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FULL LENGTH PAPER

Electrocatalytic multicomponent assembling of isatins, 3-methyl-2-pyrazolin-5-ones and malononitrile: facile and convenient way to functionalized spirocyclic [indole-3,4′-pyrano[2,3-*c*]pyrazole] system

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Abstract Electrochemically induced catalytic multicomponent transformation of isatins, 3-methyl-2-pyrazolin-5-ones and malononitrile in ethanol in an undivided cell in the presence of sodium bromide as an electrolyte results in the formation of spirooxindoles with fused functionalized pyrano[2,3-*c*]pyrazole system in 78–99% yields. The developed efficient electrocatalytic approach to medicinally relevant spirocyclic [indole-3,4′-pyrano[2,3-*c*]pyrazoles] is beneficial from the viewpoint of diversity-oriented large-scale processes and represents a novel example of facile environmentally benign synthetic concept for electrocatalytic multicomponent reaction strategy.

Keywords Electrocatalysis · Multicomponent reactions · Pyranopyrazole · Spirooxindole · Isatin · C–H acids

Introduction

The discovery of novel synthetic methodologies to facilitate the preparation of compound libraries is a pivotal focal point of research activity in the field of modern medicinal and combinatorial chemistry [1,2]. One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials [3,4]. The rapid assembly of molecular diversity utilizing MCRs has received a great deal of attention in the search for novel lead structures, especially for the design and construction of elaborate small-molecule heterocyclic frameworks possessing enhanced "drug-like" properties [5–7]. Thus, the success of combinatorial chemistry in the drug discovery process is considerably dependent on further advances in heterocyclic MCR methodology and, according to current synthetic requirements, environmentally benign multicomponent procedures are particularly welcome.

The heterocyclic spirooxindole ring system is a widely distributed structural framework present in a number of pharmaceuticals and natural products [8], including cytostatic alkaloids such as spirotryprostatins A, B, and strychnophylline [9,10]. The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets [11]. Among different heterocycles fused with spirooxindole ring system, pyrano[2,3-*c*]pyrazoles are of particular interest due to their anticancer activity through the selective inhibition of human Chk 1 kinase, which plays an essential role in the regulation of the cell cycle G2/M checkpoint [12]. The modification of the selective Chk 1 inhibitors with pharmacopeial spirooxindole fragment should prove useful to study the regulation of G2/M checkpoint from a medicinal and biological point of view [9,12]. Furthermore, the corresponding 6′-amino-3′-methyl-2-oxo-1,2-dihydro-1′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitriles appear to be effective antibacterial and antifungal agents [13].

The general approach to fuse spirooxindoles and a 6-amino-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile system utilizes linear two-step synthesis including preliminary Knoevenagel condensation of isatin and malononitrile with further addition of pyrazolone and cyclization under basic conditions [14–17]. The application of stepwise reaction sequence avoids low selectivity in concurrent condensation of isatin with the two reactive C–H acids and

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provides the target spirooxindoles in good yields, but requires the separation and purification of desired compounds after each stage. To the best of our knowledge, there is only a single report of an effective multicomponent entry to the synthesis of 6′-amino-3′-methyl-2-oxo-1,2-dihydro-1′*H*-spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitriles. In 2007 Shanthi et al. reported a three-component condensation of isatins, 3-methyl-2-pyrazolin-5-ones and malononitrile catalyzed by 20 mol% of indium(III) chloride [18]. Although this catalytic MCR leads to a number of spiro[indole-3,4′-pyrano[2,3-*c*]pyrazoles] in 70–90% yields, it requires either reflux in acetonitrile for 1.5–2 h or microwave irradiation. Furthermore, column chromatography is needed for purification of desired products. Thus, the known multicomponent procedure for the synthesis of corresponding spirocyclic [indole-3,4′-pyrano[2,3-*c*]pyrazole] system has its merits, but the essence of facile and convenient MCR methodology deserves further development.

The advances in electrosynthesis in the last few decades have provided organic chemists with a new versatile synthetic device of great promise [19]. Despite the significant synthetic potential and ecological advantages of electrochemical methods, the practical usage of electrochemical procedures is often limited due to technical complexities and generally long processing times. In the course of our study on the electrochemical transformation of organic compounds, we have found a new type of electrochemical transformation, namely the electrocatalytic chain transformation of organic compounds induced by a catalytic amount of an electrogenerated base in an undivided cell [20]. Recently, we have successfully applied this electrocatalytic procedure, developed by us, for the synthesis of a number of medicinally relevant 4*H*-chromene derivatives bearing nitrile functionality [21–23]. These unique electrochemical procedures utilize a simple undivided cell and are amenable for large-scale processes because of their catalytic nature and the use of a cheap and environmentally responsible chemical reagent—electricity. The use of the described electrocatalytic methodology in base-activated MCRs is highly promising as it allows for the combination of the synthetic virtues of the conventional MCR strategy with the ecological benefits and convenience of the facile electrocatalytic procedure.

