Asian Journal of Chemistry; Vol. 33, No. 7 (2021), 1685-1691

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2021.23196

An Efficient One Pot Four-Component Synthesis of Spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] Derivatives *via* Electrochemical Approach

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Received: 7 March 2021; *Accepted*: 5 June 2021; *Published online*: 26 June 2021; AJC-20414

An efficient, simple and one pot, synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivative by electrochemically induced condensation of β-keto ester, hydrazine hydrate, malononitrile or ethyl cyanoacetate and isatin in an undivided cell at constant current where sodium bromide was present as electrolyte in ethanol medium.

Keywords: Multicomponent reaction, Electrolysis, Isatin, β-keto ester, Spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole].

INTRODUCTION

Exploring novel pharmacological agents with minimum number of synthetic steps and less time is a major challenge for chemists. In this context, multicomponent reactions have proven to be very effective and attractive. These reactions dramatically reduce the generation of chemical waste and the cost. Multicomponent reaction (MCR) strategies offer significant advantages over conventional linear type synthesis [1,2]. It provide powerful platform to access diversity as well as complexity in few reaction steps. The conventional multi-step synthesis of compounds involve purification of compounds after each individual step [3], which leads to two main disadvantages, synthetic inefficiency and the production of large amount of waste.

Compounds with spiro skeletons not only constitute subunits in numerous alkaloids [4-8], but are also templates for drug discovery and have been used as scaffolds for combinatorial libraries [9-12]. Spirooxindoles attached with other heterocycles have drawn significant attention to organic as well as medicinal chemists due to their wide range of biological activities such as antimicrobial [13], anti-mycobacterial [14], antifungal [15], anti-tumor [16,17], anti-tubercular [18], antimalarial [19] and antioxidant activities [20]. On other hand, dihydropyrano[2,3-*c*]pyrazole moiety also show numerous biological and pharmacological properties such as anticancer [21], anti-HIV [22], ChK1 kinase inhibitors [23] and molluscicidal activities [24,25].

The biological properties of spiroindoline-pyranopyrazole derivatives have attracted many synthetic chemists to explore different methods suitable for their synthesis, though there are several methods reported in the literature for the formation of four component reaction such as by using piperidine [26,27], 4-(dimethylamino)pyridine [28], L-proline [29] $[DMBSI]HSO_4$ [30], $Mn(bpyo)_2$/MCM-41 [31] Bmim(OH)/chitosan [32], uncapped SnO_2 quantum dots [33] and meglumine [34]. Other common synthetic method for the synthesis of this class of compounds is a three-component condensation of pyrazolone, malononitrile and isatin in the presence of catalysts such as K_2CO_3 [35], $NaHCO_3$ [36], triethylamine [37], ZnS nanoparticles [38] and triethanolamine [39]. However, most of the methods for the synthesis of these products suffer from various drawbacks such as harsh reaction conditions, prolonged reaction times, low yields and the use of toxic organic solvents, expensive reagents and catalysts. Therefore, a simple, efficient and environmentally benign approaches for synthesis of spiro-[indoline-3,4′-pyrano[2,3-*c*]pyrazole] are desirable.

The advance of electrosynthesis in the last decades has provided organic chemists with a new versatile synthetic device of great promise. This procedure is advantageous for a multi-

component reaction in utilizing simple equipment, an undivided cell that would be of value for a large-scale process due to its catalytic nature and the use of cost-effective and environmentally friendly chemical reagent electricity. In continuation of our attempts for the synthesis of biologically important compound [40-45], herein a simple, safe and efficient process for synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives by using electrocatalyzed multicomponent reaction of β-keto ester, hydrazine hydrate, malononitrile and isatin in an undivided cell at 30 ºC under a constant current density is explored.

EXPERIMENTAL

All chemicals were of reagent grade and purchased from Aldrich, Alfa Aesar, Merck, Spectrochem and Qualigens and used without further purification. The reactions were monitored using pre-coated Aluminium TLC plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60 F_{254}). NMR spectra were recorded on a Bruker Avance-II 400FT spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C) in DMSO using TMS as an internal reference. Mass spectra (EIMS) were obtained on a Waters UPLC-TQD mass spectrometer. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer. Melting points were determined by open glass capillary method and are uncorrected.

