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Use of silica gel-supported aluminium chloride as reusable catalyst for expeditious synthesis of a novel series of 11-amino-12-aryl-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracene derivatives

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Abstract Efficient synthesis of a novel series of 11-amino-12-aryl-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracene derivatives has been achieved by cyclo-condensation of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitriles and cyclohexanone in the presence of silica gel-supported aluminium chloride (SiO_2–$AlCl_3$) as catalyst under thermal conditions. Thorough optimization of the experimental conditions enabled significant rate enhancement and excellent yields. The starting 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitriles were obtained by one-pot triphenylphosphine-catalyzed multicomponent condensation of 3-hydroxyindole, malononitrile, and aromatic aldehydes. The structures of all the synthesized compounds were established by use of advanced spectroscopic techniques.

Keywords Triphenylphosphine (PPh_3) · Pyrano[3,2-*b*]indole-3-carbonitrile · 11-Amino-12-aryl-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracene · Silica gel-supported aluminium chloride

Introduction

Multicomponent reactions (MCRs) are special, synthetically useful, organic reactions in which three or more different starting materials react to form a final product in a one-pot procedure. Such reactions are atom-efficient because,

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essentially, all the parts of the starting materials are incorporated into the final product. MCRs have been successfully used to generate highly diverse combinatorial libraries for high-throughput screening of biological and pharmacological activity. MCRs comply with the principles of green chemistry, in terms of economy of steps, and with many of the stringent criteria of ideal organic synthesis. These reactions are effective in building highly functionalized small organic molecules from readily available starting materials in a single step with inherent flexibility which enables creation of molecular complexity and diversity coupled with minimization of time, labor, cost, and waste production [1]. Hence, the development of multi-component reaction procedures for synthesis of heterocyclic compounds has attracted substantial interest in modern organic synthesis [2, 3].

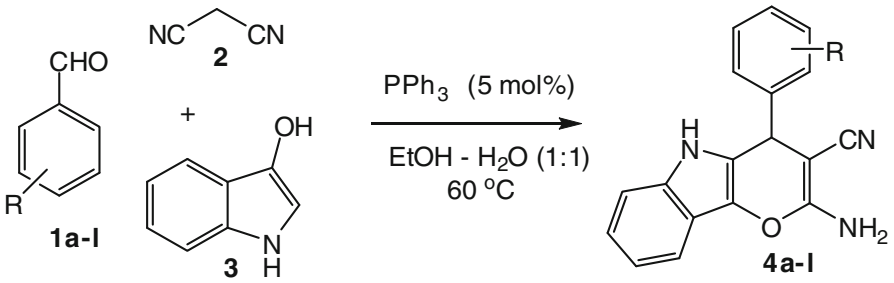
Compounds containing the 4*H*-pyran structure are important because of their interesting pharmacological and biological properties, and many of these compounds have pharmaceutical applications. They are widely used as antimicrobial [4], antiviral [5], mutagenic [6], cancer therapy [7], and antitumor [8] agents. Some of these compounds have photochemical activity [9]. Therefore, synthesis of such compounds has attracted much interest.

Considering the broad range of biological activity of indoles and α-pyrones [10–12], it was believed that combining both these structures in one compound could result in substantial improvement in the biological activity of such compounds. Consequently, many methods have been developed for synthesis of such compounds, including use of KH_2PO_4/ultrasonic irradiation-catalyzed multicomponent synthesis [13], immobilized ionic liquid-catalyzed synthesis [14], intramolecular hetero-Diels–Alder cycloaddition [15], and gold(III) chloride-catalyzed regioselective synthesis [16]. However, these methods often suffer from one or more disadvantages and most give only moderate yields even after prolonged reaction time. This clearly indicates that development of efficient and eco-sustainable methods for synthesis of pyranoindole derivatives is still required.

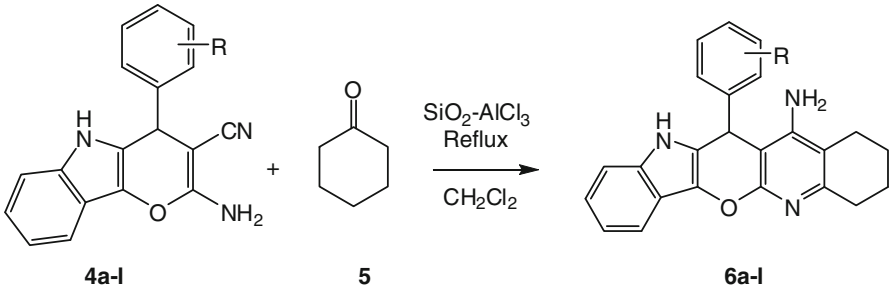
In recent years triphenylphosphine (PPh_3) has attracted much interest in a variety of organic reactions because of the experimental simplicity of its reactions [17, 18]. We have reported use of PPh_3 for synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones/thiones/imines [19] and 4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione [20]. We continue to be interested in developing environmentally benign processes for synthesis of biologically active molecules [21–25], and in this manuscript report the use of PPh_3 in the three-component reaction of aryl aldehydes, 3-hydroxyindole, and malononitrile for synthesis of novel 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives in aqueous ethanol at 60 °C (Scheme 1). This is a one-pot reaction which is not only operationally simple but also consistently gives the corresponding products in good to excellent yields.

Pyranopyridines are important heterocyclic compounds with diverse biological activity, for example anti-bacterial [26], antimyopic [27], anti-proliferative [28], cancer chemopreventive [29], and antiasthmatic [30].

Pyridine, and compounds containing this structure, for example pyranopyridines, are of interest in organic synthesis and many strategies have been adopted for their synthesis [31–33]. Among the different approaches used for synthesis of pyridines, Friedländer annulation reactions of these heterocycles and some of their derivatives



Scheme 1 Synthesis of 2-amino-4,5-dihydro-4-phenylpyrano[3,2-*b*]indole-3-carbonitrile derivatives



Scheme 2 Synthesis of 11-amino-12-aryl-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*] anthracene derivatives

are simple and straightforward. Among a variety of Friedländer syntheses, cyclocondensation of *o*-aminobenzonitrile with ketones has been little investigated, because of such problems as requirement for prolonged reaction times, use of hazardous reagents, and low yields [34–38]. Development of an efficient and convenient procedure for synthesis of compounds containing the pyridine group, for example pyranopyridines, is therefore of substantial interest.

We have achieved facile, rapid, and high-yielding synthesis of a series of 11-amino-12-aryl-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracenes (**6a-l**) by cyclocondensation of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives **4a-l** with cyclohexanone in the presence of silica gel-supported aluminium chloride (SiO_2–$AlCl_3$) in CH_2Cl_2 under reflux in dichloromethane (Scheme 2).

Experimental

Chemicals and apparatus

Chemicals were purchased from Merck, Fluka, and Aldrich. All yields refer to isolated products unless otherwise stated. ^{1}H NMR (500 MHz) and ^{13}C NMR

(125 MHz) spectra were obtained by use of a Bruker DRX-500 Avance at ambient temperature and with TMS as internal standard. In ^{1}H NMR spectra, the J values are expressed in Hz. FT-IR spectra were obtained as KBr discs by use of a Shimadzu spectrometer. Mass spectra were determined on a Varian Saturn 2000 GC–MS instrument. Elemental analysis was performed with a Perkin–Elmer 2400 CHN elemental analyzer.

General procedure for synthesis of pyrano[3,2-*b*]indole derivatives

A mixture of aldehyde (1 mmol), 3-hydroxyindole (1 mmol), malononitrile (1.1 mmol), and PPh_3 (5 mol %) in EtOH-H_2O (1:1) (5 mL) was stirred at 60 °C (Scheme 1). The reaction was monitored by TLC and, after completion of the reaction, the reaction mixture was washed with water and extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate (9:1) as mobile phase.

