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Electro-catalyzed cynoarylmethylation of isatin for synthesis of 3-hydroxy-3-cynomethyl oxindole derivatives

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An efficient and economical method has been developed for synthesis of 3-substituted oxindole by using electrochemically induced condensation of various N-substituted isatin, phenyl acetonitrile.

Keywords: Electrocatalysis, Cynoarylmethylation, Oxindole derivatives

Electrochemical multicomponent reactions (EMCRs) have held a prominent position in modern synthetic chemistry for the facile construction of complex bioactive molecules from readily accessible starting materials and become an important area of research in organic and medicinal chemistry. The synthesis is expected to be popular in future. Electrochemical methods plays important role in atom economy and green chemistry.[1] EMCR fundamentally eliminates the waste treatment and disposal of used redox reagents[2] and reduce the generation of chemical waste and cast highly reactive species such as anion, cation and free radical can be generated electrochemically at room temperature. It is unique technique for production of large scale processes.

Electrochemical synthesis becomes an alternative to conventional method of organic synthesis as only electricity is required as a catalyst no other reagent is needed. It is unique technique for the large scale process because electricity is cheap and environmentally benign chemical reagent and it has ability to produce an initial base which acts as catalyst and used in ambient temperature and pressure.[3] Electrochemistry has become an attractive alternative to conventional method as it can be originated from renewable resources. Under mild condition reaction transformation has been carried out, reactive intermediates initiated by transferring of electron between substrate molecule and electrode.

Alkyl nitriles constitute an important class of nitrogen containing compounds frequently found in many natural products and pharmaceutically important compounds used in breast cancer, central nervous system and some other diseases (Fig. 1)[4]. Since the nitrile functional group has ability to convert itself into other important functional groups, such as, aldehyde, amide, amine, and carboxylic acid.[5] Therefore, importance for synthesis of such compounds increases. Despite several methods[6] presents in the literature for the synthesis of functional alkyl nitriles the development of simple efficient and environmentally benign approaches for nitriles is highly desirable. So, we here report the synthesis of substituted nitriles via two component reaction of isatin and phenyl cynonitrile in ethanol at room temperature using electron as an inexpensive and environmentally benign catalyst (Scheme 1). In the course of our research on the development of efficient methods for the synthesis of bioactive heterocycles[7] herein we have introduced electricity as green reagent for synthesis of β-hydroxyl nitrile analogues.

Experimental Details

All chemicals were reagent grade and purchased from Aldrich, Alfa Aesar, Merck, Spectrochem and Qualigens and were used without further purification. The reactions were monitored using pre-coated

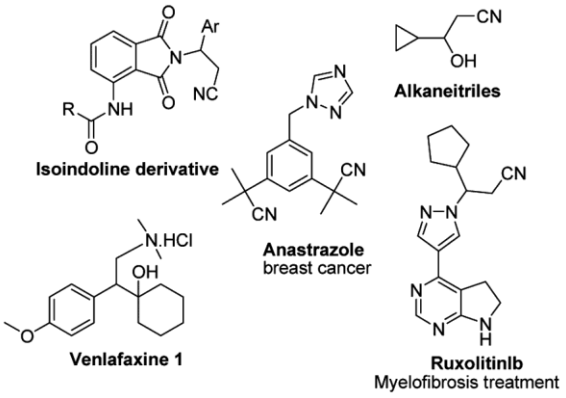
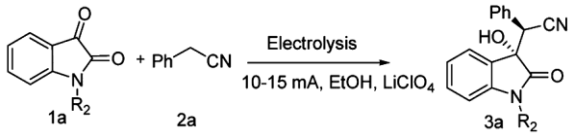


Figure 1 — Several biologically active natural product and pharmaceuticals compounds



Scheme 1 — Synthesis of 3-Hydroxy-3-cynomethyl oxindole derivatives

Aluminium TLC plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60 F-254). NMR spectra were recorded on a Bruke Avance-II 400FT spectrometer at 300 or 500 MHz (^{1}H) and 75 or 125 MHz (^{13}C) in DMSO or $CDCl_3$ 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. Elemental analyses were carried out in a Thermo Scientific (FLASH 2000) CHN Elemental Analyser. Melting points were determined by open glass capillary method and were uncorrected.