General Procedure for synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives: A solution of NaBr (0.5 mmol) in ethanol (25mL) containing hydrazine hydrate (1 mmol) and ethyl acetoacetate (1 mmol), was stirred and electrolyzed for 10 min in an undivided cell equipped with graphite rods (5 cm^2) as anode and Fe (5 cm^2) as cathode at 40 ºC. Then malononitrile (1 mmol) and isatin (1 mmol) were added to the resulting solution and electrolysis was continue for next 20 min under a constant current density of 8 mA/cm^2 (I = 48 mA). The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction (35-45 min), the solvent was evaporated under reduced pressure, reaction mixture was added by water (10 mL) and extracted with chloroform (3 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Finally, the resulting crude product was purified by recrystallization from ethanol to furnish the desired product. All the compounds were characterized by comparison of their spectral data with those reported in the literature.

6′-Amino-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5a): Light red solid, m.p.: 281-284 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.55 (s, 3H), 6.91 (s, 1H), 7.02 (s, 2H), 7.18 (s, 2H), 7.23 (s, 1H), 10.55 (s,1H), 12.25 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 9.4, 47.7, 55.3, 95.8, 110.1, 119.2, 123.0, 124.3, 129.3, 133.0, 135.2, 141.8, 155.7, 162.9, 178.5. IR (KBr, ν_{max}, cm^{-1}): 696, 931, 1054, 1155, 1207, 1320, 1409, 1517, 1583, 1642, 1710, 2182, 2687, 3134, 3337, 3389, 3420. EI-MS: *m/z* 293 (M^+). Anal. calcd. (found) % for $C_{15}H_{11}N_5O_2$: C; 61.43 (61.51), H; 3.78 (3.66), N; 23.88 (23.69).

6′-Amino-2-oxo-3′-propyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5b): Yellow solid, m.p.: 268-270 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.51 (t, 3H, *J* = 7.2 Hz), 1.08 (m, 2H), 1.85 (t, 2H, *J* = 7.6 Hz), 6.90 (d, 1H, *J* = 7.6 Hz), 6.98 (t, 1H, *J* = 7.6 Hz), 7.06 (d, 1H, *J* = 7.2 Hz), 7.26 (m, 3H), 10.62 (s, 1H), 12.30 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 11.6, 22.1, 26.7, 47.6, 55.3, 95.8, 110.1, 119.2, 123.0, 124.3, 129.3, 133.0, 135.2, 141.8, 155.7, 162.9, 178.5. IR (KBr, ν_{max}, cm^{-1}): 751, 1051, 1214, 1322, 1411, 1491, 1582, 1618, 1639, 1718, 2192, 2868, 2959, 3191, 3314. EI-MS: *m/z* 321 (M^+). Anal. calcd. (found) % for $C_{17}H_{15}N_5O_2$: C; 63.54 (63.58), H; 4.71 (4.66), N; 21.79 (21.68).

6′-Amino-3′,5-dimethyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5c): Red solid, m.p.: 279-281 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.55 (s, 3H), 2.23 (s, 3H), 6.79 (d, 1H, *J* = 8.0 Hz), 6.84 (s, 1H), 7.04 (d, 1H, *J* = 7.2 Hz), 7.15 (s, 2H), 10.45 (s, 1H), 12.23 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 9.4, 27.4, 47.9, 54.9, 95.1, 112.2, 114.7, 119.2, 127.7, 132.2, 135.2, 135.6, 141.1, 155.6, 163.0, 178.1. IR (KBr, ν_{max}, cm^{-1}): 697, 820, 1055, 1205, 1312, 1410, 1495, 1582, 1644, 1706, 2185, 2918, 3147, 3344, 3391. EI-MS: *m/z* 307 (M^+). Anal. calcd. (found) % for $C_{16}H_{13}N_5O_2$: C; 62.53 (62.57), H; 4.26 (4.28), N; 22.79 (22.83).

6′-Amino-5-chloro-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5d): White solid, m.p.: 296-298 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.60 (s, 3H), 6.93 (d, 1H, *J* = 8.4 Hz), 7.12 (s, 1H), 7.27 (s, 2H), 7.31 (m, 1H), 10.73 (s, 1H), 12.32 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 9.4, 48.0, 54.9, 95.1, 11.7, 119.1, 125.0, 127.0, 129.3, 135.1, 135.2, 140.7, 155.6, 162.9,178.2. IR (KBr, ν_{max}, cm^{-1}): 694, 824, 1053, 1159, 1300, 1412, 1497, 1580, 1643, 1714, 2183, 2969, 3136, 3346, 3391. EI-MS: *m/z* 327 (M^+). Anal. calcd. (found) % for $C_{15}H_{10}N_5O_2Cl$: C; 54.97 (55.01), H; 3.08 (3.10), N; 21.37 (21.43).