Considering our preliminary results on the electrocatalytic chain transformation of C–H acids and aryl aldehydes as well as the certain biomedical applications of spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] derivatives mentioned above, we were prompted to design a convenient and facile electrocatalytic MCR methodology for the efficient synthesis of functionalized spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] system based on electrochemically induced reaction of isatins, 3-methyl-2-pyrazolin-5-ones and malononitrile.

Experimental

General remarks

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer at ambient temperature. Chemical shifts values are relative to Me_4Si. Mass-spectra (EI = 70 eV) were obtained directly with a Finningan MAT INCOS 50 spectrometer. All starting materials were obtained from commercial sources and used without further purification.

Typical electrolysis procedure

A solution of isatin (10 mmol), 3-methyl-2-pyrazolin-5-one (10 mmol), malononitrile (0.66 g, 10 mmol), and sodium bromide (0.1 g, 1 mmol) in ethanol (20 mL) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode, and an iron cathode at ambient temperature under a constant current density indicated in Tables 2 and 3 (electrodes square 5 cm^2) until the catalytic quantity of 0.04 F/mol of electricity was passed. After the electrolysis was finished, the solution was filtered to isolate the solid product, which was then rinsed with an ice-cold ethanol/water solution (9:1, 2 mL) and dried under reduced pressure.

*6′-amino-3′-methyl-2-oxo-1′-phenyl-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**3a**)*

White powder, yield 95%, 3.51 g; mp 236–237 °C (lit [16] mp 237 °C). ^{1}H NMR (300 MHz, [D_6]DMSO), δ_H 1.54 (s, 3H, CH_3), 6.94 (d, $^{3}J_{H,H}$ = 7.7 Hz, 1H, Ar), 7.03 (t, $^{3}J_{H,H}$ = 7.4 Hz, 1H, Ar), 7.18 (d, $^{3}J_{H,H}$ = 7.3 Hz, 1H, Ar), 7.28 (t, $^{3}J_{H,H}$ = 7.6 Hz, 1H, Ar), 7.35 (t, $^{3}J_{H,H}$ = 7.9 Hz, 1H, Ph), 7.52 (t, $^{3}J_{H,H}$ = 7.9 Hz, 2H, Ph), 7.57 (s, 2H, NH_2), 7.78 (d, $^{3}J_{H,H}$ = 7.9 Hz, 2H, Ph), 10.74 (s, 1H, NH) ppm.

*6′-amino-1,3′-dimethyl-2-oxo-1′-phenyl-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**3b**)*

White powder, yield 89%, 3.41 g; mp 226–227 °C (lit [16] mp 227 °C). ^{1}H NMR (300 MHz, [D_6]DMSO), δ_H 1.46 (s, 3H, CH_3), 3.25 (s, 3H, NCH_3), 7.06–7.20 (m, 2H, Ar), 7.24 (d, $^{3}J_{H,H}$ = 7.5 Hz, 1H, Ar), 7.30–7.45 (m, 2H, Ar, Ph), 7.52 (t, $^{3}J_{H,H}$ = 7.9 Hz, 2H, Ph), 7.61 (s, 2H, NH_2), 7.79 (d, $^{3}J_{H,H}$ = 7.9 Hz, 2H, Ph) ppm.

*6′-amino-1-benzyl-3′-methyl-2-oxo-1′-phenyl-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**3c**)*

Brown powder, yield 85%, 3.90 g; mp 214 − 215 °C. MS, *m/z* (%) = 459 (M^+, 5), 393 (17), 368 (24), 302 (14), 285 (23), 174 (42), 91 (100), 77 (67). Anal. Calcd. for $C_{28}H_{21}N_5O_2$ (459.5): C, 73.19%; H, 4.61%; N, 15.24%, Found C, 73.11%; H, 4.66%; N, 15.08%. ^{1}H NMR (300 MHz, [D$_6$]DMSO), δ_H 1.35 (s, 3H, CH_3), 4.93 (d, $^2J_{H,H}$ = 15.9 Hz, 1H, CH_2Ph), 5.06 (d, $^2J_{H,H}$ = 15.9 Hz, 1H, CH_2Ph), 7.03–7.14 (m, 2H, Ar), 7.23–7.38 (m, 6H, Ar), 7.39–7.47 (m, 2H, Ar), 7.49–7.57 (m, 2H, Ar), 7.65 (s, 2H, NH_2), 7.79 (d, $^3J_{H,H}$ = 7.7 Hz, 2H, Ar) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO), δ_C 12.2, 43.8, 48.0, 56.4, 96.6, 110.0, 118.4, 120.6 (2C), 123.9, 125.3, 127.1, 128.0 (3C), 129.0 (2C), 129.8, 129.9 (2C), 131.8, 136.5, 137.7, 142.6, 144.3, 145.5, 161.6, 176.6 ppm.