General procedure for the synthesis of 3 substituted indoles

The mixture of *N*-methyl isatin **1** (1.5 mmol) and phenyl acetonitrile **2** (1.6 mmol) and lithium perchlorate (0.5 mmol) in ethanol (20 mL) was electrolyzed in beaker equipped with a magnetic stirrer, graphite anode and iron cathode, under constant current density of 10 mA/cm^2). After completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure and reaction mixture was added by water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel chromatography using a mixture of hexane/ethyl acetate as eluent to afford an analytically pure sample of product **3**. All the compounds are known and were characterized by comparison of their spectral data with those reported in the literature.

2-(3-Hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile(3a): Pale yellow solid; 77.9 mg, 92% yield, 99:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (dd, J = 7.2 Hz, 0.8 Hz, 1H), 7.34−7.30 (m, 1H), 7.23−7.19 (m, 1H), 7.17−7.14 (m, 1H), 7.07−7.04 (m, 2H), 6.75 (d, J = 7.2 Hz, 2H), 6.61 (d, J = 8.0 Hz, 1H), 5.17 (s, 1H), 3.73 (s, 1H), 2.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 175.6, 143.4, 131.0, 129.0, 128.8, 128.7, 128.2, 126.2, 125.0, 123.6, 118.5, 109.1, 77.6, 46.2, 26.2. IR (KBr): v 3348, 2921, 2245, 1735, 1709, 1613, 1469, 1114 694 cm^{-1}. HRMS (ESI) m/z: [M+ Na]+calcd for $C_{17}H_{14}N_2O_2Na$, 301.0947; found, 301.0955.

2-(3-Hydroxy-1,5-dimethyl-2-oxoindolin-3-yl)-2-phenylacetonitrile(3b): Yellow solid; 89.1 mg, 92% yield, 99:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.78 (s, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.12− 7.05 (m, 3H), 6.78 (d, J = 7.6 Hz, 2H), 6.50 (d, J = 7.6 Hz, 1H), 4.89 (s, 1H), 3.80 (s, 1H), 2.82 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 175.4, 141.0, 133.4, 131.2, 129.2, 128.8, 128.8, 128.2, 126.2, 125.7, 118.5, 108.7, 77.7, 46.4, 26.2, 21.3. IR (KBr): v 3265, 2918, 2245, 1713, 1620, 1498, 1367, 1117, 699 cm^{-1}. HRMS (ESI) m/z: [M + Na]+calcd for $C_{18}H_{16}N_2O_2Na$, 315.1104; found, 315.1113.

2-(5-Chloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3c):. Pale yellow solid; 87.2 mg, 91% yield, 99:1 dr. ^{1}HNMR (400 MHz, $CDCl_3$): δ (ppm) 7.90 (s, 1H), 7.31 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.21 (t, J = 7.2 Hz, 1H), 7.15−7.11 (m, 2H), 6.89−6.87 (m, 2H), 6.53 (d, J = 8.4 Hz, 1H), 4.78 (br, 1H), 4.08 (s, 1H), 2.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 175.3, 141.9, 131.0, 129.3, 129.1, 128.7, 128.5, 128.5, 127.8, 125.5, 118.1, 110.0, 77.6, 46.4, 26.3. IR (KBr): v 3269, 3068, 2945, 2250, 1713, 1609, 1490, 1364, 1117, 700 cm^{-1}. HRMS (ESI) m/z: [M + Na]+calcd for $C_{17}H_{13}ClN_2O_2Na$, 335.0558; found, 335.0564.

2-(5-Bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile(3d): White solid; 73.9 mg, 91% yield, 97:3 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.02 (d, J = 2.0 Hz, 1H), 7.47 (dd, J = 8.0Hz, 2.0 Hz, 1H), 7.23−7.20 (m, 1H), 7.16−7.13 (m, 2H), 6.93 (d, J = 7.2 Hz, 2H), 6.47 (d, J = 8.4 Hz, 1H), 4.34 (s, 1H), 4.26 (s, 1H), 2.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 174.6, 142.4, 134.0, 129.2, 128.8, 128.6, 128.5, 128.3, 127.9, 117.9, 116.5, 110.2, 46.6, 26.2. IR (KBr): v 3263, 2967, 2250, 1712, 1605,

1487, 1114, 699 cm^{-1}. HRMS (ESI) m/z: [M + Na]+calcd for $C_{17}H_{13}BrN_2O_2Na$, 379.0053; found, 379.0061.