Spectral data for the pyrano[3,2-*b*]indole derivatives (**4a-l**)

*2-Amino-4,5-dihydro-4-phenylpyrano [3,2-b]indole-3-carbonitrile (**4a**)*

IR (KBr, cm^{-1}): 3,282 and 3,250 (–NH_2), 2,221 (–CN), 1,669 (–NH); ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 5.29 (s, 1H, CH), 6.82 (bs, 2H, NH_2), 6.89–7.04 (m, 2H, Ar–H); 7.11–7.21 (m, 5H, Ar–H); 7.44 (d, 1H, $J = 7.4$, Ar–H); 7.72 (d, 1H, $J = 7.8$, Ar–H), 9.88 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 29.8, 59.1, 103.4, 111.7, 116.9, 120.6, 122.5, 125.5, 128.0, 128.7, 130.3, 130.7, 135.2, 135.4, 137.6, 176.7 ppm; MS (ESI): *m/z* 288 $(M + H)^+$; Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63 %. Found: C, 75.20; H, 4.54; N, 14.55 %.

*2-Amino-4,5-dihydro-4-(4-nitrophenyl)-pyrano[3,2-b]indole-3-carbonitrile (**4b**)*

IR (KBr, cm^{-1}): 3,268 and 3,240 (–NH_2), 2,211 (–CN), 1,664 (–NH); ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 5.29 (s, 1H, CH), 6.71 (bs, 2H, NH_2), 6.81–6.95 (m, 2H, Ar–H); 7.11–7.24 (m, 4H, Ar–H); 7.49 (d, 1H, $J = 7.4$, Ar–H); 7.78 (d, 1H, $J = 7.8$, Ar–H), 9.80 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 31.6, 59.7, 102.6, 110.5, 117.6, 120.5, 122.4, 125.0, 128.0, 128.6, 130.6, 131.3, 135.3, 136.2, 137.9, 177.4 ppm; MS (ESI): *m/z* 333 $(M + H)^+$; Anal. Calcd for $C_{18}H_{12}N_4O_3$: C, 65.06; H, 3.61; N, 16.87 %. Found: C, 65.02; H, 3.53; N, 16.78 %.

*2-Amino-4,5-dihydro-4-(4-chlorophenyl)-pyrano[3,2-b]indole-3-carbonitrile (**4c**)*

IR (KBr, cm^{-1}): 3,270 and 3,232 (–NH_2), 2,215 (–CN), 1,663 (–NH); ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 5.19 (s, 1H, CH), 6.81 (bs, 2H, NH_2), 6.90–7.01 (m, 2H, Ar–H); 7.08–7.17 (m, 4H, Ar–H); 7.39 (d, 1H, $J = 7.4$, Ar–H); 7.80 (d, 1H, $J = 7.8$, Ar–H), 9.77 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 30.5,

60.6, 103.2, 111.2, 118.1, 121.5, 122.4, 125.9, 127.5, 128.5, 130.2, 131.2, 135.0, 135.7, 138.1, 176.1 ppm; MS (ESI): *m/z* 322.5 $(M + H)^+$; Anal. Calcd for $C_{18}H_{12}ClN_3O$: C, 67.19; H, 3.73; N, 13.06 %. Found: C, 67.17; H, 3.66; N, 12.98 %.

*2-Amino-4,5-dihydro-4-(4-N,N-dimethylaminophenly)-pyrano[3,2-b]indole-3-carbonitrile(**4d**)*

IR (KBr, cm^{-1}): 3,280 and 3,246 ($–NH_2$), 2,216 (–CN), 1,655 (–NH); ^1H NMR (500 MHz, DMSO-d_6) *δ:* 2.88 (s, 6H, $N(CH_3)_2$), 5.27 (s, 1H, CH), 6.87 (bs, 2H, NH_2), 6.93–7.05 (m, 2H, Ar–H); 7.13–7.31 (m, 4H, Ar–H); 7.50 (d, 1H, $J = 7.4$, Ar–H); 7.78 (d, 1H, $J = 7.8$, Ar–H), 9.81 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 31.1, 42.7, 60.4, 103.7, 111.7, 118.1, 121.3, 122.3, 125.0, 127.5, 128.4, 130.7, 131.3, 135.7, 136.2, 138.5, 177.2 ppm; MS (ESI): *m/z* 331 $(M + H)^+$; Anal. Calcd for $C_{20}H_{18}N_4O$: C, 72.72; H, 5.45; N, 16.96 %. Found: C, 72.66; H, 5.38; N, 16.89 %.

*2-Amino-4,5-dihydro-4-(4-methylphenyl)-pyrano[3,2-b]indole-3-carbonitrile (**4e**)*

IR (KBr, cm^{-1}): 3,262 and 3,233 ($–NH_2$), 2,213 (–CN), 1,665 (–NH); ^1H NMR (500 MHz, DMSO-d_6) *δ:* 2.23 (s, 3H, CH_3), 5.17 (s, 1H, CH), 6.85 (bs, 2H, NH_2), 6.93–7.05 (m, 2H, Ar–H); 7.11–7.19 (m, 4H, Ar–H); 7.50 (d, 1H, $J = 7.4$, Ar–H); 7.87 (d, 1H, $J = 7.8$, Ar–H), 9.89 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 18.9, 30.7, 61.0, 102.5, 111.4, 117.7, 121.3, 122.4, 125.3, 127.6, 128.5, 130.2, 131.1, 135.0, 135.5, 138.0, 176.5 ppm; MS (ESI): *m/z* 302 $(M + H)^+$; Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.75; H, 4.98; N, 13.95 %. Found: C, 75.76; H, 4.92; N, 13.84 %.

*2-Amino-4,5-dihydro-4-(4-bromophenyl)-pyrano[3,2-b]indole-3-carbonitrile (**4f**)*

IR (KBr, cm^{-1}): 3,277 and 3,244 ($–NH_2$), 2,214 (–CN), 1,659 (–NH); ^1H NMR (500 MHz, DMSO-d_6) *δ:* 5.19 (s, 1H, CH), 6.77 (bs, 2H, NH_2), 6.85–6.97 (m, 2H, Ar–H); 7.16–7.27 (m, 4H, Ar–H); 7.55 (d, 1H, $J = 7.4$, Ar–H); 7.80 (d, 1H, $J = 7.8$, Ar–H), 9.84 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 30.7, 58.9, 103.3, 110.6, 117.6, 121.1, 122.2, 125.4, 128.1, 128.4, 130.1 130.7, 135.5, 135.9, 138.0, 177.4 ppm; MS (ESI): *m/z* 366.9 $(M + H)^+$; Anal. Calcd for $C_{18}H_{12}BrN_3O$: C, 59.03; H, 3.28; N, 11.48 %. Found: C, 58.97; H, 3.29; N, 11.36 %.

*2-Amino-4,5-dihydro-4-(2-nitrophenyl)-pyrano[3,2-b]indole-3-carbonitrile (**4g**)*

IR (KBr, cm^{-1}): 3,277 and 3,246 ($–NH_2$), 2,219 (–CN), 1,660 (–NH); ^1H NMR (500 MHz, DMSO-d_6) *δ:* 5.33 (s, 1H, CH), 6.71 (bs, 2H, NH_2), 6.91–7.02 (m, 2H, Ar–H); 7.08–7.24 (m, 4H, Ar–H); 7.44 (d, 1H, $J = 7.4$, Ar–H); 7.70 (d, 1H, $J = 7.8$, Ar–H), 9.88 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 31.6, 59.5, 102.4, 110.6, 117.8, 121.2, 122.4, 125.2, 128.1, 128.4, 130.1, 130.5, 135.6,

136.4, 137.6, 176.8 ppm; MS (ESI): *m/z* 333 $(M + H)^+$; Anal. Calcd for $C_{18}H_{12}N_4O_3$: C, 65.06; H, 3.61; N, 16.87 %. Found: C, 65.011; H, 3.54; N, 16.88 %.

*2-Amino-4,5-dihydro-4-(4-cyanophenyl)-pyrano[3,2-b]indole-3-carbonitrile (**4h**)*

IR (KBr, cm^{-1}): 3,263 and 3,235 ($–NH_2$), 2,223 (–CN), 1,677 (–NH); ^1H NMR (500 MHz, DMSO-d_6) *δ:* 5.19 (s, 1H, CH), 6.71 (bs, 2H, NH_2), 6.83–6.97 (m, 2H, Ar–H); 7.10–7.31 (m, 4H, Ar–H); 7.58 (d, 1H, $J = 7.4$, Ar–H); 7.87 (d, 1H, $J = 7.8$, Ar–H), 9.81 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 31.3, 59.5, 102.4, 110.4, 116.7, 117.5, 120.5, 122.3, 125.7, 128.5, 128.9, 130.4 130.8, 135.4, 135.8, 138.0, 177.2 ppm; MS (ESI): *m/z* 313 $(M + H)^+$; Anal. Calcd for $C_{19}H_{12}N_4O$: C, 73.07; H, 3.85; N, 17.95 %. Found: C, 73.05; H, 3.77; N, 17.88 %.

