, ArH), 4.64 (q, 2H, C_2-OC**H**$_2$CH$_3$, J = 7.20 Hz), 2.95–2.90 (m, 2H, CH_2), 2.87–2.83 (m, 2H, CH_2), 2.58 (s, 3H, CH_3), 1.52 (t, 3H, C_2-OCH$_2$C**H**$_3$, J = 7.20 Hz); Anal. calcd. for $C_{25}H_{21}N_3O$: C, 79.13; H, 5.58; N, 11.07; Found: C, 79.20; H, 5.54; N, 11.01%.

2.5e *2-Ethoxy-4-(thiophen-2-yl)-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile (**6e**)*: Yellow solid; yield: 255 mg (69%); M.p. 255−257 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3316 (NH), 2216 (CN), 1557 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.77 (br s, 1H, NH), 7.58 (d, 1H, ArH, J_o = 8.00 Hz), 7.53 (d d, 1H, ArH, J_m = 1.20 Hz & J_o = 4.80 Hz), 7.43 (d, 1H, ArH, J_o = 8.00 Hz), 7.29 (d d, 1H, ArH, J_m = 1.20 Hz & J_o = 6.80 Hz), 7.21–7.12 (m, 3H, ArH), 4.61 (q, 2H, C_2-OC**H**$_2$CH$_3$, J = 7.20 Hz), 3.03–2.96 (m, 4H, CH_2), 1.50 (t, 3H, C_2-OCH$_2$C**H**$_3$, J = 7.20 Hz);^{13}C NMR(100 MHz, $CDCl_3$) (ppm) δ_C: 163.5, 148.6, 147.0, 137.9, 134.9, 132.1, 129.0, 127.7, 127.4, 126.7, 124.7, 122.6, 120.3, 119.9, 119.1 (CN), 115.5, 111.7, 94.0, 63.1 (O**C**H$_2$CH$_3$), 25.4, 19.3, 14.5 (OCH$_2$**C**H$_3$); Anal. calcd. for $C_{22}H_{17}N_3OS$: C, 71.14; H, 4.61; N, 11.31; Found: C, 71.23; H, 4.57; N, 11.36%.

2.5f *2-Ethoxy-10-methyl-4-(thiophen-2-yl)-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile (**6f**)*: Yellow solid; yield: 250 mg (65%); M.p. 253−255 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3349 (NH), 2214 (CN), 1552 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.56 (br s, 1H, NH), 7.53 (d d, 1H, ArH, J_m = 1.20 Hz & J_o = 4.80 Hz), 7.43 (d, 1H, ArH, J_o = 7.60 Hz), 7.21–7.14 (m, 2H, ArH), 7.08–7.04 (m, 2H, ArH), 4.63 (q, 2H, C_2-OC**H**$_2$CH$_3$, J = 7.20 Hz), 3.03–2.95 (m, 4H, CH_2), 2.57 (s, 3H, CH_3), 1.50 (t, 3H, C_2-OCH$_2$C**H**$_3$, J = 7.20 Hz); Anal. calcd. for $C_{23}H_{19}N_3OS$: C, 71.66; H, 4.97; N, 10.90; Found: C, 71.72; H, 4.93; N, 10.97%.

2.5g *2-ethoxy-4-(4′-chlorophenyl)-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile (**6g**)*: Yellow solid; yield: 231 mg (58%); M.p. 249−250 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3286 (NH), 2220 (CN), 1644 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.79 (br s, 1H, NH), 7.57 (d, 1H, ArH, J_o = 7.20 Hz), 7.50–7.47 (m, 2H, ArH), 7.44 (d, 1H, ArH, J_o = 8.80 Hz), 7.39–7.38 (m, 1H, ArH), 7.31–7.27 (m, 2H, ArH), 7.16–7.12 (m, 1H, ArH), 4.62 (q, 2H, C_2-OC**H**$_2$CH$_3$, J = 6.80 Hz), 2.97–2.93 (m, 2H, CH_2), 2.85–2.81 (m, 2H, CH_2), 1.50 (t, 3H, C_2-OCH$_2$C**H**$_3$, J = 6.80 Hz); Anal. calcd. for $C_{24}H_{18}ClN_3O$: C, 72.09; H, 4.54; N, 10.51; Found: C, 72.09; H, 4.54; N, 10.51%.

2.5h *2-ethoxy-10-methyl-4-(4′-chlorophenyl)-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile (**6h**)*: Yellow solid; yield: 231 mg (56%); M.p. 250−252 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3267 (NH), 2214 (CN), 1552 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.59 (br s, 1H, NH), 7.51–7.47 (m, 2H, ArH), 7.43 (d, 1H, ArH, J_o = 6.40 Hz), 7.30–7.27 (m, 2H, ArH), 7.10–7.05 (m, 2H, ArH), 4.64 (q, 2H, C_2-OC**H**$_2$CH$_3$, J = 7.20 Hz), 2.96–2.92 (m, 2H, CH_2),



Scheme 1. Synthesis of 7-chloro-benzo[6',7'-*a*']quino[2',3'-*a*]-5,6-dihydrocarbazoles **3**.

Table 1. Scope of the modified Friedlander synthesis of Benzoquinoline-carbazole derivatives.

Entry	R_1	R_2	R_3	Product	Time (h)	Yield (%)
1.	H	H	H	**3a**	5	80
2.	CH_3	H	H	**3b**	5	69
3.	H	H	CH_3	**3c**	5.5	67
4.	Cl	H	H	**3d**	5.5	55

2.85–2.81 (m, 2H, CH_2), 2.57 (s, 3H, CH_3), 1.50 (t, 3H, C_2-$OCH_2C\mathbf{H}_3$, J = 7.20 Hz); Anal. calcd. for $C_{25}H_{20}ClN_3O$: C, 72.55; H, 4.87; N, 10.15; Found: C, 72.55; H, 4.87; N, 10.15%.