2-(5-Fluoro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3e): White solid; 74.3 mg, 90% yield, 95:5 dr. ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) 7.23−7.22 (m, 3H), 7.16−7.06 (m, 5H), 6.81−6.78 (m, 1H), 4.95 (s, 1H), 2.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6): δ (ppm) 173.9, 157,7 (d,1JCF = 237.0 Hz), 139.3 (d, 4JCF = 1.6 Hz), 130.0, 129.3 (d, 3JCF = 7.9 Hz), 129.0, 128.5, 128.0, 118.2, 116.2 (d, 2JCF = 23.1 Hz), 112.6 (d, 2JCF = 25.1 Hz), 109.5 (d, 3JCF= 8.2 Hz), 76.3, 43.7, 25.8. IR (KBr): v 3334, 2923, 2239, 1703, 1625, 1490, 1474, 1112, 662 cm^{-1}. HRMS (ESI) m/z: [M + Na]+calcd for $C_{17}H_{13}FN_2O_2Na$, 319.0853; found, 319.0858.

2-(6-Bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3f): White solid; 62.8 mg, 88% yield, 81:19 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (d, J = 8.0 Hz, 1H), 7.34−7.31 (m, 1H), 7.22−7.18 (m, 1H), 7.17−7.12 (m, 2H), 6.94−6.90 (m, 2H), 6.72(d, J = 2.0 Hz, 1H), 4.65 (s, 1H), 4.44 (s, 1H), 2.79 (s, 3H). ^{13}C NMR (100 MHz, CDCl3): δ (ppm) 175.0, 144.5, 129.7, 129.2, 128.8,128.5, 126.6, 126.4, 124.9, 124.8, 118.1, 112.2, 77.4, 46.5, 26.2. IR (KBr): v 3385, 2924, 2250, 1718, 1607, 1493, 1373, 1062, 698 cm^{-1}. HRMS (ESI) m/z: [M + Na]+calcd for $C_{17}H_{13}BrN_2O_2Na$, 379.0053; found, 379.0062.

2-(7-Bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3g): Pale yellow solid; 62.8 mg, 89% yield, 96:4 dr. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86 (d, J = 7.6 Hz, 1H), 7.46−7.44 (m, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.18−7.14 (m, 2H), 7.09−7.05 (m, 1H), 6.90 (d, J = 8.0 Hz, 2H), 4.44 (s, 1H), 3.86 (br, 1H), 3.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 175.7, 140.6, 136.6, 129.3, 129.0, 128.7, 128.5, 124.9, 124.1, 117.9, 102.9, 77.1, 47.0, 29.8. IR (KBr): v 3357, 2924, 2248, 1710, 1454, 1116, 699 cm^{-1}. HRMS (ESI) m/z: [M + Na]+calcd for $C_{17}H_{13}BrN_2O_2Na$, 379.0053; found, 379.0060.

2-(7-Chloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3h): Yellow solid; 59.8 mg, 91% yield, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (dd, J = 7.2 Hz, 1.2 Hz, 1H), 7.26− 7.22 (m, 2H), 7.16−7.11 (m, 3H), 6.88 (d, J = 7.6 Hz, 2H), 4.55 (s, 1H), 4.44 (s, 1H), 3.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 175.5, 139.2, 133.3, 129.3, 128.7, 128.7, 128.5, 124.5, 123.6, 117.9, 116.2, 47.0, 29.6. IR (KBr): v 3282, 2926, 2248, 1713, 1606, 1461, 1116, 699 cm^{-1}. HRMS (ESI) m/z: [M + Na]$^+$calcd for $C_{17}H_{13}ClN_2O_2Na$, 335.0558; found, 335.0563.

2-(3-Hydroxy-5-methoxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile(3i): White solid; 53.0 mg, 88% yield, 98:2 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (d, J = 2.0 Hz, 1H), 7.18 (t, J = 7.2Hz, 1H), 7.10 (t, J = 7.6 Hz, 2H), 6.89−6.83 (m, 3H), 6.49 (d, J = 8.8Hz, 1H), 4.84 (s, 1H), 4.16 (s, 1H), 3.86 (s, 3H), 2.80 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ (ppm) 175.2, 156.7, 136.5, 129.1, 128.8, 128.7, 128.2, 127.2, 118.4, 115.9, 111.7, 109.5, 78.0, 56.1, 46.5, 26.2. IR (KBr): v 3296, 2836, 2245, 1703, 1495, 1291, 1050, 697 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$calcd for $C_{18}H_{16}N_2O_3H$, 309.1234; found, 309.1227.