*2-Amino-4,5-dihydro-4-(3-methylphenyl)-pyrano[3,2-b]indole-3-carbonitrile (**4i**)*

IR (KBr, cm^{-1}): 3,259 and 3,245 ($–NH_2$), 2,210 (–CN), 1,679 (–NH); ^1H NMR (500 MHz, DMSO-d_6) *δ:* 2.24 (s, 3H, CH_3), 5.22 (s, 1H, CH), 6.79 (bs, 2H, NH_2), 6.88–6.98 (m, 2H, Ar–H); 7.07–7.19 (m, 4H, Ar–H); 7.59 (d, 1H, $J = 7.4$, Ar–H); 7.84 (d, 1H, $J = 7.8$, Ar–H), 9.84 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 18.9, 30.1, 59.7, 102.7, 110.5, 117.9, 121.5, 122.5, 125.6, 127.8, 128.7, 130.4, 131.2, 135.3, 135.9, 137.9, 177.4 ppm; MS (ESI): *m/z* 302 $(M + H)^+$; Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.75; H, 4.98; N, 13.95 %. Found: C, 75.73; H, 4.91; N, 13.84 %.

*2-Amino-4,5-dihydro-4-(2-chlorophenyl)-pyrano[3,2-b]indole-3-carbonitrile (**4j**)*

IR (KBr, cm^{-1}): 3,275 and 3,241 ($–NH_2$), 2,212 (–CN), 1,663 (–NH); ^1H NMR (500 MHz, DMSO-d_6) *δ:* 5.19 (s, 1H, CH), 6.88 (bs, 2H, NH_2), 6.95–7.07 (m, 2H, Ar–H); 7.13–7.19 (m, 4H, Ar–H); 7.42 (d, 1H, $J = 7.4$, Ar–H); 7.87 (d, 1H, $J = 7.8$, Ar–H), 9.83 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 31.2, 60.9, 103.4, 111.3, 117.9, 121.4, 122.6, 125.3, 127.3, 128.1, 130.2, 131.4, 135.4, 136.0, 138.3, 176.9 ppm; MS (ESI): *m/z* 322.5 $(M + H)^+$; Anal. Calcd for $C_{18}H_{12}ClN_3O$: C, 67.19; H, 3.73; N, 13.06 %. Found: C, 67.15; H, 3.67; N, 12.97 %.

*2-Amino-4,5-dihydro-4-(3-bromophenyl)-pyrano[3,2-b]indole-3-carbonitrile (**4k**)*

IR (KBr, cm^{-1}): 3,269 and 3,240 ($–NH_2$), 2,218 (–CN), 1,659 (–NH); ^1H NMR (500 MHz, DMSO-d_6) *δ:* 5.29 (s, 1H, CH), 6.79 (bs, 2H, NH_2), 6.87–6.99 (m, 2H, Ar–H); 7.11–7.24 (m, 4H, Ar–H); 7.54 (d, 1H, $J = 7.4$, Ar–H); 7.81 (d, 1H, $J = 7.8$, Ar–H), 9.92 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 30.1, 59.4, 102.1, 110.4, 117.3, 121.0, 122.3, 125.4, 128.4, 128.7, 130.0 130.6, 135.5, 135.9, 137.3, 176.2 ppm; MS (ESI): *m/z* 366.9 $(M + H)^+$; Anal. Calcd for $C_{18}H_{12}BrN_3O$: C, 59.03; H, 3.28; N, 11.48 %. Found: C, 58.91; H, 3.22; N, 11.44 %.

*2-Amino-4,5-dihydro-4-(4-fluorophenyl)-pyrano[3,2-b]indole-3-carbonitrile (**4l**)*

IR (KBr, cm^{-1}): 3,279 and 3,239 (–NH_2), 2,219 (–CN), 1,666 (–NH); ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 5.16 (s, 1H, CH), 6.79 (bs, 2H, NH_2), 6.91–7.04 (m, 2H,Ar–H); 7.11–7.23 (m, 4H, Ar–H); 7.48 (d, 1H, $J = 7.4$, Ar–H); 7.80 (d, 1H, $J = 7.8$, Ar–H), 9.90 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 30.2, 60.2, 102.1, 110.4, 117.9, 121.2, 122.6, 125.5, 127.4, 128.8, 130.3, 131.4, 135.6, 136.3, 138.7, 177.3 ppm; MS (ESI): *m/z* 306 $(M + H)^+$; Anal. Calcd for $C_{18}H_{12}FN_3O$: C, 70.82; H, 3.93; N, 13.77 %. Found: C, 70.69; H, 3.81; N, 13.69 %.

Preparation of SiO_2–$AlCl_3$

Anhydrous $AlCl_3$ (5.1 g) was added to silica gel (Merck, grade 60, 230–400 Å, washed with 1 M HCl, and dried under vacuum at 80 °C for 72 h; 10.2 g) in carbon tetrachloride (30 mL). The mixture was stirred by use of a magnetic stirrer under reflux for 2 days, in an N_2 atmosphere, then filtered, washed with 50 mL dry CCl_4, and dried under vacuum at 60 °C for 3 h. The determined loading of $AlCl_3$ was 1.3 mmol/g [39].

General procedure for synthesis of substituted hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracenes

A mixture of substituted 2-amino-4,5-dihydro-4-phenylpyrano [3,2-b]indole-3-carbonitrile **4** (1 mmol), cyclohexanone **5** (1.3 mmol), and SiO_2–$AlCl_3$ (0.12 mmol) in CH_2Cl_2 (5 mL) was stirred at reflux (Scheme 2). After completion of the reaction (monitored by TLC), the catalyst was isolated by filtration and washed with CH_2Cl_2. The reaction mixture was poured into a beaker containing ice-cold water. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure and the resulting crude product was purified by column chromatography (40 % ethyl acetate in hexane) to afford pure product **6**. Spent catalyst from different experiments was washed with ether and used again without further drying. The activity of the catalyst was unaffected, even after five cycles.

Spectral data for 11-amino-12-aryl-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracene derivatives (**6a-l**)

*11-Amino-12-aryl-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6a**)*

IR (KBr, cm^{-1}): 3,402, 3,372, 2,929, 1,677, 1,630, 1,466, 1,244, 1,169; ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.77 (m, 4H, CH_2), 2.11 (m, 2H, CH_2), 2.40 (m, 2H, CH_2), 5.28 (s, 1H, CH), 5.58 (s, 2H, NH_2), 6.94–7.02 (m, 2H, Ar–H); 7.17–7.29 (m, 5H, Ar–H); 7.47 (d, 1H, $J = 7.2$, Ar–H); 7.70 (d, 1H, $J = 7.8$, Ar–H), 9.85 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 23.1, 27.3, 31.2, 32.2, 34.7, 103.5, 105.6, 110.9, 117.0, 121.1, 123.0, 127.8, 128.5, 130.1, 131.0, 134.9, 135.5, 137.1, 157.7,

161.0, 166.4 ppm; MS (ESI): *m/z* 368 $(M + H)^+$; Anal. Calcd for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.44 %. Found: C, 78.36; H, 5.73; N, 11.39 %.

*11-Amino-12-(4-nitrophenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6b**)*

IR (KBr, cm^{-1}): 3,408, 3,363, 2,937, 1,670, 1,628, 1,469, 1,242, 1,173; ^1H NMR (500 MHz, DMSO-d_6) *δ:* 1.80 (m, 4H, CH_2), 2.12 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 5.21 (s, 1H, CH), 5.56 (s, 2H, NH_2), 6.88–7.03 (m, 2H, Ar–H); 7.13–7.27 (m, 4H, Ar–H); 7.42 (d, 1H, $J = 7.4$, Ar–H); 7.77 (d, 1H, $J = 8.0$, Ar–H), 9.87 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 22.4, 27.5, 31.0, 32.4, 35.0, 104.0, 105.4, 110.8, 117.3, 121.3, 123.2, 127.9, 128.6, 130.3, 131.2, 135.2, 135.7, 137.0, 157.9, 160.6, 166.8 ppm; MS (ESI): *m/z* 413 $(M + H)^+$; Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58 %. Found: C, 69.80; H, 4.87; N, 13.54 %.