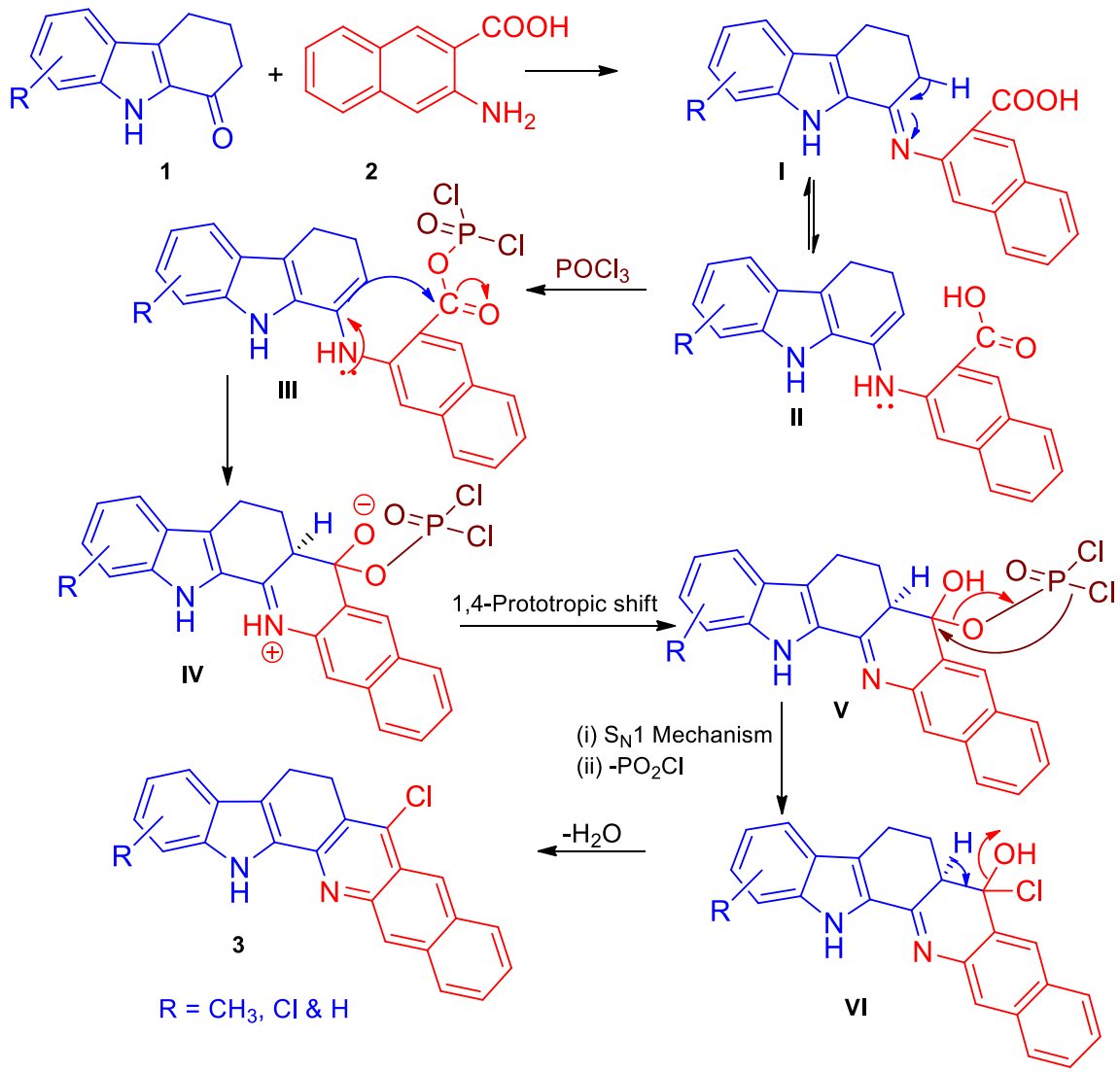
2.5i *2-ethoxy-4-(4′-methylphenyl)-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile* (***6i***): Yellow solid; yield: 333 mg (88%); M.p. 263−265 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3336 (NH), 2216 (CN), 1555 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.79 (br s, 1H, NH), 7.57 (d, 1H, ArH, J_o = 8.40 Hz), 7.44 (d, 1H, ArH, J_o = 8.40 Hz), 7.31 (d, 2H, ArH, J_o = 8.00 Hz), 7.26–7.22 (m, 2H, ArH), 7.13 (t, 1H, ArH, J = 8.00 Hz), 4.61 (q, 2H, C_2-$OC\mathbf{H}_2CH_3$, J = 7.20 Hz), 2.96–2.91 (m, 2H, CH_2), 2.89–2.84 (m, 2H, CH_2), 2.43 (s, 3H, C_4'-CH_3), 1.50 (t, 3H, C_2-$OCH_2C\mathbf{H}_3$, J = 7.20 Hz); ^{13}C NMR(100 MHz, $CDCl_3$) (ppm) δ_C: 163.4, 154.4, 148.5, 138.9, 137.8, 132.5, 132.3, 129.3, 128.3, 126.7, 124.5, 121.4, 120.2, 119.8, 118.7 (CN), 115.8, 111.7, 93.4, 62.9 ($O\mathbf{C}H_2CH_3$), 25.2, 21.36, 19.4 (C_4'-CH_3), 14.5 ($OCH_2\mathbf{C}H_3$); Anal. calcd. for $C_{25}H_{21}N_3O$: C, 79.13; H, 5.58; N, 11.07; Found: C, 79.22; H, 5.54; N, 11.14%.