2-(3-Hydroxy-1,5,7-trimethyl-2-oxoindolin-3-yl)-2-phenylacetonitrile (3j): White solid; 96.0 mg, 86% yield, 99:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (s, 1H), 7.18 (d, J = 6.8 Hz, 1H), 7.10− 7.09 (m, 2H), 6.85 (s, 1H), 6.74 (d, J = 6.0 Hz, 2H), 4.84 (s, 1H), 3.69 (s, 1H), 3.07 (s, 3H), 2.36 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 176.1, 138.8, 135.1, 133.2, 129.5, 128.8, 128.8, 128.1, 126.9, 123.4, 120.4, 118.4, 77.1, 46.6, 29.5, 21.0, 18.6. IR (KBr): v 3422, 2921, 2242, 1728, 1704, 1105, 700 cm^{-1}. HRMS (ESI) m/z: [M + Na]$^+$calcd for $C_{19}H_{18}N_2O_2Na$, 329.1260; found, 329.1270

2-(4,7-Dichloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)-2-phenylacetonitrile(3k): White solid; 60.4 mg, 85% yield, 96:4 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.25 (d, J = 7.6 Hz, 1H), 7.19−7.15 (m,2H), 7.13 (d, J = 8.8 Hz, 1H), 7.02−6.99 (m, 3H), 5.05 (s, 1H), 3.80 (s, 1H), 3.23 (s, 3H). 13C NMR (100 MHz, $CDCl_3$): δ (ppm) 173.6, 141.2, 134.1, 130.4, 129.4, 128.8, 128.6, 128.3, 125.1, 125.1, 116.7, 114.8, 77.4, 43.9, 29.5. IR (KBr): v 3385, 2935, 2248, 1709, 1600, 1449, 1112, 699 cm^{-1}. HRMS (ESI) m/z: [M + H]+calcd for $C_{17}H_{12}C_{l2}N_2O_2H$, 347.0349; found, 347.0354.

2-(3-Hydroxy-1-methyl-2-oxo-5-(trifluoromethoxy) indolin-3-yl)- 2-phenylacetonitrile (3l): Yellow solid; 68.8 mg, 90% yield, 99:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.79 (s, 1H), 7,23−7.19 (m, 2H), 7.15−7.11 (m, 2H), 6.96−6.92 (m, 2H), 6.56 (d, J = 8.8 Hz, 1H), 4.45 (d, J = 7.6 Hz, 1H), 4.16 (br, 1H), 2.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 175.2, 145.4 (q, 3JCF = 2.1 Hz), 141.8, 129.2, 128.6, 128.5, 127.4, 124.2, 119.3, 117.8, 109.4, 77.7, 46.6, 26.3. IR (KBr): v 3270, 2932, 2250, 1714, 1496, 1254, 1214, 1167, 1113, 703 cm^{-1}. HRMS (ESI) m/z:

[M + H]$^+$calcd for $C_{18}H_{13}F_3N_2O_3H$, 363.0951; found, 363.0949.

2-(3-Hydroxy-2-oxoindolin-3-yl)-2-phenylacetonitrile (3m): White solid; 42.3 mg, 89% yield, 84:16 dr. ^{1}H NMR (400 MHz,MeOD): δ (ppm) 7.79 (d, J = 8.0 Hz, 1H), 7.28−7.18 (m, 3H), 7.15− 7.10 (m, 3H), 6.97−6.95 (m, 2H), 6.62 (d, J = 8.0 Hz, 1H), 4.52 (s, 1H). 13C {1H} NMR (100 MHz, MeOD): δ (ppm) 178.6, 143.2, 131.7, 131.1, 130.2, 129.7, 129.3, 128.5, 126.2, 123.6, 120.0, 111.2, 78.5, 46.7. IR (KBr): v 3345, 3181, 2926, 2248, 1735, 1709, 1613, 1469, 1114, 752 cm^{-1}. HRMS (ESI/) m/z: [M + Na]+calcd for $C_{16}H_{12}N_2O_2Na$, 287.0791; found, 287.0798.