6′-Amino-5-bromo-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-5'-carbonitrile (5e): White solid, m.p.: 281-283 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.61 (s, 3H), 6.89 (d, 1H, *J* = 8.0 Hz), 7.23 (s, 1H), 7.27 (s, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 10.74 (s, 1H), 12.33 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 9.4, 47.9, 54.9, 95.1, 112.2, 114.6, 119.1, 127.7, 132.2, 135.2, 135.5, 141.1, 155.6, 162.9, 178.0. IR (KBr, ν_{max}, cm^{-1}): 694, 821, 946, 1055, 1158, 1209, 1300, 1410, 1498, 1583, 1642, 1713, 2184, 3128, 3346, 3394, 3412. EI-MS: *m/z* 371 (M^+). Anal. calcd. (found) % for $C_{15}H_{10}N_5O_2Br$: C; 48.41 (48.51), H; 2.71 (2.69), N; 18.82 (18.90).

6′-Amino-6-bromo-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5f): White solid, m.p.: 301-304 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.57 (s, 3H), 7.05 (m, 2H), 7.17 (d, 1H, *J* = 7.6 Hz), 7.25 (s, 2H), 10.73 (s, 1H), 12.30 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 15.99, 54.08, 61.74, 101.68, 119.52, 125.41, 128.32, 132.12, 133.34, 138.90, 141.76, 150.09, 162.18, 169.44, 184.74. IR (KBr, ν_{max}, cm^{-1}): 753, 919, 1043, 1316, 1409, 1486, 1603, 1639, 1704, 2199, 2813, 3032, 3117, 3177, 3247, 3302, 3471. EI-MS: *m/z* 371 (M^+). Anal. calcd. (found) % for $C_{15}H_{10}N_5O_2Br$: C; 48.41 (48.49), H; 2.71 (2.65), N; 18.82 (18.88).

6′-Amino-1,3′-dimethyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5g): White solid, m.p. 270-272 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.46 (s, 3H), 3.21 (s, 3H), 7.09 (t, 2H, *J* = 6.0 Hz), 7.12 (s, 1H), 7.24

(s, 2H), 7.35 (t, 1H, *J* = 6.0 Hz), 12.27 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 9.4, 28.8, 45.2, 55.3, 95.8, 110.1, 119.2, 123.0, 124.3, 129.3, 133.0, 135.2, 141.8, 159.4, 161.4, 178.4. IR (KBr, ν_{max}, cm^{-1}): 758, 921, 1081, 1255, 1347, 1406, 1494, 1597, 1642, 1705, 2189, 2925, 3128, 3327, 3381. EI-MS: *m/z* 307 (M^+). Anal. calcd. (found) % for $C_{16}H_{13}N_5O_2$: C; 62.53 (62.61), H; 4.26 (4.16), N; 22.79 (22.63).

6′-Amino-2-oxo-3′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5h): White solid, m.p.: 280-281 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.74 (d, 1H, *J* = 8.0 Hz), 6.80 (d, 2H, *J* = 7.6 Hz), 6.92 (t, 1H, *J* = 7.6 Hz), 7.04 (d, 1H, *J* = 7.6 Hz), 7.16 (m, 3H), 7.24 (d, 1H, *J* = 8.4 Hz), 7.29 (s, 2H), 10.51 (s, 1H), 12.90 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 48.1, 56.7, 95.7, 110.2, 119.0, 122.9, 124.8, 127.6, 128.4, 128.8, 129.2, 129.4, 134.4, 139.5, 142.0, 156.3, 162.2, 178.7. IR (KBr, ν_{max}, cm^{-1}): 750, 927, 1060, 1213, 1321, 1406, 1495, 1593, 1649, 1707, 2188, 2906, 3141, 3240, 3311, 3387. EI-MS: *m/z* 355 (M^+). Anal. calcd. (found) % for $C_{20}H_{13}N_5O_2$: C; 67.60 (67.71), H; 3.69 (3.69), N; 19.71 (19.75).