2.5j *2-ethoxy-10-methyl-4-(4′-methylphenyl)-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile* (***6j***): Yellow solid; yield: 337 mg (86%); M.p. 261−263 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3355 (NH), 2214 (CN), 1554 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.58 (br s, 1H, NH), 7.43–7.40 (m, 1H, ArH), 7.31 (d, 2H, ArH, J_o = 7.60 Hz), 7.25–7.22 (m, 2H, ArH), 7.08–7.04 (m, 2H, ArH), 4.63 (q, 2H, C_2-$OC\mathbf{H}_2CH_3$, J = 6.80 Hz), 2.94–2.92 (m, 2H, CH_2), 2.90–2.84 (m, 2H, CH_2), 2.57 (s, 3H, CH_3), 2.42 (s, 3H, C_4'-CH_3), 1.50 (t, 3H, C_2-$OCH_2C\mathbf{H}_3$, J = 6.80 Hz); Anal. calcd. for $C_{26}H_{23}N_3O$: C, 79.36; H, 5.89; N, 10.68; Found: C, 79.25; H, 5.84; N, 10.72%.

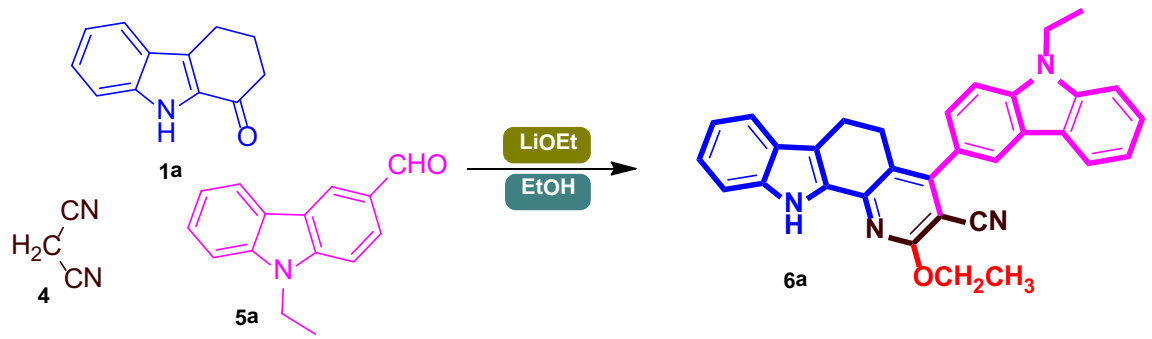
2.5k *2-ethoxy-10-methyl-4-(4′-methoxyphenyl)-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile* (***6k***): Yellow solid; yield: 290 mg (71%); M.p. 256−258 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3299 (NH), 2215 (CN), 1640 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.58 (br s, 1H, NH), 7.43–7.41 (m, 1H, ArH), 7.28 (d d, 2H, ArH, J_m = 2.00 Hz & J_o = 6.80 Hz), 7.12–7.06 (m, 2H, ArH), 7.03 (d d, 2H, ArH, J_m = 2.00 Hz & J_o = 6.80 Hz), 4.63 (q, 2H, C_2-$OC\mathbf{H}_2CH_3$, J = 6.80 Hz), 3.87 (s, 3H, C_4'-OCH_3), 2.93-2.89 (m, 4H, CH_2), 2.57 (s, 3H, CH_3), 1.51 (t, 3H, C_2-$OCH_2C\mathbf{H}_3$, J = 6.80 Hz); Anal. calcd. for $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.66; N, 10.26; Found: C, 76.34; H, 5.64; N, 10.33%.

2.5l *2-Methoxy-4-(9-ethyl-9H-carbazol-3-yl)-10-methyl-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile* (***7a***): Yellow solid; yield: 318 mg (68%); M.p. 263−265 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3375 (NH), 2216 (CN), 1557 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.86 (br s, 1H, NH), 8.10 (d, 1H, ArH, J_o = 7.20 Hz), 8.06 (s, 1H, ArH, J_m = 1.20 Hz), 7.57 (d, 1H, ArH, J_o = 8.00 Hz), 7.54–7.48 (m, 2H, ArH), 7.46–7.42 (m, 3H, ArH), 7.30–7.26 (m, 2H, ArH), 7.13 (t, 1H, ArH, J_o = 7.60 Hz), 4.62 (q, 2H, N_9'-$C\mathbf{H}_2CH_3$, J = 7.20 Hz), 4.18 (s, 3H, C_2-OCH_3), 2.98–2.93 (m, 4H, CH_2), 1.49 (t, 3H, N_9'-$CH_2C\mathbf{H}_3$, J = 7.20 Hz); ^{13}C NMR(100 MHz, $CDCl_3$) (ppm) δ_C: 163.7, 155.4, 148.4, 140.4, 140.0, 137.9, 132.3, 126.1, 126.7, 126.2, 125.7, 124.5, 123.6, 122.7, 122.1, 120.7, 120.6, 120.2, 119.3 (CN), 119.2, 118.8, 111.7, 108.7, 108.6, 54.3 (OCH_3), 37.7 (N_9'-$\mathbf{C}H_2CH_3$), 25.4, 19.4, 13.8 (N_9'-$CH_2\mathbf{C}H_3$); Anal. calcd. for $C_{31}H_{24}N_4O$: C, 79.46; H, 5.16; N, 11.96; Found: C, 79.55; H, 5.12; N, 11.89%.

2.5m *2-Methoxy-4-(9′-ethyl-9H-carbazol-3'-yl)-10-methyl-5,6-dihydro-11H-pyrido[2,3-a]carbazole-3-carbonitrile* (***7b***): Yellow solid; yield: 313 mg (65%); M.p.



Scheme 2. Machanistic rationalization for the formation of **3**.



Scheme 3. Synthesis of 2-ethoxy-4-(9′-ethyl-9H-carbazol-3′-yl)-5,6-dihyro-11H-pyrido[2,3-a]carbazole-3-carbonitrile **6a**.