*11-Amino-12-(4-chlorophenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6c**)*

IR (KBr, cm^{-1}): 3,419, 3,367, 2,939, 1,669, 1,622, 1,464, 1,233, 1,172; ^1H NMR (500 MHz, DMSO-d_6) *δ:* 1.79 (m, 4H, CH_2), 2.16 (m, 2H, CH_2), 2.43 (m, 2H, CH_2), 5.27 (s, 1H, CH), 5.63 (s, 2H, NH_2), 6.95–7.06 (m, 2H, Ar–H); 7.15–7.32 (m, 4H, Ar–H); 7.45 (d, 1H, $J = 7.2$, Ar–H); 7.75 (d, 1H, $J = 8.0$, Ar–H), 9.86 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 23.0, 27.6, 31.3, 32.3, 35.0, 104.1, 105.3, 111.3, 116.6, 120.5, 123.2, 128.4, 128.8, 130.2, 131.0, 134.8, 135.3, 137.3, 157.8, 160.4, 166.7 ppm; MS (ESI): *m/z* 402 $(M + H)^+$; Anal. Calcd for $C_{24}H_{20}ClN_3O$: C, 71.73; H, 5.02; N, 10.46 %. Found: C, 71.66; H, 4.99; N, 10.40 %.

*11-Amino-12-(4-N,N-dimethylaminophenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6d**)*

IR (KBr, cm^{-1}): 3,422, 3,370, 2,930, 1,666, 1,634, 1,465, 1,235, 1,170; ^1H NMR (500 MHz, DMSO-d_6) *δ:* 1.78 (m, 4H, CH_2), 2.10 (m, 2H, CH_2), 2.41 (m, 2H, CH_2), 2.79 (s, 6H, $N(CH_3)_2$), 5.32 (s, 1H, CH), 5.60 (s, 2H, NH_2), 6.87–7.00 (m, 2H, Ar–H); 7.14–7.30 (m, 4H, Ar–H); 7.52 (d, 1H, $J = 7.4$, Ar–H); 7.74 (d, 1H, $J = 7.8$, Ar–H), 9.89 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 22.7, 28.0, 31.0, 32.1, 34.7, 43.5, 103.5, 105.5, 111.5, 116.5, 120.6, 122.8, 128.3, 128.9, 130.6, 130.9, 135.3, 135.7, 137.6, 158.2, 160.7, 165.8 ppm; MS (ESI): *m/z* 411 $(M + H)^+$; Anal. Calcd for $C_{26}H_{26}N_4O$: C, 76.07; H, 6.38; N, 13.65 %. Found: C, 76.00; H, 6.31; N, 13.59 %.

*11-Amino-12-(4-methylphenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6e**)*

IR (KBr, cm^{-1}): 3,416, 3,368, 2,944, 1,675, 1,630, 1,467, 1,237, 1,175; ^1H NMR (500 MHz, DMSO-d_6) *δ:* 1.79 (m, 4H, CH_2), 2.09 (m, 2H, CH_2), 2.20 (s, 3H, CH_3),

2.39 (m, 2H, CH_2), 5.31 (s, 1H, CH), 5.57 (s, 2H, NH_2), 6.93–7.07 (m, 2H, Ar–H); 7.13–7.29 (m, 4H, Ar–H); 7.49 (d, 1H, $J = 7.4$, Ar–H); 7.82 (d, 1H, $J = 7.8$, Ar–H), 9.92 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 18.4, 23.1, 27.5, 30.9, 32.6, 34.5, 103.7, 105.8, 111.4, 116.8, 120.8, 122.6, 128.4, 128.9, 130.5, 131.0, 134.8, 135.6, 137.4, 158.4, 161.2, 165.7 ppm; MS (ESI): *m/z* 382 $(M + H)^+$; Anal. Calcd for $C_{25}H_{23}N_3O$: C, 78.71; H, 6.08; N, 11.02 %. Found: C, 78.66; H, 6.02; N, 10.98 %.

*11-Amino-12-(4-bromophenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6f**)*

IR (KBr, cm^{-1}): 3,410, 3,355, 2,931, 1,680, 1,626, 1,464, 1,231, 1,177; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.81 (m, 4H, CH_2), 2.10 (m, 2H, CH_2), 2.40 (m, 2H, CH_2), 5.28 (s, 1H, CH), 5.60 (s, 2H, NH_2), 6.87–6.99 (m, 2H, Ar–H); 7.17–7.33 (m, 4H, Ar–H); 7.50 (d, 1H, $J = 7.2$, Ar–H); 7.80 (d, 1H, $J = 8.0$, Ar–H), 9.94 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 22.6, 27.4, 30.8, 32.5, 34.6, 103.9, 105.7, 111.6, 117.3, 120.9, 122.7, 127.7, 128.5, 130.4, 130.9, 135.3, 135.7, 137.5, 158.0, 160.8, 166.4 ppm; MS (ESI): *m/z* 447 $(M + H)^+$; Anal. Calcd for $C_{24}H_{20}BrN_3O$: C, 64.58; H, 4.52; N, 9.41 %. Found: C, 64.50; H, 4.51; N, 9.39 %.

*11-Amino-12-(2-nitrophenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6g**)*

IR (KBr, cm^{-1}): 3,400, 3,360, 2,935, 1,681, 1,629, 1,466, 1,240, 1,166; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.84 (m, 4H, CH_2), 2.12 (m, 2H, CH_2), 2.46 (m, 2H, CH_2), 5.25 (s, 1H, CH), 5.64 (s, 2H, NH_2), 6.95–7.06 (m, 2H, Ar–H); 7.16–7.34 (m, 4H, Ar–H); 7.51 (d, 1H, $J = 7.2$, Ar–H); 7.74 (d, 1H, $J = 8.0$, Ar–H), 9.90 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 22.8, 27.2, 31.3, 32.3, 34.8, 104.0, 105.6, 111.8, 116.8, 120.5, 122.9, 128.2, 128.6, 130.0, 130.8, 135.5, 135.9, 137.3, 158.1, 160.7, 166.7 ppm; MS (ESI): *m/z* 413 $(M + H)^+$; Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58 %. Found: C, 69.84; H, 4.907; N, 13.51 %.

*11-Amino-12-(4-cyanophenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6h**)*

IR (KBr, cm^{-1}): 3,413, 3,367, 2,928, 1,680, 1,631, 1,473, 1,235, 1,168; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.83 (m, 4H, CH_2), 2.11 (m, 2H, CH_2), 2.43 (m, 2H, CH_2), 5.22 (s, 1H, CH), 5.59 (s, 2H, NH_2), 6.88–7.01 (m, 2H, Ar–H); 7.19–7.35 (m, 4H, Ar–H); 7.54 (d, 1H, $J = 7.4$, Ar–H); 7.70 (d, 1H, $J = 7.8$, Ar–H), 9.96 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.0, 28.2, 31.2, 32.0, 34.9, 103.6, 105.4, 110.5, 116.6, 117.2, 121.2, 123.1, 128.3, 128.8, 130.4, 130.9, 134.9, 135.3, 137.7, 157.8, 161.2, 165.9 ppm; MS (ESI): *m/z* 393$(M + H)^+$; Anal. Calcd for $C_{25}H_{20}N_4O$: C, 76.51; H, 5.14; N, 14.28 %. Found: C, 76.44; H, 5.10; N, 14.25 %.

*11-Amino-12-(3-methylphenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6i**)*

IR (KBr, cm^{-1}): 3,417, 3,372, 2,930, 1,676, 1,630, 1,472, 1,237, 1,170; ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.77 (m, 4H, CH_2), 2.07 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.37 (m, 2H, CH_2), 5.30 (s, 1H, CH), 5.61 (s, 2H, NH_2), 6.90–7.03 (m, 2H, Ar–H); 7.15–7.29 (m, 4H, Ar–H); 7.49 (d, 1H, $J = 7.2$, Ar–H); 7.69 (d, 1H, $J = 7.8$, Ar–H), 9.89 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 19.0, 22.5, 27.7, 31.5, 32.5, 35.2, 103.9, 105.5, 110.8, 117.3, 121.4, 123.0, 128.4, 128.9, 130.6, 131.2, 135.5, 135.8, 137.8, 157.9, 161.0, 165.8 ppm; MS (ESI): *m/z* 382 $(M + H)^+$; Anal. Calcd for $C_{25}H_{23}N_3O$: C, 78.71; H, 6.08; N, 11.02 %. Found: C, 78.63; H, 6.07; N, 11.00 %.