2-(1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)-2-phenylacetonitrile (3n): White solid; 62.4 mg, 91% yield, 99:1 dr. ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) 7.74 (d, J = 7.2 Hz, 1H), 7.36 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.27−7.11 (m, 8H), 6.89 (d, J = 7.6 Hz, 2H), 6.61 (d, J = 6.8 Hz, 2H), 6.53 (d, J = 8.0 Hz, 1H), 4.75 (s, 1H), 4.72 (d, J = 16.4 Hz, 1H), 4.47 (d, J = 16.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d6): δ (ppm) 174.2, 142.5, 135.1, 130.3, 129.8, 129.0, 128.7, 128.4, 128.3, 127.0, 126.9, 126.4, 124.4, 122.7, 119.3, 109.4, 76.2, 44.7, 42.6. IR (KBr): v 3438, 3034, 2907, 2248, 1724, 1613, 1491, 1368, 1048, 697 cm^{-1}. HRMS (ESI) m/z: [M + H]+calcd for $C_{23}H_{18}N_2O_2H$, 355.1441; found, 355.1446.

2-(3-Hydroxy-1-methyl-2-oxoindolin-3-yl)-2-(4-(trifluoromethyl) phenyl)acetonitrile (3o): White solid; 65.8 mg, 90% yield, 99:1 dr. ^{1}H NMR(400 MHz, $CDCl_3$): δ (ppm) 7.98 (d, J = 7.6 Hz, 1H), 7.38−7.32 (m, 3H), 7.23 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 7.6 Hz, 1H), 5.50 (s, 1H), 3.54 (s, 1H), 2.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 175.5, 143.3, 133.0, 131.4, 131.1 (q, 2JCF = 32.8 Hz), 129.2, 125.8, 125.1 (q, 3JCF = 3.7 Hz), 125.0, 123.8, 123.7 (q, 1JCF = 270.8 Hz), 117.9, 109.6, 45.8, 26.3. IR (KBr): v 3410 2921 2244 1707 1613 1325 1116 1069 755 cm−1. HRMS (ESI) m/ z: [M + Na]+calcd for $C_{18}H_{13}F_3N_2O_2Na$, 369.0821; found, 369.0823.

2-(4-Fluorophenyl)-2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)- acetonitrile (3p): White solid; 50.4 mg, 85% yield, 99:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.92 (d, J = 7.6 Hz, 1H), 7.36 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.24−7.20 (m, 1H), 6.89−6.87 (m, 2H), 6.82−6.78 (m, 2H), 6.61 (d, J = 7.6 Hz, 1H), 4.36 (s, 1H), 4.12 (br, 1H), 2.87 (s, 3H). ^{13}C NMR(100 MHz, $CDCl_3$): δ (ppm) 175.4, 162.9 (d, 1JCF = 247.5 Hz), 143.4, 131.2, 130.6 (d, 3JCF = 8.4 Hz), 125.9, 125.0, 125.0 (d, 4JCF = 3.3 Hz), 123.8, 118.3, 115.3 (d, 2JCF = 21.7 Hz), 109.1, 77.6, 45.6, 26.2. IR (KBr): v 3340 2926 2248 1713 1698 1613 1511 1246 1116 757 cm−1. HRMS (ESI) m/z: [M + Na]+calcd for $C_{17}H_{13}FN_2O_2Na$, 319.0853; found, 319.0862.

2-(4-Chlorophenyl)-2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)- acetonitrile (3q): White solid; 56.7 mg, 89% yield, 97:3 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.93 (d, J = 7.6 Hz, 1H), 7.34 (td, J = 8.0 Hz, 1.2 Hz, 1H), 7.22−7.18 (m, 1H), 7.04 (d, J = 8.4 Hz, 2H), 6.69− 6.66 (m, 3H), 5.34 (s, 1H), 3.65 (s, 1H), 2.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 175.4, 143.4, 135.1, 131.2, 130.1, 128.5, 127.7, 125.9, 125.0, 123.7, 118.1, 109.3, 45.6, 26.3. IR (KBr): v 3397,2923, 2250, 1708, 1613, 1494, 1470, 1093, 757 cm−1. HRMS (ESI) m/z: [M + Na]+calcd for C17H13ClN2O2Na, 335.0558; found, 335.0565.