260−262 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3391 (NH), 2215 (CN), 1556 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 8.75 (br s, 1H, NH), 8.10 (d, 1H, ArH, J_o = 8.60 Hz), 8.58 (d, 1H, ArH, *Jm* = 1.60 Hz), 7.54–7.48 (m, 2H, ArH), 7.46 (m, 2H, ArH), 7.35–7.33 (m, 2H, ArH), 7.27–7.26 (m, 1H, ArH), 7.11 (d d, 1H, ArH, J_m = 1.60 Hz & J_o = 7.60 Hz), 4.42 (q, 2H, N_9'-C**H**$_2$CH$_3$, J = 7.20 Hz), 4.17 (s, 3H, C_2-OCH_3), 2.96–2.90 (m, 4H, CH_2), 2.44 (s, 3H, CH_3),

1.49 (m, 3H, N_9'-$CH_2C\mathbf{H}_3$); Anal. calcd. for $C_{32}H_{26}N_4O$: C, 79.64; H, 5.43; N, 11.61; Found: C, 79.73; H, 5.47; N, 11.54%.

3. Results and Discussion

The two-component Friedländer reaction of 2-aminoaryl ketones with carbonyl compounds containing a reactive α-methylene group in order to obtain benzoquinoline compounds has been known for a long time.[17–22] However, to the best of our knowledge, none of these report the synthesis of benzoquinoline-carbazole derivatives *via* a $POCl_3$ promoted Friedländer reaction.

Prompted by the encouraging importance of benzoquinoline-carbazole derivatives *via* Friedländer reaction, we embarked on the synthesis of 7-chloro-benzo[6′,7′-*a*′]quino[2′,3′-*a*]-5,6-dihydrocarbazole **3** by a modified Friedländer hetero-annulation reaction of 2,3,4,9-tetrahydrocarbazol-1-one **1** with 3-amino-2-naphthoic acid **2** using catalytic amounts of $POCl_3$ under solvent-free condition (Scheme 1). All these reactions were carried out by refluxing an equimolar ratio of the reactants at 120 °C.

Next, we examined the scope of the transformation utilizing the reactivity of different substituted 2,3,4,9-tetrahydrocarbazol-1-ones **1** (**a**–**d**) as substrates; all of the reactions afforded the corresponding benzoquinoline-carbazole products **3** (**a**–**d**) in moderate to good yields (Table 1).

The proposed structures of the synthesized compounds were consistent with their FT-IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analyses. The FT-IR spectral data of **3a** displayed prominent absorption peaks at 3436 and 1592 cm^{-1} due to indole NH and C=N stretchings respectively. The ^{1}H NMR spectrum of **3a** exhibited a broad singlet for the indole NH at δ 9.47 ppm. Two singlets at δ 8.66 and δ 8.52 ppm assigned to C_8 and C_{13} protons. The two multiplet signals in the region of δ 8.04–7.98 ppm due to C_{12} & C_9 protons and δ 7.52–7.47 ppm were attributed to the C_{11} & C_{10}aromatic protons respectively. The signal due to C_4 proton occurred as a doublet at δ 7.62 (J_o = 7.60 Hz) ppm and a doublet at δ 7.39 (J_o = 8.40 Hz) arising from the C_1 proton. A multiplet at δ 7.29-7.27 ppm was assigned to a C_3 proton, a triplet at δ 7.13 (J_o = 7.20 Hz) was assigned to the C_2 proton while the aliphatic protons (C_6 and C_5) resonated as multiplets centered at δ 3.50 ppm and 3.19 ppm respectively. The ^{13}C NMR spectrum of **3a** displayed 23 resonances in agreement with the proposed structure.

The plausible mechanism for the formation of compound **3** has been shown in Scheme 2 as reported earlier by our research group.[23] Initially, 2,3,4,9-tetrahydrocarbazol-1-one **1** is condensed with 3-amino-2-naphthoic acid **2** in the presence of an acid $POCl_3$ as a catalyst to afford the stable geometrical isomer **E** as intermediate **I**. Upon tautomerisation the more stable imine intermediate **I** gave an enamine intermediate **II**. The addition of $POCl_3$ to the carboxylic acid intermediate **II** causes the formation of a mixed anhydride intermediate **III**, which then underwent an intramolecular electrophilic substitution reaction to yield the intermediate **IV** and this intermediate on subsequent 1,4-prototropic shift followed by an S_N1 reaction *cum* PO_2Cl elimination afforded the intermediate **VI**. The trans dehydration of intermediate **VI** gave the hybrid compound, 7-chloro-benzo[6′,7′-*a*′]quino[2′,3′-*a*]-5,6-dihydrocarbazole **3**.

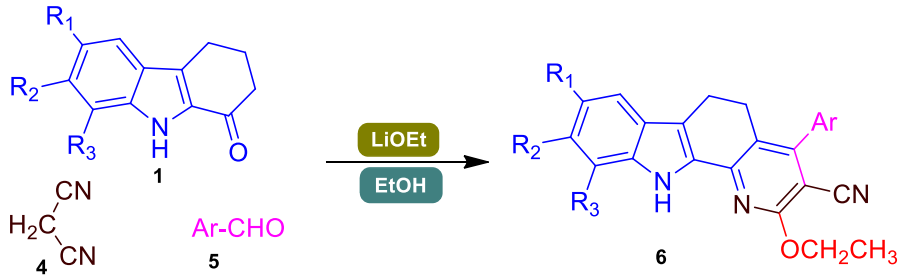
Table 2. Screening of catalyst for the multicomponent synthesis of **6a**[a].