*11-Amino-12-(2-chlorophenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6j**)*

IR (KBr, cm^{-1}): 3,421, 3,364, 2,932, 1,674, 1,632, 1,470, 1,233, 1,171; ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.80 (m, 4H, CH_2), 2.11 (m, 2H, CH_2), 2.40 (m, 2H, CH_2), 5.27 (s, 1H, CH), 5.64 (s, 2H, NH_2), 6.92–7.06 (m, 2H, Ar–H); 7.12–7.30 (m, 4H, Ar–H); 7.48 (d, 1H, $J = 7.4$, Ar–H); 7.71 (d, 1H, $J = 7.8$, Ar–H), 9.87 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 22.4, 27.5, 31.6, 32.7, 35.0, 103.7, 105.9, 110.9, 116.7, 121.0, 122.5, 127.7, 128.4, 130.3, 131.3, 135.6, 135.9, 137.4, 158.0, 160.5, 166.4 ppm; MS (ESI): *m/z* 402 $(M + H)^+$;Anal. Calcd for $C_{24}H_{20}ClN_3O$: C, 71.73; H, 5.02; N, 10.46 %. Found: C, 71.64; H, 5.03; N, 10.44 %.

*11-Amino-12-(3-bromophenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6k**)*

IR (KBr, cm^{-1}): 3,424, 3,360, 2,937, 1,672, 1,627, 1,464, 1,237, 1,173; ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.85 (m, 4H, CH_2), 2.17 (m, 2H, CH_2), 2.47 (m, 2H, CH_2), 5.26 (s, 1H, CH), 5.60 (s, 2H, NH_2), 6.88–7.00 (m, 2H, Ar–H); 7.16–7.33 (m, 4H, Ar–H); 7.47 (d, 1H, $J = 7.4$, Ar–H); 7.73 (d, 1H, $J = 8.0$, Ar–H), 9.91 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 22.3, 27.6, 31.3, 32.5, 35.2, 103.5, 104.9, 111.4, 116.9, 120.8, 122.7, 128.4, 128.8, 130.4, 130.9, 134.7, 135.5, 137.3, 158.5, 160.7, 166.9 ppm; MS (ESI): *m/z* 447 $(M + H)^+$; Anal. Calcd for $C_{24}H_{20}BrN_3O$: C, 64.58; H, 4.52; N, 9.41 %. Found: C, 64.54; H, 4.53; N, 9.35 %.

*11-Amino-12-(4-fluorophenyl)-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-b]anthracene (**6l**)*

IR (KBr, cm^{-1}): 3,411, 3,362, 2,940, 1,673, 1,625, 1,463, 1,235, 1,175; ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.81 (m, 4H, CH_2), 2.15 (m, 2H, CH_2), 2.45 (m, 2H, CH_2), 5.28 (s, 1H, CH), 5.63 (s, 2H, NH_2), 6.87–7.03 (m, 2H, Ar–H); 7.17–7.31 (m, 4H, Ar–H); 7.52 (d, 1H, $J = 7.2$, Ar–H); 7.75 (d, 1H, $J = 8.0$, Ar–H), 9.89 (bs, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 22.2, 27.9, 30.7, 32.4, 34.7, 103.8, 104.8, 111.6, 117.4, 120.9, 122.8, 128.2, 128.6, 130.5, 131.1, 135.3, 135.7 137.7, 158.2,

160.9, 166.0 ppm; MS (ESI): *m*/*z* 386 $(M + H)^+$; Anal. Calcd for $C_{24}H_{20}FN_3O$: C, 74.79; H, 5.23; N, 10.90 %. Found: C, 74.73; H, 5.19; N, 10.85 %.

Results and discussion

Herein we report a green, efficient, and rapid procedure, with SiO_2–$AlCl_3$ as catalyst, for synthesis of 11-amino-12-aryl-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracene derivatives in excellent yields by reaction of 2-amino-4,5-dihydro-4-phenylpyrano[3,2-*b*]indole-3-carbonitrile derivatives and cyclohexanone. To synthesize the 2-amino-4,5-dihydro-4-phenyl-pyrano[3,2-*b*]indole-3-carbonitrile derivatives, we investigated the three-component condensation of benzaldehyde **1a**, malononitrile **2**, and 3-hydroxyindole **3**, as model reaction, in the presence of 5 mol% PPh_3 as catalyst, under different conditions at 60 °C (Table 1).

Initially, we tested the effect of different solvents. Use of 1,4-dioxane, CH_2Cl_2, water, and ethanol was investigated (Table 1, entries 1–4). Reaction without solvent at 60 °C was not very successful (Table 1, entry 5). Reaction under reflux in protic solvents, for example H_2O or EtOH, gave better yields (Table 1, entries 3 and 4). Hence, the model reaction was studied at different EtOH–H_2O solvent mixtures. When the reaction was performed in EtOH–H_2O (30:70 *v*/*v*) and EtOH–H_2O (70:30 *v*/*v*) the yield was 73 and 85 % respectively (Table 1, entries 6 and 8). EtOH–H_2O (50:50 *v*/*v*) was proved to be the most suitable solvent for this condensation in terms of yield and reaction time (Table 1, entry 7). We also evaluated the amount of PPh_3 required for the reaction. It was found that when the amount of catalyst was reduced from 5 to 2 mol%, the yield decreased from 92 to 77 % (Table 1, entry 9). Use of 5 mol% of PPh_3 maintained the yield at 92 %, so this amount is sufficient to promote the reaction. In the presence of more than this amount of catalyst, neither

Table 1 Synthesis of 2-amino-4,5-dihydro-4-phenyl-pyrano[3,2-*b*]indole-3-carbonitrile (**4a**) in the presence of PPh_3 as catalyst under different reaction conditions

Entry	Solvent	Amount of PPh_3 catalyst (mol%)	Time (min)	Yield (%)[a]
1	1,4-Dioxane	5	120	52
2	CH_2Cl_2	5	120	61
3	H_2O	5	120	70
4	EtOH	5	120	76
5	None	5	120	33
6	EtOH–H_2O (30:70 *v*/*v*)	5	60	73
7	EtOH–H_2O (50:50 *v*/*v*)	5	40	92
8	EtOH–H_2O (70:30 *v*/*v*)	5	60	85
9	EtOH–H_2O (50:50 *v*/*v*)	2	40	77
10	EtOH–H_2O (50:50 *v*/*v*)	8	40	92

Reaction conditions: benzaldehyde (1 mmol), 3-hydroxyindole (1 mmol), malononitrile (1.1 mmol) at 60 °C

[a] Isolated yield

yield nor the reaction time was improved (Table 1, entry 10). Thus, the best result was obtained by use of 5 mol% catalyst in 50 % aqueous ethanol under reflux (Table 1, entry 7).

It is worth mentioning that it has previously been reported [12] that use of ultrasonic irradiation with KH_2PO_4 as catalyst resulted in no reaction in the presence of proton acids and classical Lewis acids, for example $AlCl_3$, $ZnCl_2$, TsOH, NH_2SO_3H, $Cu(OTf)_2$, and $Zn(OTf)_2$, as catalysts. Hence, we used PPh_3 as catalyst in 50 % aqueous ethanol under thermal conditions, which enabled synthesis of the expected products in excellent yields. To show that PPh_3 is an efficient catalyst, we conducted the model reaction in the presence of $AlCl_3$, ferric hydrogen sulfate $Fe(HSO_4)_3$), hexadecyldimethylbenzyl ammonium bromide (HDMBAB), KF/Al_2O_3, and $NaHCO_3$ as catalysts (Table 2, entries 1–5). Yields were lower than when PPh_3 was used.

Encouraged by the success of this three-component reaction, synthesis of diverse 2-amino-4,5-dihydro-4-phenyl-pyrano[3,2-*b*]indole-3-carbonitrile derivatives **4a-l** was undertaken. Aromatic aldehydes bearing electron-withdrawing and electron-donating groups were found to result in very good yields (Table 3, entries 1–12).