6′-Amino-1-methyl-2-oxo-3′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5i): White solid, m.p.: 285-286 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.97 (s, 3H), 6.72 (d, 2H, *J* = 7.2 Hz), 6.89 (d, 1H, *J* = 7.6 Hz), 6.97 (t, 1H, *J* = 7.6 Hz), 7.07 (d, 1H, *J* = 7.2 Hz), 7.18 (t, 2H *J* = 8.0 Hz), 7.24 (m, 2H *J* = 7.6 Hz), 7.32 (s, 2H), 12.91 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 28.8, 45.6, 56.7, 95.7, 110.2, 119.0, 122.9, 124.8, 127.6, 128.4, 128.8, 129.2, 129.4, 134.4, 139.5, 142.0, 159.8, 160.7, 178.7. IR (KBr, ν_{max}, cm^{-1}): 701, 921, 1037, 1400, 1503, 1604, 1637, 1697, 2192, 2927, 3031, 3172, 3297, 3456. EI-MS: *m/z* 369 (M^+). Anal. calcd. (found) % for $C_{21}H_{15}N_5O_2$: C; 68.28 (68.39), H; 4.09 (4.08), N; 18.96 (19.01).

6′-Amino-5-bromo-2-oxo-3′-phenyl-1′*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5j): Red solid, m.p.: 255-257 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.71 (d, 1H, *J* = 6.8 Hz), 6.85 (s, 2H), 7.23 (m, 7H), 10.66 (s, 1H), 12.95 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 56.01, 62.70, 117.54, 118.0, 119.20, 122.80, 125.89, 134.16, 134.80, 135.21, 136.73, 139.20, 142.20, 142.27, 144.80, 145.91, 162.76, 164.16, 168.83, 185.20. IR (KBr, ν_{max}, cm^{-1}): 699, 819, 1052, 1218, 1401, 1495, 1587, 1631, 1715, 2191, 2972, 3060, 3148, 3276, 3332, 3397. EI-MS: m/z 433 (M^+), Anal. calcd. (found) % for $C_{20}H_{12}N_5O_2Br$: C; 55.32 (55.43), H; 2.79 (2.76), N; 16.13 (16.19).

6′-Amino-5-fluoro-2-oxo-3′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5k): White solid, m.p.: 255-257 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.69 (m, 1H, *J* = 4.4 Hz), 6.86 (d, 2H, *J* = 7.6 Hz), 6.99 (m, 2H), 7.19 (t, 2H, *J* = 7.6 Hz), 7.27 (t, 1H, *J* = 7.6 Hz), 7.32 (s, 2H), 10.55 (s, 1H), 12.93 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 55.01, 62.69, 117.46, 117.54, 118.96, 119.20, 122.41, 125.28, 134.16, 135.21, 135.80, 142.20, 142.27, 144.80, 145.91, 162.76, 164.16, 166.53, 168.83, 185.21. IR (KBr, cm^{-1}): 698, 872, 1055, 1180, 1405, 1487, 1589, 1643, 1712, 2192, 2999, 3058, 3155, 3252, 3313, 3384. EI-MS: *m/z* 373 (M^+). Anal. calcd. (found) % for $C_{20}H_{12}N_5O_2F$: C; 64.34 (64.44), H; 3.24 (3.21), N; 18.76 (18.83).

6′-Amino-5-methyl-2-oxo-3′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (5l): Brown solid, m.p.: 247-249 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.19 (s, 3H), 6.63 (d, 1H, *J* = 7.6 Hz), 6.81 (d, 2H, *J* = 8.0 Hz), 6.88 (s, 1H), 6.98 (d, 1H, *J* = 8.0 Hz,), 7.17 (t, 2H, *J* = 7.6 Hz), 7.28 (m, 3H), 10.38 (s, 1H), 12.88 (s,1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 27.49, 54.56, 63.46, 102.30, 116.44, 125.43,131.82, 134.13, 135.18, 135.41, 135.69, 136.13, 138.28, 141.27, 145.80, 146.03, 162.81, 168.56, 184.87; IR (KBr, ν_{max}, cm^{-1}): 697, 812, 1059, 1203, 1309, 1409, 1494, 1593, 1654, 1706, 2189, 3132, 3239, 3311, 3379. EI-MS: *m/z* 369 (M^+). Anal. calcd. (found) % for $C_{21}H_{15}N_5O_2$: C; 68.28 (68.36), H; 4.09 (4.12), N; 18.96 (19.03).