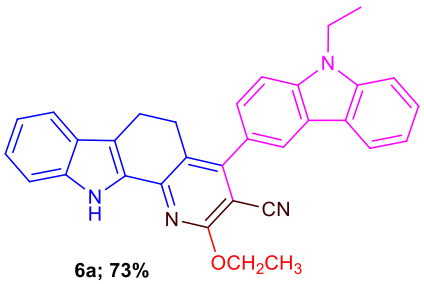
Entry	Solvent	Catalyst (equiv)	Time	Yield[b]
1.	EtOH	Catalyst-free	12	–[c]
2.	EtOH	NaOH	8	20
3.	EtOH	K_2CO_3	8	29
4.	EtOH	Et_3N	6	57
5.	EtOH	DABCO	6	31
6.	EtOH	Morpholine	6	27
7.	EtOH	Piperidine	5	38
8.	EtOH	NaOEt (1)	5	47
9.	EtOH	LiOEt (1)	3	58
10.	EtOH	LiOEt (1.5)	3	61
11.	EtOH	LiOEt (2)	3	68
12.	EtOH	LiOEt (3)	3	73
13.	EtOH	LiOEt (4)	6	67

[a]Reaction of 2, 3, 4, 9-tetrahydrocarbazol-1-one **1a** (1.0 mmol), malononitrile **4** (1.0 mmol) and 9-ethyl-3-carbazolecarboxaldehyde **5a** (1.0 mmol) using LiOEt (3 equiv) under EtOH.
[b]Isolated yields, [c]Trace product.

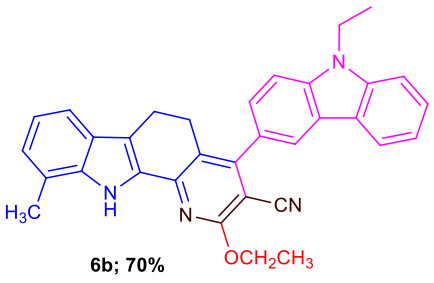
9-Ethyl-3-carbazolecarboxaldehyde derivatives have been utilized as versatile coupling components in the preparation of a number of nitrogen-containing heteroaromatics.[24] The simple carbazoles reported so far from our laboratory were found to have anticancer, antibacterial, antioxidant and photophysical activities.[16] However, the dimerised carbazoles/carbazolyl carbazole derivatives have an electron-rich structure, high thermal stability and unique electrical and optical properties[25,26] compared to its simple carbazoles. The conjugated carbazole dimer enhanced greatly the fluorescence of carbazole.[27] The importance of pyridocarbazole and carbazole dimer derivatives prompted us to design a practical and efficient multicomponent reaction for the preparation of highly functionalized carbazole substituted pyridocarbazole derivatives. Recently, our research group envisaged the possibility of pseudo

Table 3. Scope of aryl/heteroaryl substituted pyrido [2, 3-*a*] carbazoles **6** (**a–k**).

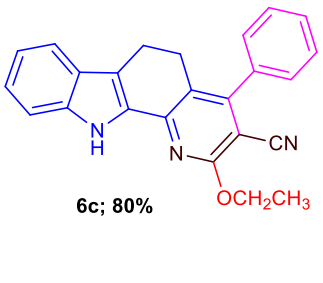




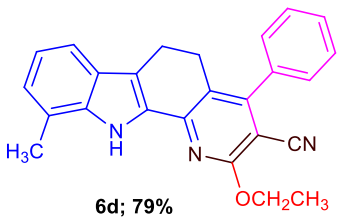
6a; 73%



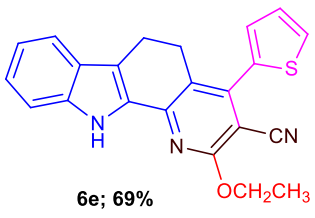
6b; 70%



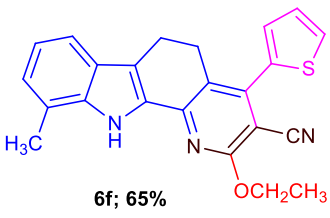
6c; 80%



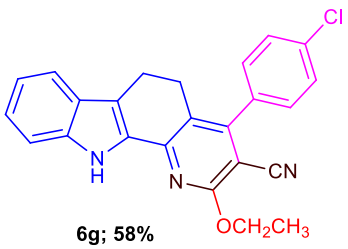
6d; 79%



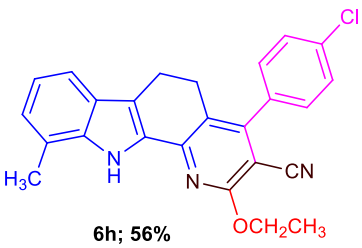
6e; 69%



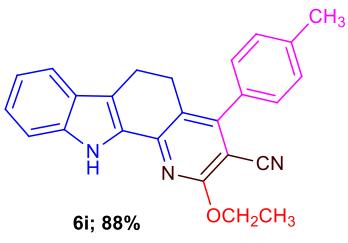
6f; 65%



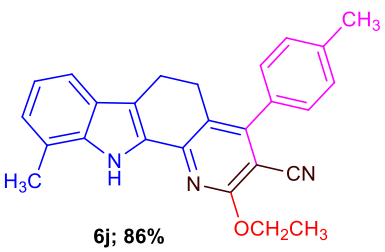
6g; 58%



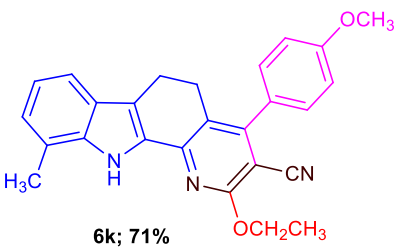
6h; 56%



6i; 88%



6j; 86%



6k; 71%

multicomponent reaction for the preparation of pyridocarbazoles.[28]

The synthetic pathways employed to prepare the targeted derivatives are depicted in Scheme 3. In a one-pot, pseudo three-component heterocyclo condensation process, 2-ethoxy-4-(9′-ethyl-9*H*-carbazol-3′-yl)-5,6-dihyro-11*H*-pyrido[2,3-*a*]carbazole-3-carbonitrile **6a** was obtained *via* a base mediated Michael addition-cyclization of 2,3,4,9-tetrahydrocarbazol-1-one **1a** with malononitrile **4** and 9-ethyl-3-carbazolecarboxaldehyde **5a** in refluxing EtOH. In this reaction, the solvent ethanol could act as both a reactant and a solvent.