The mechanism proposed for preparation of the 2-amino-4,5-dihydro-4-phenyl-pyrano[3,2-*b*]indole-3-carbonitrile derivatives is illustrated in Scheme 3. Olefination of the aldehydes with malononitrile is induced by activation of the aldehydes by PPh_3, producing intermediate **a**. This intermediate undergoes coupling with malononitrile to form 2-arylidenemalononitrile, with loss of the Ph_3P. 2-Arylidenemalononitrile is not sufficiently reactive to react with Ph_3P, and attachment of 1*H*-indol-3-ol occurs, giving intermediate **b**. Activation of the nitrile group by Ph_3P (intermediate **c**), hydrogen shift, and cyclization, with loss of Ph_3P, results in formation of intermediate **d**, which is converted into the desired product via a 1,3 hydrogen shift.

Because catalyst reusability is extremely important in commercial applications, recovery and reusability of the PPh_3 was investigated. After completion of the reaction, the reaction mixture was cooled to ambient temperature, CH_2Cl_2 was added, and the PPh_3 was isolated by filtration. The recycled catalyst has been used

Table 2 Evaluation of the activity of different catalysts in the condensation of benzaldehyde, malononitrile, and 3-hydroxyindole in EtOH–H_2O (50:50 *v/v*) at 60 °C

Entry	Catalyst	Amount of catalyst (mol%)	Time (min)	Yield (%)[a]
1	$AlCl_3$	10	120	48
2	$Fe(HSO_4)_3$	10	120	54
3	HDMBAB	10	180	69
4	KF–Al_2O_3	10	180	74
5	$NaHCO_3$	10	240	59
6	PPh_3	5	40	92

Reaction conditions: benzaldehyde (1 mmol), 3-hydroxyindole (1 mmol), malononitrile (1.1 mmol) at 60 °C

[a] Isolated yield

Table 3 Synthesis of 2-amino-4,5-dihydro-4-phenyl-pyrano[3,2-*b*]indole-3-carbonitrile derivatives from aromatic aldehydes, 3-hydroxyindole, and malononitrile with PPh_3 (5 mol%) as catalyst

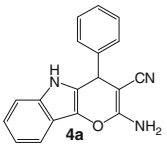
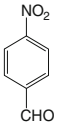
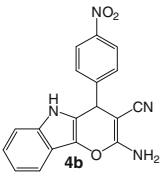
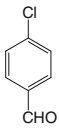
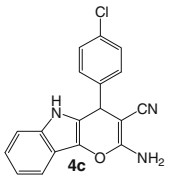
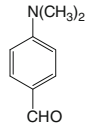
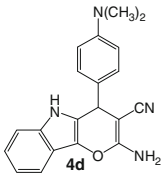
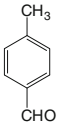
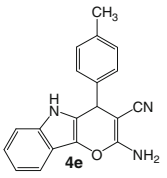
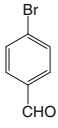
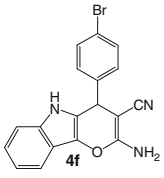
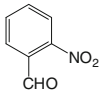
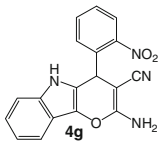
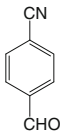
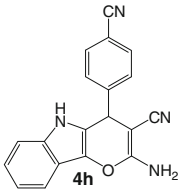
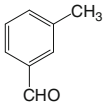
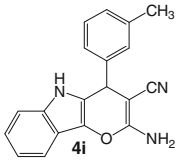
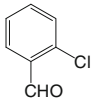
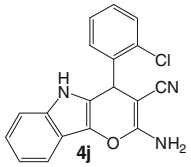
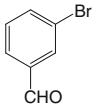
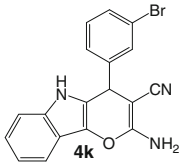
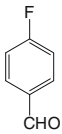
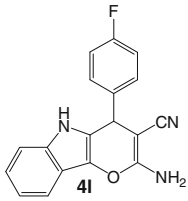
Entry	Aldehyde	Product	Time (min)	Yield (%)[b]
1		 **4a**	40	92
2		 **4b**	30	90
3		 **4c**	30	91
4		 **4d**	50	85
5		 **4e**	50	86
6		 **4f**	30	91
7		 **4g**	40	89

Table 3 continued

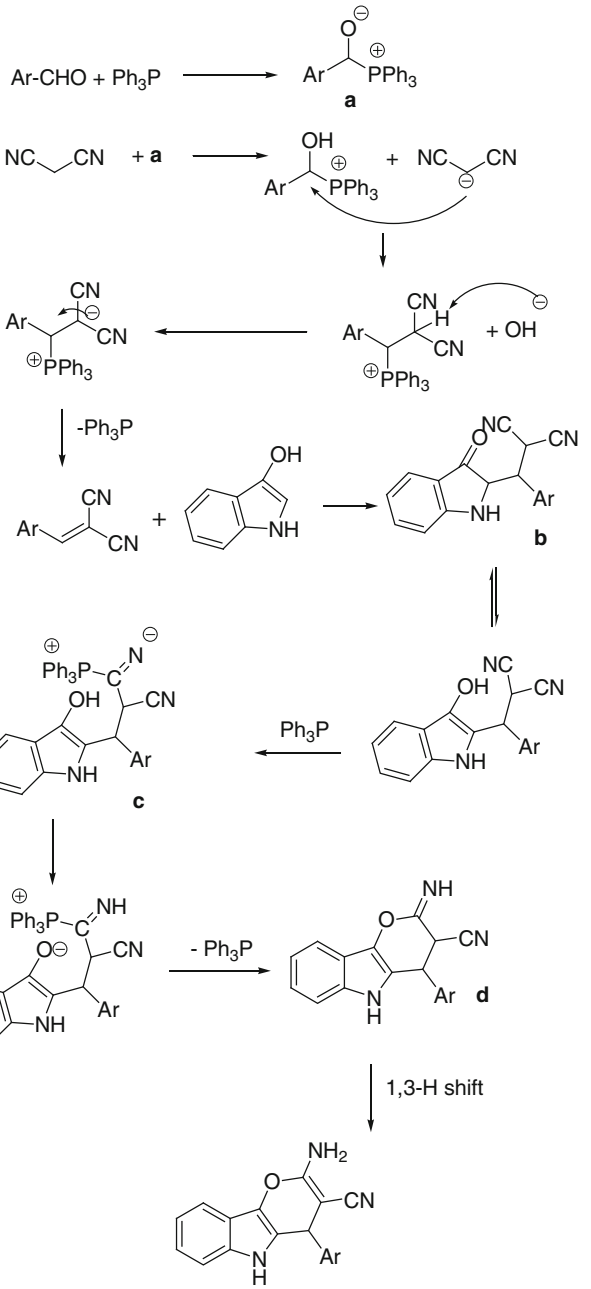
Entry	Aldehyde	Product	Time (min)	Yield (%)[b]
8		 **4h**	40	88
9		 **4i**	50	87
10		 **4j**	50	87
11		 **4k**	30	89
12		 **4l**	30	92

Reaction conditions: aromatic aldehyde (1 mmol), 3-hydroxyindole (1 mmol), malononitrile (1.1 mmol), PPh_3 (5 mol%) in EtOH–H_2O (50:50 *v*/*v*) at 60 °C

[a] Isolated yield

in the next run. The PPh_3 catalyst could be reused four times without any loss of its activity (Fig. 1).

After synthesis of the 2-amino-4,5-dihydro-4-aryl-pyrano[3,2-*b*]indole-3-carbonitrile derivatives **4a-l**, we synthesized 11-amino-12-aryl-hexahydro-5-oxa-6,13-



Scheme 3 Proposed mechanism for preparation of 2-amino-4,5-dihydro-4-phenyl-pyrano[3,2-*b*]indole-3-carbonitrile derivatives

diaza-indeno[1,2-*b*]anthracene derivatives **6a-l**. To optimize the reaction conditions, we initially investigated synthesis of the pyranopyridine **6a** by reaction of **4a** with cyclohexanone **5**, with $AlCl_3$ as catalyst, in CH_2Cl_2 under reflux. The product was obtained in 62 % yield in 2.0 h (Table 4, entry 1).