2-(4-Bromophenyl)-2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-acetonitrile (3r): White solid; 63.6 mg, 85% yield, 97:3 dr. ^{1}H NMR(400 MHz, $CDCl_3$): δ (ppm) 7.92 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 7.6Hz, 1H), 7.23−7.19 (m, 3H), 6.72−6.70 (m, 2H), 6.65 (d, J = 7.6 Hz,1H), 4.78 (s, 1H), 4.04 (br, 1H), 2.89 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 175.1, 143.3, 131.5, 131.3, 130.4, 128.1, 125.7, 125.0, 123.9, 123.3, 118.0, 109.2, 77.4, 45.8, 26.3. IR (KBr): v 3386,2914, 2245, 1707, 1613, 1493, 1470, 1115, 755 cm^{-1}. HRMS (ESI) m/z: [M + Na]+calcd for $C_{17}H_{13}BrN_2O_2Na$, 379.0053;found, 379.0062.

Results and Discussion

Initially, the model reaction of *N*-methyl isatin **1** and phenylacetonitrile **2** was investigated under catalytic electrolytic conditions (Table 1). In the present work a catalyst free reaction using *N*-methyl isatin, phenyl acetonitrile reactants, and lithium perchlorate were used as an electrolyte and ethanol as solvent. The electrochemical synthesis was carried out in an undivided cell equipped with a platinum electrode used as working as well as a counter electrode at room temperature at constant potential. The progress of the reaction was monitored by thin layer chromatography. After the electrolysis was complete (6 h) the mixture was filtered and solvent was evaporated under vacuum, washed with water and petroleum ether to furnish the desired product.

Different potentials were applied to monitor the reaction under mentioned condition for conversion of starting material into product. It was observed that when the electrochemical synthesis was carried out in

Table 1 — Optimization of reaction conditions[a]

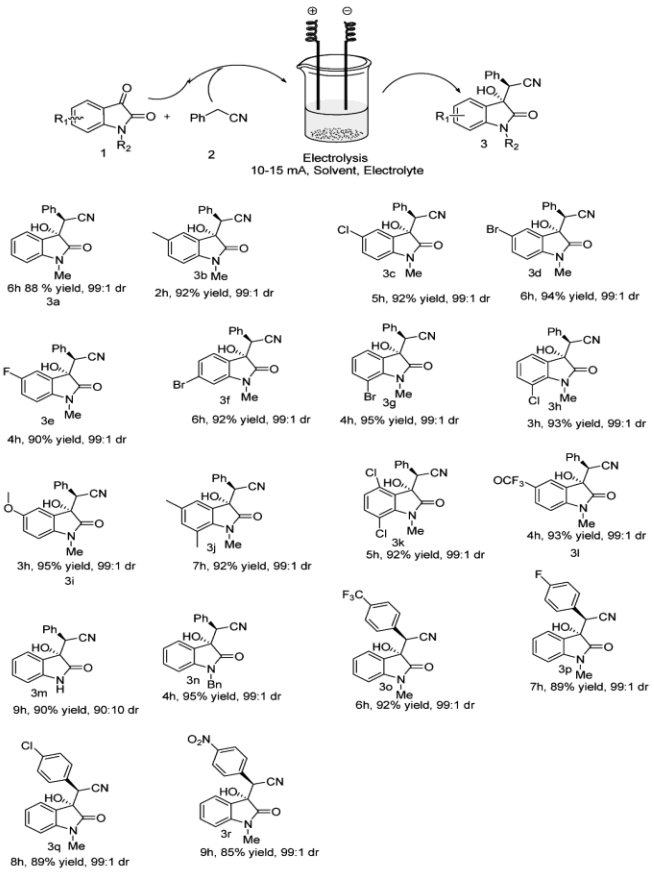
Entry	Solvent	Potential (V)	Current (mA)	Time (h)	Electrolyte	Yield(%)[b]
1	MeOH	1.5	10	12	$LiClO_4$	75
2	MeOH	1.5	10	8	$LiClO_4$	70
3	EtOH	1.5	5	15	$LiClO_4$	65
4	EtOH	1.4	10	6	$LiClO_4$	70
5	EtOH	1.0	10	10	$LiClO_4$	65
6	EtOH	1.5	10	6	$LiClO_4$	92
7	EtOH	1.5	15	10	$LiClO_4$	75
8	EtOH	1.5	20	10	$LiClO_4$	68
9	EtOH	1.5	10	10	KBr	65
10	EtOH	1.5	10	12	NaBr	66
11	EtOH	1.5	15	20	Bu_4NClO_4	65
12	MeCN	1.5	10	8	$LiClO_4$	60
13	*n*-PrOH	1.5	10	20	$LiClO_4$	65