Table 2 shows the results obtained from using different reaction conditions for the synthesis of **6a**. In order to justify the significance of base in this multicomponent process, the reaction was first performed in the absence of base wherein the reaction failed to occur even at prolonged reaction time (Table 2, entry 1). In the presence of sodium hydroxide or potassium carbonate, the reaction occurred with isolated yields of **6a** after 8 h of 20% and

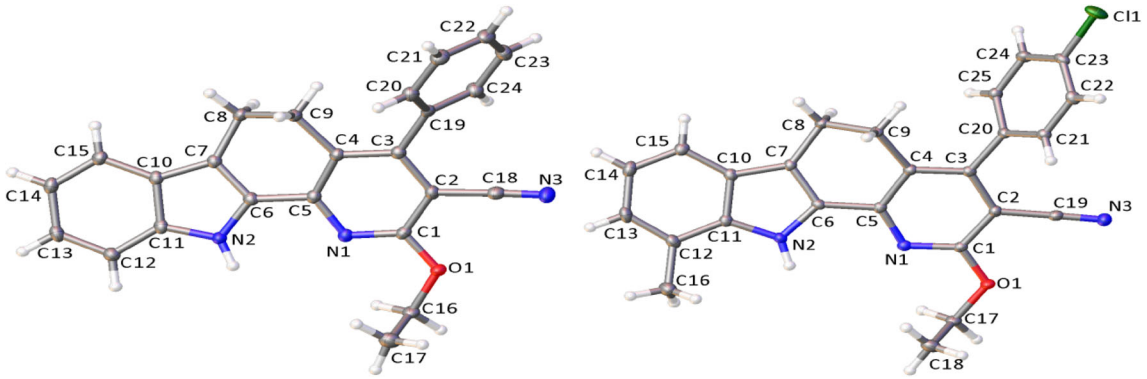
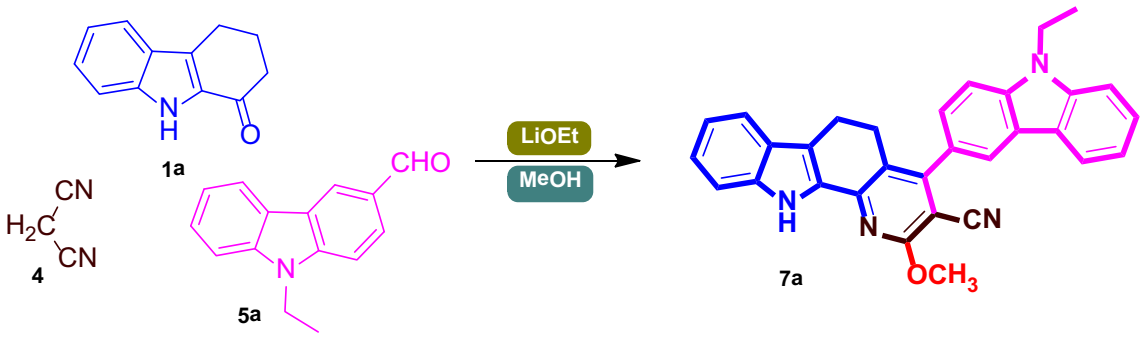


Figure 1. Illustration of the structures of **6c** (left) and **6h** (right) (only one unique molecule shown). Anisotropic displacement parameters are depicted at the 50% probability level.