Ethyl 6′-amino-2-oxo-3′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carboxylate (5m): White solid, m.p.: 241-243 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.68 (t, 3H, *J* = 7.2 Hz), 3.67 (q, 2H, *J* = 6.8 Hz), 6.50 (d, 1H, *J* = 7.6 Hz), 6.61 (d, 2H, *J* = 7.6 Hz), 6.85 (t, 1H, *J* = 7.2 Hz), 6.95 (d, 1H, *J* = 7.2 Hz), 7.07 (t, 1H, *J* = 7.2 Hz), 7.15 (t, 2H, *J* = 7.6 Hz), 7.30 (t, 1H, *J* = 7.6 Hz), 8.06 (s, 2H), 9.95 (s, 1H), 12.62 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 13.19, 47.41, 58.90, 74.72, 97.92, 109.13, 121.50, 122.89, 127.55, 127.93, 128.57, 128.87, 138.33, 139.29, 142.73, 154.62, 162.57, 168.29, 179.92. IR (KBr, ν_{max}, cm^{-1}): 750, 927, 1040, 1096, 1143, 1290, 1401, 1474, 1614, 1662, 1714, 2977, 3055, 3172, 3264, 3362, 3481. EI-MS: *m/z* 402 (M^+). Anal. calcd. (found) % for $C_{22}H_{18}N_4O_4$: C; 65.66 (65.74), H; 4.51 (4.56), N; 13.92 (13.96).

Ethyl 6′-amino-5-bromo-2-oxo-3′-phenyl-1′*H*-spiro-[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carboxylate (5n): White solid, m.p.: 258-259 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.70 (t, 3H, *J* = 6.0 Hz), 3.70 (q, 2H, *J* = 6.8 Hz), 6.42 (d, 1H, *J* = 8.0 Hz), 6.67 (d, 2H, *J* = 6.4 Hz), 7.11 (s, 1H), 7.21 (d, 3H, *J* = 7.2 Hz), 7.32 (s, 1H), 8.12 (s, 2H), 10.11 (s, 1H), 12.68 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 13.24, 58.92, 74.27, 97.51, 110.94, 112.92, 125.66, 127.98, 128.63, 128.96, 130.15, 130.80 139.35, 140.52, 141.99, 154.54, 162.78, 165.94, 168.05, 179.47. IR (KBr, ν_{max}, cm^{-1}): 960, 1380, 1475, 1491, 1543, 1618, 1677, 1718, 3260, 3421. EI-MS: *m/z* 480 (M^+). Anal. calcd. (found) % for $C_{22}H_{17}N_4O_4Br$: C; 54.90 (55.01), H; 3.56 (3.59), N; 11.64 (11.67).

Ethyl 6′-amino-5-chloro-2-oxo-3′-phenyl-1′*H*-spiro-[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carboxylate (5o): White solid, m.p.: 264-267 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.70 (t, 3H, *J* =6.8 Hz), 3.69 (q, 2H, *J* = 7.2 Hz), 6.47 (d, 1H, *J* = 8.0 Hz), 6.69 (d, 2H, *J* = 7.2 Hz), 7.01 (s, 1H), 7.10 (d, 1H, *J* = 7.6 Hz), 7.20 (t, 2H, *J* = 7.2 Hz), 7.36 (t, 1H *J* = 7.6 Hz), 8.12 (s, 2H), 10.11 (s, 1H), 12.69 (s, 1H). IR (KBr, ν_{max}, cm^{-1}): 696, 811, 1047, 1101, 1286, 1400, 1475, 1543, 1619, 1685, 1708, 2982, 3259, 3347. EI-MS: *m/z* 450 (M^+). Anal. calcd. (found) % for $C_{23}H_{19}N_4O_4Cl$: C; 61.27 (61.40), H; 4.25 (4.27), N; 12.43 (12.49).

Ethyl 6′-amino-5-methyl-2-oxo-3′-phenyl-1′*H*-spiro-[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carboxylate (5p): White solid, m.p.: 261-263 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.71 (t, 3H, *J* = 7.2 Hz), 2.20 (s, 3H), 3.68 (q, 2H, *J* = 7.2 Hz), 6.42 (d, 1H, *J* = 7.6 Hz), 6.62 (d, 2H, *J* = 8.0 Hz),

6.80 (s, 1H), 6.90 (d, 1H, *J* = 7.6 Hz), 7.17 (t, 2H, *J* = 7.2 Hz), 7.31 (t, 1H, *J* = 7.6 Hz), 9.84 (s, 1H), 12.60 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 13.24, 23.82, 59.92, 74.27, 97.51, 110.94, 112.92, 122.96, 127.75, 127.98, 128.20, 128.63, 131.70, 135.66, 138.20, 141.99, 154.54, 162.78, 165.94, 168.05, 179.47. IR (KBr, ν_{max}, cm^{-1}): 3423, 698, 1048, 1100, 1290, 1400, 1493, 1544, 1610, 1668, 1720, 2980, 3267. EI-MS: *m/z* 416 (M^+). Anal. calcd. (found) % for $C_{23}H_{20}N_4O_4$: C; 66.34 (66.46), H; 4.84 (4.89), N; 13.45 (13.51).