Aluminium chloride is one of the most widely used Lewis acids. It is very active, soluble in many organic solvents, and inexpensive. Unfortunately, it is often too powerful as an acid, giving unwanted side reactions. When the reaction is complete, the only viable method for separating the aluminium chloride is by use of a destructive water quench, leading to large volumes of hazardous waste. Thus, use of aluminium chloride can lead to violations of several of the principles of green chemistry by release into the environment of hazardous substances, by use of volatile organic solvents, by use of reagent-like quantities that are lost on work up, and as a result of unselective reactions that do not lead to maximum incorporation of the starting materials in the product. There have been several attempts to immobilize aluminium chloride to help overcome these problems.

A literature survey revealed that the acidic properties of $AlCl_3$ change when it is supported on the surface of solid material such as silica, resulting in a material with strong Brønsted and Lewis acidity [40]. Thus our use as catalyst of SiO_2–$AlCl_3$ prepared by addition of anhydrous $AlCl_3$ to silica gel in CCl_4 under reflux [39].

We then performed the reaction with SiO_2–$AlCl_3$ (0.12 mmol) as catalyst in CH_2Cl_2 under reflux, and the desired pyranopyridine **6a** was formed in 88 % in 1.2 h (Table 4, entry 2). We then optimized the quantity of catalyst. Reducing the molar proportion of SiO_2–$AlCl_3$ substantially reduced the yield of **6a** (Table 4, entries 3 and 4) whereas increasing the molar proportion did not improve the yield (Table 4, entry 5). No products were detectable when other Lewis acids, for example $CaCl_2$, $Bi(NO_3)_3$, $BiCl_3$, $Cu(OTf)_2$, $InCl_3$, and $FeCl_3$ (Table 4, entries

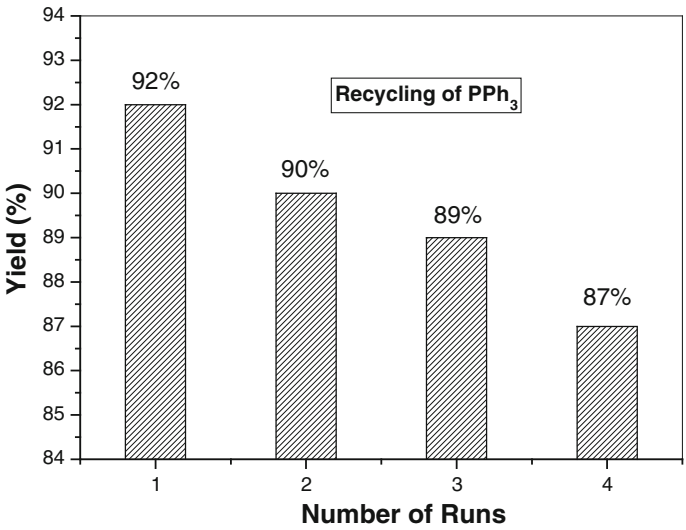


Fig. 1 Recyclability of the catalyst. PPh_3 could be reused four times as catalyst without loss of its activity in the synthesis of 2-amino-4,5-dihydro-4-phenyl-pyrano[3,2-*b*]indole-3-carbonitrile

9–14), or other solvents, for example ethanol, methanol, and acetonitrile, were used (Table 4, entries 6–8). It is concluded from the table that SiO_2–$AlCl_3$ in CH_2Cl_2 under reflux affords the best result. Unlike $AlCl_3$, SiO_2–$AlCl_3$ is a milder catalyst which forms no stable complex with the starting materials and/or products. The efficiency of SiO_2–$AlCl_3$ may also be attributed to its large surface area and its remarkable ability to act as a water scavenger.

Synthesis of a novel series of 11-amino-12-aryl-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracene derivatives **6a-l** was achieved by cyclocondensation of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives **4a–l** with cyclohexanone in the presence of SiO_2–$AlCl_3$ in CH_2Cl_2 under reflux. The results are given in Table 5. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into a beaker containing ice-cold water and extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (with 40 % ethyl acetate in hexane as mobile phase) to afford pure product **6** in good yield. It is important to mention that under the reaction conditions investigated pyranopyridines **6** are exclusively obtained as the only isolable product with no measurable side product.

A reasonable mechanism for preparation of 11-amino-12-aryl-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracene derivatives was proposed on the basis of activation of cyclohexanone by SiO_2–$AlCl_3$ as the first step (Scheme 4). Interaction of SiO_2–$AlCl_3$ with cyclohexanone depends on the ability of the catalyst to act as a Brønsted or Lewis acid [40]. Subsequent intermolecular nucleophilic attack by the NH_2 group on the carbonyl carbon followed by dehydration produces the intermediate **1**, which is in equilibrium with the enamine **2**. In the next step,

Table 4 Optimization of the reaction conditions using compound **4a** as reference

Entry	Catalyst	Amount of catalyst	Solvent	Time (h)	Yield (%)[a]
1	$AlCl_3$	1.2 equiv	CH_2Cl_2	2.0	62
2	SiO_2–$AlCl_3$	0.12 mmol	CH_2Cl_2	1.2	88
3	SiO_2–$AlCl_3$	0.08 mmol	CH_2Cl_2	1.8	58
4	SiO_2–$AlCl_3$	0.10 mmol	CH_2Cl_2	1.4	71
5	SiO_2–$AlCl_3$	0.14 mmol	CH_2Cl_2	1.2	87
6	SiO_2–$AlCl_3$	0.12 mmol	Ethanol	3.0	–
7	SiO_2–$AlCl_3$	0.12 mmol	Methanol	3.0	–
8	SiO_2–$AlCl_3$	0.12 mmol	CH_3CN	3.0	–
9	$CaCl_2$	1.5 equiv	CH_2Cl_2	2.0	–
10	$Bi(NO_3)_3$	1.5 equiv	CH_2Cl_2	2.0	–
11	$BiCl_3$	1.5 equiv	CH_2Cl_2	2.0	–
12	$Cu(OTf)_2$	1.5 equiv	CH_2Cl_2	2.0	–
13	$InCl_3$	1.5 equiv	CH_2Cl_2	2.0	–
14	$FeCl_3$	1.5 equiv	CH_2Cl_2	2.0	–

Reaction conditions: compound **4a** (1 mmol), cyclohexanone (1.3 mmol) in solvent (5 mL) at reflux

[a] Isolated yield

Table 5 Synthesis of 11-amino-12-aryl-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracene derivatives from compound **4** and cyclohexanone catalyzed by SiO_2–$AlCl_3$ (0.12 mmol)

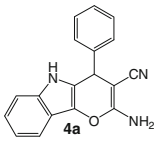
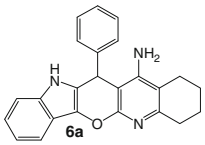
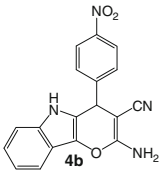
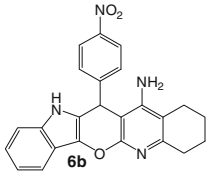
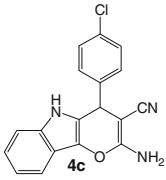
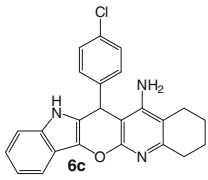
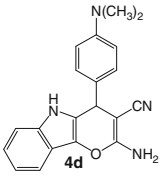
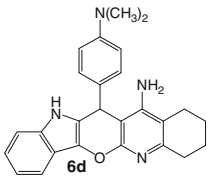
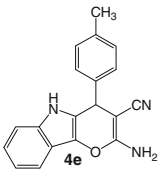
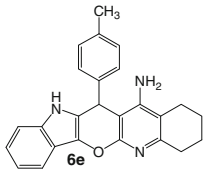
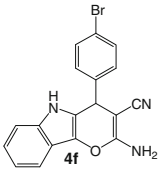
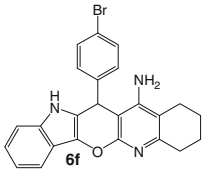
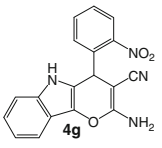
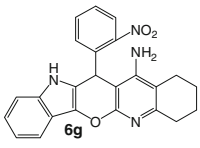
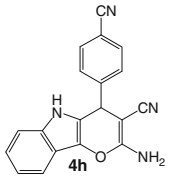
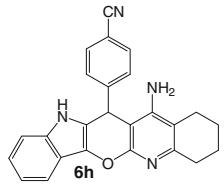
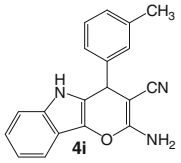
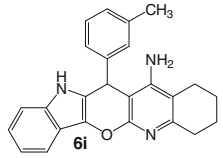
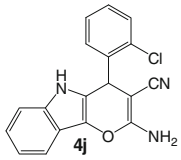
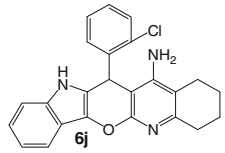
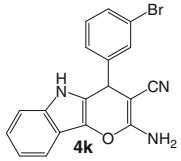
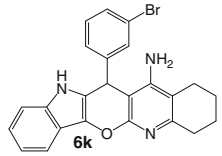
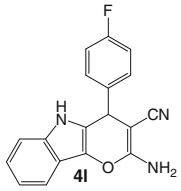
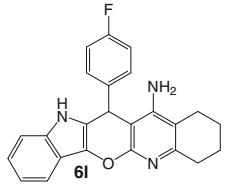
Entry	Compound	Product	Time (h)	Yield (%)[b]
1	 **4a**	 **6a**	1.2	88
2	 **4b**	 **6b**	1.0	90
3	 **4c**	 **6c**	1.0	91
4	 **4d**	 **6d**	1.5	85
5	 **4e**	 **6e**	1.5	86
6	 **4f**	 **6f**	1.0	91
7	 **4g**	 **6g**	1.2	89