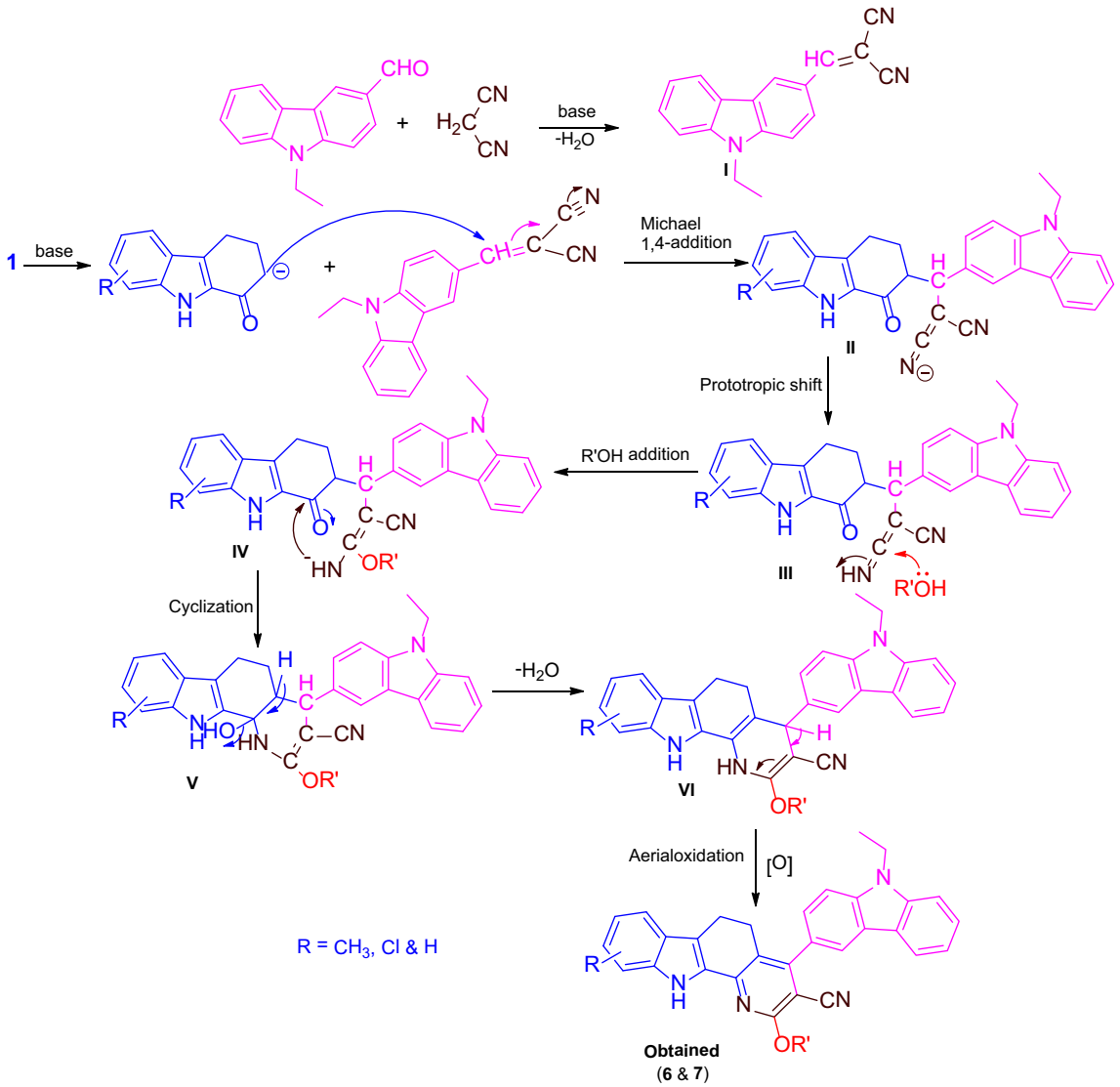


Scheme 4. Synthesis of 2-methoxy-4-(9′-ethyl-9H-carbazol-3′-yl)-5,6-dihyro-11H-pyrido[2,3-a]carbazole-3-carbonitrile **7a**.

29% respectively (Table 2, entries 2 and 3). Carrying out the reaction in the presence of triethylamine (Table 2, entry 4) for 6 h led to a significant increase in the yield of **6a**. The reaction was then performed with bases such as DABCO, morpholine and piperidine (Table 2, entries 5–7), however, these bases were not as effective and resulted in low yields (< 38%) after 5–6 h. Our research group has previously reported the use of NaOEt as a base to afford simple pyridocarbazoles.[28] However, in our present work, the use of NaOEt as a catalyst yielded only 47% of carbazole compound (Table 2, entry 8). Interestingly, the use of one equivalent of LiOEt instead of NaOEt increases the product yield up to 58% after 3 h (Table 2, entry 9). The optimum quantity of LiOEt required was screened and it was found that on increasing the amount of catalyst from 1.0 to 3.0 equiv, the yield of the reaction increased gradually but beyond 3.0 equiv, there was no significant improvement in the rate or yield of the reaction even at prolonged time (Table 2, entries 9–13). From the results, LiOEt was found to be the optimum catalyst for this transformation, wherein 73% of product **6a** was obtained in 3h. The literature survey revealed the catalytic potential of LiOEt in many MCRs.[29]

Based on the appropriate reaction conditions, a series of 2-ethoxy-4-aryl/heteroaryl-5, 11-dihyro-6*H*-pyrido [2, 3-*a*] carbazole-3-carbonitrile derivatives **6** (**a–k**) were synthesized. The results are summarized in Table 3.

The structures of compounds **6** (**a–k**) were established on the basis of their elemental analyses and spectral data. The important diagnostic bands in the FT-IR spectrum of **6a** were assigned, with the stretching vibrations at 3259 and 1544 cm^{-1} corresponding to indole NH and C=N groups respectively and the cyano group stretching vibration assigned to a sharp band at 2216 cm^{-1}. The ^1H NMR spectrum displayed a broad singlet at δ 8.81 ppm attributed to the indole NH proton while the signal from C_5'-H was visible as a doublet at δ 8.10 (J_o = 8.00 Hz) and a sharp singlet at δ 8.06 ppm was assigned to C_4' proton. The six aromatic protons at C_8', C_2', C_1', C_7, C_{10} and C_7' positions resonated as multiplets in the region of δ 7.58–7.44 ppm and the C_6' aromatic proton appeared as a multiplet at δ 7.29–7.27 ppm. The C_9 and C_8 protons were visible as a multiplet at δ 7.15–7.11 ppm, the OCH_2CH_3 protons appeared as a quartet at δ 4.64 (J = 7.20 Hz). The two protons of N_9'-CH_2 appeared as a quartet at δ 4.42 ppm (J = 7.20 Hz)