Ethyl 6′-amino-1-methyl-2-oxo-3′-phenyl-1′*H*-spiro-[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carboxylate (5q): White solid, m.p.: 223-226 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.45 (s, 3H), 3.46 (m, 2H), 6.42 (m, 3H), 7.10 (m, 6H), 7.97 (s, 2H), 12.50 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 13.46, 18.65, 25.56, 30.76, 46.92, 56.21, 58.72, 74.36, 98.34, 107.64, 122.15, 122.42, 127.81, 128.64, 128.82, 137.21, 139.19, 143.46, 154.50, 162.87, 168.14, 177.91. IR (KBr, ν_{max}, cm^{-1}): 693, 1083, 1100, 1287, 1375, 1399, 1475, 1491, 1543, 1611, 1685, 1701, 3186, 3266, 3394, 3463. EI-MS: *m/z* 416 (M^+). Anal. calcd. (found) % for $C_{23}H_{20}N_4O_4$: C; 66.34 (66.41), H; 4.84 (4.87), N; 13.45 (13.49).

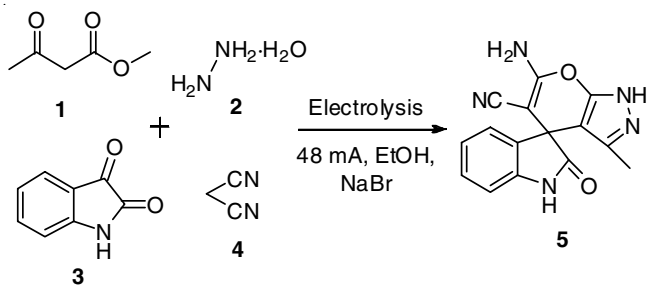
Ethyl 6′-amino-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carboxylate (5r): White solid, m.p.: 281-282 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.68 (t, 3H, *J* = 7.5 Hz), 1.55 (s, 3H), 3.65 (q, 2H, *J* = 7.5 Hz), 6.79 (m, 4H, Ar-H), 8.02 (s, 2H), 10.37 (s, 1H), 12.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 9.4, 13.6, 47.4, 59.1, 74.5, 97.5, 109.1, 122.0, 123.0, 127.7, 131.9, 135.1, 137.0, 142.3, 154.8, 163.2, 168.6, 180.1. IR (KBr, ν_{max}, cm^{-1}): 767, 923, 1036, 1098, 1155, 1222, 1290, 1400, 1472, 1539, 1613, 1665, 1715, 2854, 2925, 3027, 3083, 3188, 3281, 3385. EI-MS: *m/z* 340 (M^+). Anal. calcd. (found) % for $C_{17}H_{16}N_4O_4$: C; 59.99 (60.08), H; 4.74 (4.78), N; 16.46 (16.54).

RESULTS AND DISCUSSION

By studying the various methods reported in literature, it was observed that the synthesis of spiro[indoline-3,4′-pyrano-[2,3-*c*]pyrazole] motif require excess of solvent, costly catalyst, oxidants and generate huge amount of side waste. Hence, it is necessary to develop a cleaner, safer and proficient procedure for the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]. Present study is based on the electrochemically induced conversion of ethyl acetoacetate, hydrazine hydrate, malononitrile and isatin to spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile under optimum reaction conditions (current density 8 mA/cm^2, 1.20 F/mol passed electricity at 30 ºC, using EtOH) by electrolysis in an undivided cell. The synthetic pathway is shown in **Scheme-I**.

The electrode system is considered as heterogeneous catalyst in electrochemical reaction. The various set of these heterogeneous catalysts as electrode pair (*i.e.* anode and cathode) were employed in several reactions like, graphite-graphite, RVC-graphite, graphite-iron, *etc*. at constant current density. And finally, it was observed that graphite-iron electrode pair is more suitable in terms of maximum yield (Table-1).