[a]All reactions were run with N-methyl isatin 1 and phenyl acetonitrile 2various electrolyte (0.5 M), platinum cathode (5 cm^2), platinum anode (5 cm^2).) in various solvents (20 mL) in a beaker, for 6- 20 h and reaction mixture was monitored by TLC.
[b]Isolated yield of the product **3**

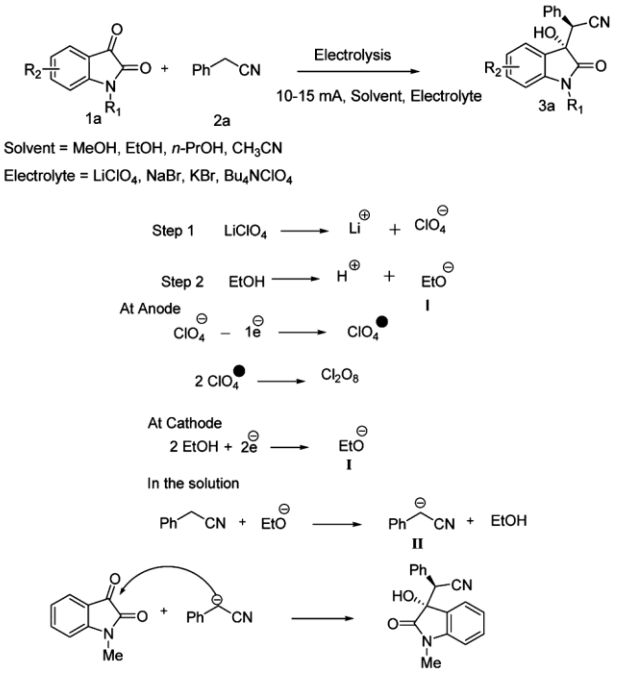
an undivided cell equipped with Pt electrode surface (1 cm^2) and potential of reaction 1.50 V was found to be optimal using lithium perchlorate as electrolyte and ethanol as solvent at room temperature. The reaction conditions were optimized with various solvents and potentials. The reactions are tested with solvents such as EtOH, MeCN, *n*-PrOH, and MeOH at a constant potential (1.5 V) the yield of β hydroxyl nitrile (**3**) was good, EtOH was the best solvent in terms of the reaction time, current and excellent yields (Table 1, entry 6), which indicates that the reaction is not very sensitive to reaction media. Hence it was used as standard condition throughout the present work.

With the optimized electrolysis parameters in hand we applied the method to a range of substrate in order to elucidate the scope and the generality of the protocol by examining the reactions of β hydroxyl nitrile (**3a**). We are pleased to find that reaction works with wide range of *N* substituted isatin1a (Table 2 entries **3a-r**), phenyl acetonitrile 2a.

Table 2 — Substrate scope for the preparation of 3 substituted 3-Hydroxy-3-cynomethyl oxindole derivatives



[a]For experimental procedure, see supporting information
[b]All compounds are known and were characterized by comparison of their spectral data with those reported in the literature[6b]
[c]Yields of isolated pure compounds 3



Scheme 2 — Reaction mechanism

In present work we report a catalyst free two component reaction using N substituted isatin **1a** (1.5 mmol), phenyl acetonitrile **2a** (1.6 mmol), lithium perchlorate (0.5 M) was used as an electrolyte and ethanol (20 mL) as solvent. The electrochemical synthesis was carried out in an undivided cell equipped with platinum rods (5 cm^2) as anode and platinum (5 cm^2) as cathode at room temperature under constant reaction potential (1.5 V). The progress of the reaction was monitored by TLC using hexane/ethyl acetate mixture.

Initially, we selected N-methyl isatin **1a** and phenyl acetonitrile **2a** as the model starting materials to optimize the reaction. Subsequently, the influence of solvents, electrolyte and current density was studied (Table 1). Performing the electrolysis in various solvent such as MeOH, EtOH, *n*-PrOH and MeCN (Table 1, entries 1-12) reaction proceeded in all these solvents, among these solvent we found that EtOH (Table 1, entry 6) is found to be best in terms of yield. Current density rendered the best yieldswith 10 mA cm^{-2} (Table 1, entry 6), whereas lower (5 mA cm^{-2}) (Table 1, entry 3) or higher (20 mA cm^{-2}) (Table 1, entry 8) current densities resulted in decreased yields. We examined similar transformation in various phase transfer catalyst such as $LiClO_4$, NaBr, KBr, Bu_4NClO_4 (Table 1, entries 1-13) among these catalyst $LiClO_4$ (Table 1, entry 6) is found to be best in terms of yield.