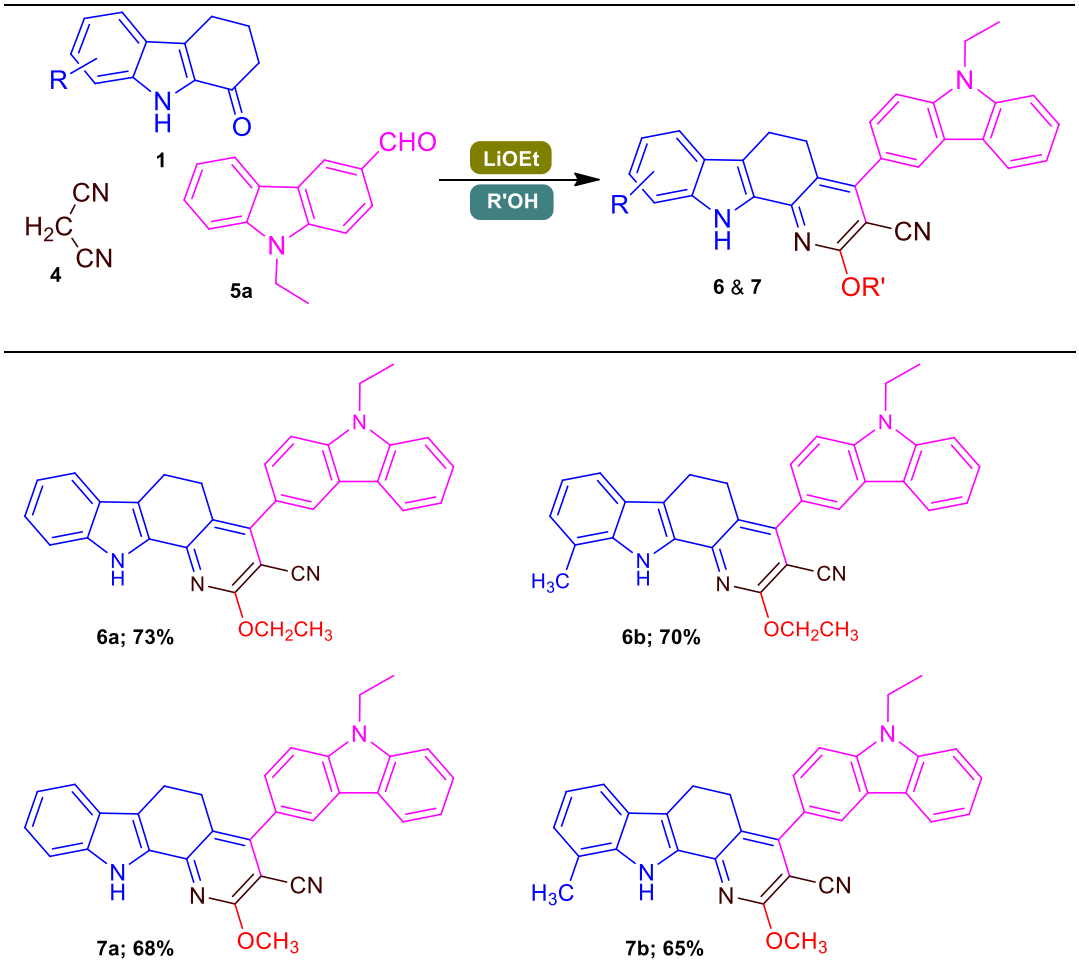
Scheme 5. Machanistic rationalization for the formation of **6** & **7**.

while the methylene protons of C_5 and C_6 resonated as a multiplet at δ 2.97–2.94 ppm. Six methyl protons of $OCH_2\mathbf{CH}_3$ and N_9'-$CH_2\mathbf{CH}_3$ appeared as a multiplet at δ 1.54–1.48 ppm. The ^{13}C NMR spectrum of **6a** displayed 32 resonances in agreement with the proposed structure. The resonance signals at δ 63.1, 37.7, 14.6 and 13.8 were attributed to $O\mathbf{C}H_2CH_3$, N_9'- $\mathbf{C}H_2CH_3$, $OCH_2\mathbf{C}H_3$ and N_9'- $CH_2\mathbf{C}H_3$ carbons. The structures of **6c** and **6h** were further confirmed by single X-ray diffraction studies (Figure 1).

After the successful synthesis of 2-ethoxy-4-(9′-ethyl-9*H*-carbazol-3′-yl)-5,6-dihyro-11*H*-pyrido[2,3-*a*]carbazole-3-carbonitrile **6a,** this catalytic system was used for the synthesis of 2-methoxy-4-(9′-ethyl-9*H*-carbazol-3′-yl)-5,6-dihyro-11*H*-pyrido[2,3-*a*]carbazo le-3-carbonitrile **7a** by the condensation of same reactants in the presence of MeOH instead of EtOH as solvent (Scheme 4).

The analysis of the ^{1}H NMR and ^{13}C NMR data of the products led us to conclude that, when MeOH or EtOH was used as a solvent the reaction mechanism changed from a three-component to a four-component pathway, as depicted in Scheme 5. Initially, the intermediate **I** was formed *via* Knoevenagel condensation of 9-ethyl-3-carbazolecarboxaldehyde with malononitrile in the presence of a base. On subsequent base promoted the 1,4-Michael addition of electron deficient Knoevenagal adduct to the carbanion, derived from the synthon, 2,3,4,9-tetrahydro-1*H*-carbazol-1-one affords the dinitrile intermediate **II**, which undergoes prototropic shift and alcoholic addition facilitated by the base, LiOEt to form an intermediate **IV** through the intermediate **III**. An intramolecular cyclization of intermediate **IV** could furnish the intermediate **V**, which upon dehydration and aerial oxidation could give rise to the product **6/7**.

Table 4. The scope of various 9-ethyl-3-carbazolecarboxaldehyde substituted pyrido [2, 3-*a*] carbazole derivatives.



The scope and general applicability of this methodology have been investigated by using different 2, 3, 4, 9-tetrahydrocarbazol-1-ones **1** (**a, b**) with 9-ethyl-3-carbazolecarboxaldehyde **5a** in different solvent conditions (Table 4).

4. Conclusion

In conclusion, we have demonstrated that differently substituted 2, 3, 4, 9-tetrahydrocarbazol-1-ones and 3-amino-2-naphthoic acid undergo an efficient Friedlander condensation reaction in the presence of $POCl_3$ to yield benzoquinoline-carbazoles. The synthon, 2, 3, 4, 9-tetrahydrocarbazol-1-ones further undergo a pseudo three-component reaction with malononitrile and 9-ethyl-3-carbazole carboxaldehyde to afford a carbazole engrafted pyridocarbazole derivatives. The investigation on solvent effect on this reaction procedure revealed that solvent could change reaction mechanism from three-component to four-component pathway. On the whole, the methods presented here are significant in terms of good yields, short reaction time, cost-effectiveness, readily available substrates and wide scope for production of a diversity of the products and potentially bioactive compounds.

Supplementary Information (SI)

All additional information pertaining to characterization of the compounds using ^{1}H NMR and ^{13}C NMR spectra (Figures S1–S21) and table of Crystal data are given in the supporting information.

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