During the reaction, many solvents were screened and observed that reaction proceed well in ethanol at current density



Scheme-I: Synthesis of 6′-amino-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile

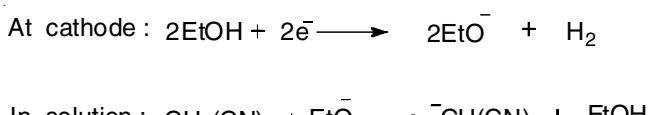
TABLE-1
ELECTRODE OPTIMIZATION FOR
THE SYNTHESIS OF COMPOUND **5**

Entry	Anode/cathode	Current density (mA/cm^2)	Yield[b] (%)
1	Graphite/iron	1.0	40
2	Graphite/iron	4.0	78
3	Graphite/iron	8.0	85
4	Graphite/graphite	8.0	32
5	Platinum/graphite	8.0	48
6	Platinum/graphite	4.0	20
7	RVC/graphite	N/A	N/A

[a]All reactions were run with **1** (1 mmol), **2** (1.0 mmol), **3** (1 mmol), **4** (1 mmol) and NaBr (0.5 mmol) as electrolyte in EtOH (30 mL) at 30 °C for 40 min under air atmosphere. [b]Isolated yield of **5**.

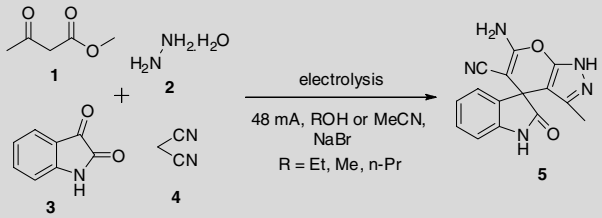
of 8 mA/cm^2 (I = 48 mA, electrode surface = 6 cm^2). A range of current for the similar reaction was employed and found that at 8 mA/cm^2 current densities (when 1.20 F/mol of electricity passed), the yield of reaction was excellent (Table-2, entry 7). To understand the effect of various substituents on the rate and yield of reaction, the reaction was run with various isatin derivatives, but no substantial effect of substituent on yields of reaction was observed. Reaction with all the possible substrate occurs efficiently and produces the desired products quickly in good yields (Table-3).

Initially, alkoxide anion formed by the deprotonation of an alcohol at the cathode. Then alkoxide anion reacts with malononitrile to gives malononitrile anion (**Scheme-II**). This malononitrile anion (**4**) undergoes Knoevenagel condensation with isatin (**3**) to formed corresponding intermediate **C**. On other hand, the reaction of ethyl acetoacetate (**1**) and hydrazine hydrate (**2**) afforded compound A, which was enolised in the presence of ethoxide ion to formed compound **B**. Subsequently, the enolizable compound **B** condensed with the Knoevenagel adducts **C** *via* Michael addition to give intermediate **D** followed by intramolecular cyclization leads to corresponding final product **5**. A possible mechanism for the synthesis of final products is outlined in **Scheme-III**.



Scheme-II: Synthesis of malanonitrile anion in alcohal

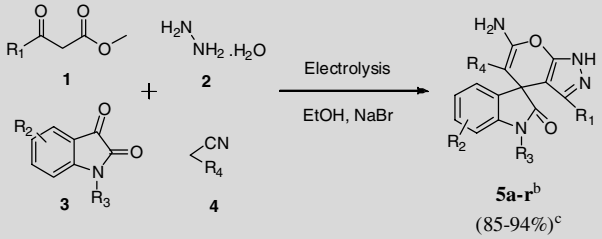
TABLE-2
OPTIMIZATION OF REACTION CONDITIONS[a]