We anticipate that anion of phenyl acetonitrile II act as intermediates, which is directly generated at the anode by reaction of phenyl acetonitrile and in situ generation ethoxide ion in ethanol solvent. Knoevenagel reaction of *N*-methyl isatin with phenyl acetonitrile anion takes place in the solution to give the adduct **III** furnishes the desired product **3** in the 92 % yield Scheme 2.

The substrate scope of the reaction was investigated after deriving the optimized electrolysis parameters in hand, we applied the method to a range of substrates in order to elucidate the scope of the reaction (Table 2). We were pleased to find that reaction works with wide range of isatins (Table 2, entries 3a-r) lead to the transformation of desired product. Isatin bearing electron withdrawing and electron donating substituents seemed to be beneficial to the catalysis, and the steric hindrance seemed to have few effects on the results (Table 2, entries 3g-h, 3k). It is worthy to mention here that reaction works with N benzylated isatin (Table 2, entries 3n) and isatin with free NH (Table 2, entries 3m) in higher yield.

Conclusion

An environmentally friendly, electrochemical reaction protocol for the synthesis of β-hydroxyl nitrilesis demonstrated here. These reactions were conducted using in platinum electrodes in a beaker open to air, and $LiClO_4$ was used as the supporting electrolyte. The reaction procedure was simple, efficient and the reaction conditions were mild.

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References

1 (a) Anastas P T & Kirchhoff M M, *Acc Chem Res*, *35* (2002) 686; (b) Anastas P T & Warner J C, *Green Chemistry*: *Theory and Practice* (Oxford University Press, New York) 1997.

2 (a) Hilt G, *Angew Chem Int Ed*, 42 (2003) 1720; (b) Seka S, Burize O, Jean-Yves N & Jacques P, *Chem A Eur J*, 8 (2002) 2534; (c) Gomes P, Gosmini C, Pe´richon J, *J Org Chem*, 68 (2003) 1142; (d) Grigg R, Putnikovic B & Urch C J, *Tetrahedron Lett*, 38 (1997) 6307; (e) Hilt G, *Angew Chem Int Ed*, 41(2002) 3586; (f) Nematollahi D & Rahchamani R A, *J Electroanal Chem*, 520 (2002) 145.

3 Wang L, Gao J, Wan L, Wang Y & Yao C, *Res Chem Intermed*, 41 (2015) 2775.

4 (a) Fleming F F, *Nat Prod Rep*, 16 (1999) 597; (b) Fleming F F, Yao L H, Ravikumar P C, Funk L & Shook B C, *J Med Chem*, 53 (2010) 7902; (c) Mesa R A, Yasothan U, Kirkpatrick P, *Nat Rev Drug Discovery*, 11 (2012) 103.

5 (a) Rappoport Z & Patai S, *Chemistry of the Cyano Group*, (Wiley: London), 1970; (b) Fleming F F & Wang Q, *Chem Rev*, 103 (2003) 2035.

6 (a) López R & Palomo C, *Angew Chem Int Ed*, 54 (2015) 13170; (b) Zhang Y, Luo L, Ge J, Yan S Q, Peng Y X, Liu Y R, Liu J X, Liu C, Ma T & Luo H Q, *J Org Chem*, 84 (2019) 4000.

7 (a) Singh V K, Sharma L K & Singh R K P, *Tetrahedron Lett*, 57 (2016) 407; (b) Upadhyay A, Sharma L K, Singh V K & Singh R K P, *Tetrahedron Lett*, 57 (2016) 5599; (c) Singh V K, Upadhyay A & Singh R K P, *Tetrahedron Lett*, 58 (2017) 156; (d) Upadhyay A, Sharma L K, Singh V K, Dubey R, Kumar N & Singh R K P, *Tetrahedron Lett*, 58 (2017) 1245; (e) Dubey R, Singh V K, Sharma L K, Upadhyay A, Kumar N & Singh R K P, *New J. Chem*, 41 (2017) 7836; (f) Singh V K, Dubey R, A. Upadhyay, Sharma L K & Singh R K P, *Tetrahedron Lett*, 58 (2017) 4227.