Table 5 continued

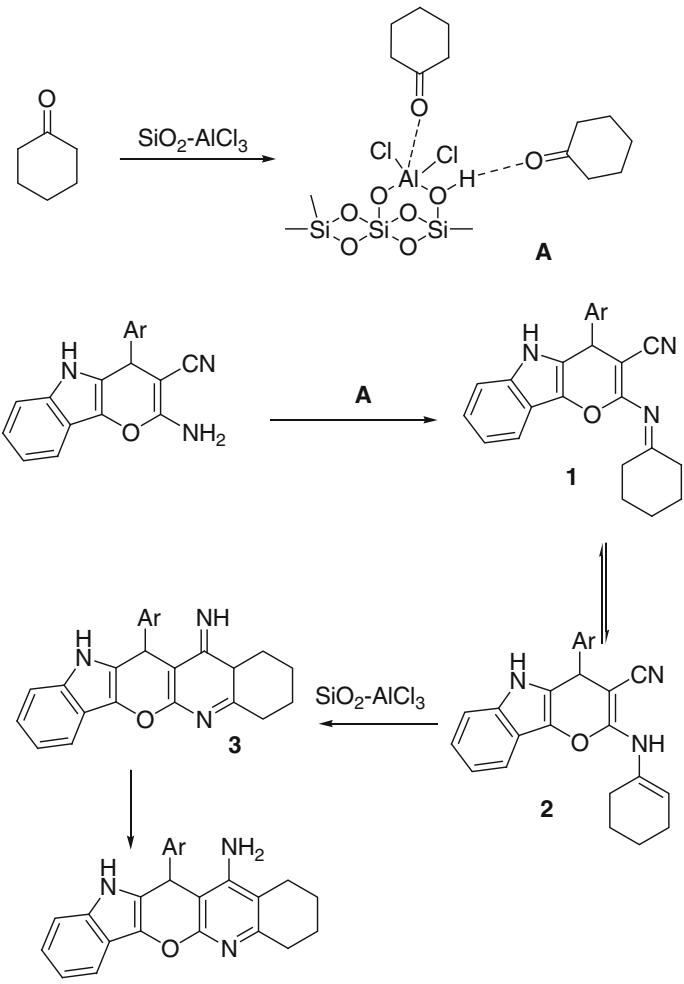
Entry	Compound	Product	Time (h)	Yield (%)[b]
8	 **4h**	 **6h**	1.2	86
9	 **4i**	 **6i**	1.5	85
10	 **4j**	 **6j**	1.2	85
11	 **4k**	 **6k**	1.2	92
12	 **4l**	 **6l**	1.0	93

Reaction conditions: **4** (1 mmol), cyclohexanone (1.3 mmol), SiO_2–$AlCl_3$ (0.12 mmol) in CH_2Cl_2, at reflux

[a] Isolated yield

activation of the nitrile group by SiO_2–$AlCl_3$ followed by intramolecular attachment of the carbon nucleophile forms the intermediate **3**, which is converted to the desired product via imine–enamine equilibrium.

Ease of recycling of the catalyst is a valuable advantage of our method. In the reaction of **4a** with cyclohexanone, even after five cycles SiO_2–$AlCl_3$ still results in excellent yields, implying that SiO_2–$AlCl_3$ can be reused without significant loss of activity (Fig. 2).



Scheme 4 Mechanism proposed for preparation of 11-amino-12-aryl-7,8,9,10,12,13-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracene derivatives

The nature of $AlCl_3$ as a Lewis acid could be changed when it is supported on the surface of the SiO_2. Aluminium chloride is soluble in most organic solvents and, because of its high activity, can react with the small water content of these solvents to form $Al(OH)_3$ as by-product. This results in strongly acidic media, because of quantitative release of HCl into the reaction mixture, which results in unwanted side reactions. The discovery of silica-supported aluminium chloride has overcome these problems. $AlCl_3$ binds to the hydroxyl groups of the silica, forming proton-donating complexes. If the supported catalyst is produced in toluene or CCl_4 under reflux, SiO_2–$AlCl_2$ is formed, with loss of HCl. Sites on the surface of SiO_2–$AlCl_2$ have strong Brønsted and Lewis acidity. The Brønsted acidity of SiO_2–$AlCl_2$ commonly arises as a result of Lewis acid–

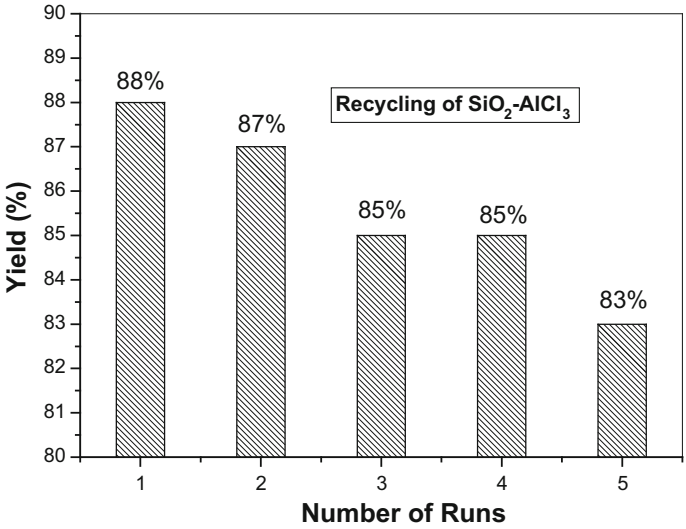
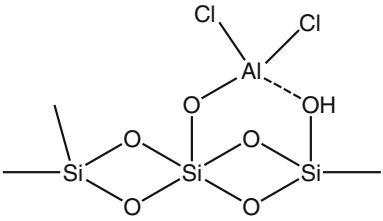


Fig. 2 Recovery and reuse of the catalyst SiO_2–$AlCl_3$ in the synthesis of 11-amino-12-aryl-hexahydro-5-oxa-6,13-diaza-indeno[1,2-*b*]anthracene in CH_2Cl_2 at reflux

Scheme 5 Brønsted acidity arising as a result of the inductive effect of Lewis acid–base complexation



base complexation (Scheme 5). Covalent bonding of $AlCl_3$ with silica furnishes a heterogeneous form of $AlCl_3$ which can be recycled several times [40–43].

Conclusions

In conclusion, we report facile PPh_3-catalyzed multicomponent condensation of 3-hydroxyindole, malononitrile, and aromatic aldehydes to afford 2-amino-4,5-dihydro-4-phenyl-pyrano[3,2-*b*]indole-3-carbonitrile derivatives. Subsequent reaction of these with cyclohexanone, in the presence of SiO_2–$AlCl_3$, furnishes novel pyranopyridine derivatives. Advantages include improved yield, easier work-up, shorter reaction time, and mild reaction conditions.

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