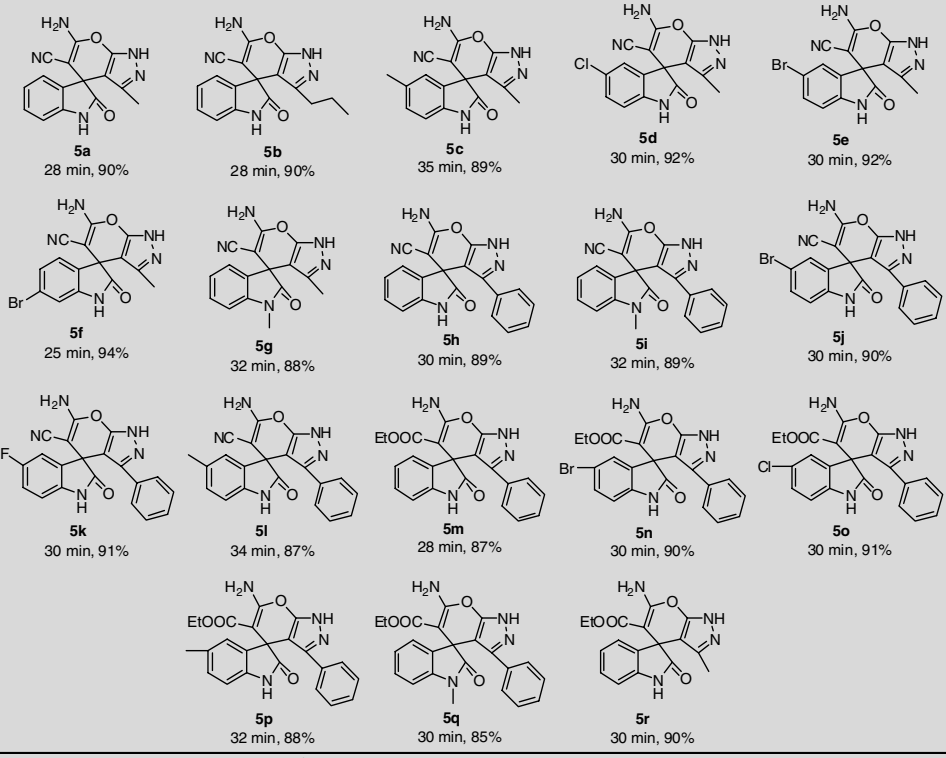


Solvent	I (mA)	Current density (mA/cm^2)	Time (min)	Electricity passed (F/mol)	Temp. (°C)	Yield[b] (%)
EtOH	12	2	240	1.79	20	10
EtOH	48	8	240	7.16	20	20
EtOH	96	16	240	14.32	20	32
EtOH	6	1	120	0.44	30	40
EtOH	12	2	120	0.89	30	65
EtOH	36	4	70	1.57	30	78
EtOH	48	8	40	1.20	30	85
MeOH	48	8	45	1.34	30	75
n-PrOH	48	8	50	1.49	30	60
MeCN	48	8	55	1.64	30	55

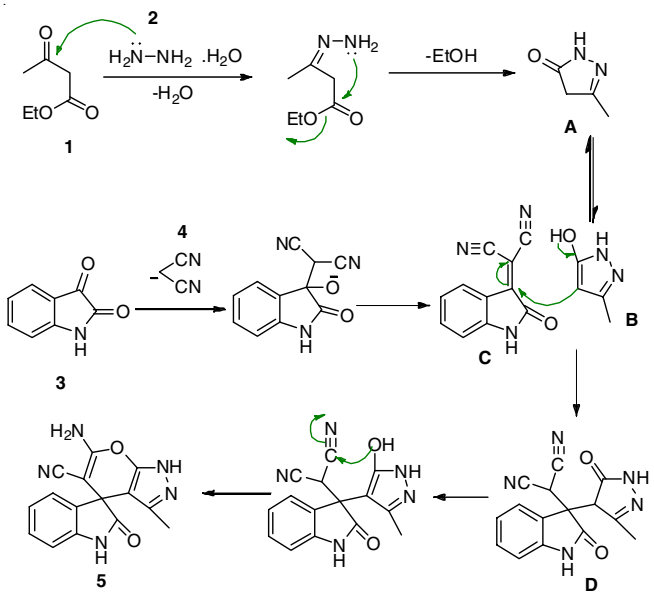
[a]All reactions were run with **1** (1 mmol), **2** (1.0 mmol), **3** (1 mmol), **4** (1 mmol) and NaBr (0.5 mmol) in EtOH (25 mL) at 30 °C for 40 min. under air atmosphere. [b]Isolated yield of **5**.

TABLE-3
SUBSTRATE SCOPE FOR THE PREPARATION OF SPIRO[INDOLINE-3,4'-PYRANO[2,3-*c*]PYRAZOLE]-5'-CARBONITRILE[a]





[a]For experimental procedure, see supporting material. [b]All compounds are known and were characterized by comparison of their spectral data with those reported in the literature [16-18,21]; [c]Yields of isolated pure compounds **5**.



Scheme-III: A plausible mechanism for the formation of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole-5′-carbonitrile

Conclusion

A simple, efficient, economical method for the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives, by one-pot four-component reaction in ethanol in an undivided cell, in the presence of NaBr as an electrolyte. The use of cheap and environmental friendly chemical reagent electricity, low cast starting materials, non-hazardous reaction conditions, very high yields and ease of separation of products through simple filtration are some significance of proposed protocol.

ACKNOWLEDGEMENTS

The authors sincerely thank SAIF, Punjab University, Chandigarh, India for providing the microanalyses and spectral characterization.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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