*6′-amino-5-chloro-3′-methyl-2-oxo-1′-phenyl-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**3d**)*

White powder, yield 83%, 3.35 g; mp 232–234 °C (lit [24] mp 230 − 232 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO), δ_H 1.59 (s, 3H, CH_3), 6.96 (d, $^3J_{H,H}$ = 8.1 Hz, 1H, Ar), 7.30–7.41 (m, 3H, Ar, Ph), 7.52 (t, $^3J_{H,H}$ = 7.9 Hz, 2H, Ph), 7.63 (s, 2H, NH_2), 7.79 (d, $^3J_{HH}$ = 7.8 Hz, 2H, Ph), 10.88 (s, 1H, NH) ppm.

*6′-amino-3′,5-dimethyl-2-oxo-1′-phenyl-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**3e**)*

White powder, yield 98%, 3.76 g; mp 288–289 °C. MS, *m/z* (%) = 383 (M^+, 0.5), 371 (9), 289 (10), 288 (10), 222 (11), 209 (100), 208 (22), 174 (69). Anal. Calcd. for $C_{22}H_{17}N_5O_2$ (383.4): C, 68.92%; H, 4.47%; N, 18.27%, Found C, 68.79%; H, 4.52%; N, 18.13%. ^{1}H NMR (300 MHz, [D$_6$]DMSO), δ_H 1.56 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 6.83 (d, $^3J_{H,H}$ = 7.7 Hz, 1H, Ar), 7.00 (s, 1H, Ar), 7.08 (d, $^3J_{H,H}$ = 7.7 Hz, 1H, Ar), 7.35 (t, $^3J_{H,H}$ = 7.9 Hz, 1H, Ph), 7.51 (d, $^3J_{H,H}$ = 8.0 Hz, 2H, Ph), 7.55 (s, 2H, NH_2), 7.78 (d, $^3J_{H,H}$ = 8.1 Hz, 2H, Ph), 10.63 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$] DMSO), δ_C 11.8, 20.6, 47.9, 56.4, 96.5, 109.6, 118.1, 120.2 (2C), 125.4, 126.6, 129.5 (2C), 129.6, 131.7, 132.3, 137.3, 139.2, 144.1, 145.0, 161.0, 177.5 ppm.

*6′-amino-3′-methyl-2-oxo-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**3f**)*

White powder, yield 85%, 2.49 g; mp 278–280 °C (decomp) (lit [14] mp 275 °C). ^{1}H NMR (300 MHz, [D$_6$]DMSO), δ_H 1.52 (s, 3H, CH_3), 6.90 (d, $^3J_{H,H}$ = 7.8 Hz, 1H, Ar), 6.95–7.05 (m, 2H, Ar), 7.17–7.27 (m, 3H, Ar, NH_2), 10.58 (s, 1H, NH), 12.28 (s, 1H, NH) ppm.

*6′-amino-1,3′-dimethyl-2-oxo-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**3g**)*

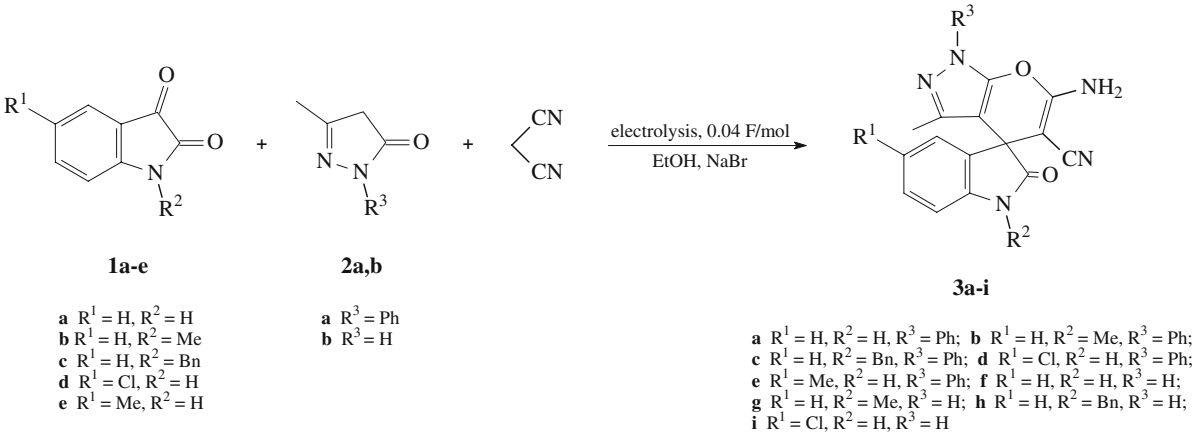
White powder, yield 99%, 3.04 g; mp >320 °C. MS, *m/z* (%) = 307 (M^+, 30), 281 (45), 279 (46), 278 (100), 222 (30), 154 (12), 140 (15). Anal. Calcd. for $C_{16}H_{13}N_5O_2$ (307.3): C, 62.53%; H, 4.26%; N, 22.79%, Found C, 62.46%; H, 4.32%; N, 22.64%. ^{1}H NMR (300 MHz, [D$_6$]DMSO), δ_H 1.45 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 7.06–7.14 (m, 3H, Ar), 7.25 (s, 2H, NH_2), 7.31–7.41 (m, 1H, Ar), 12.29 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO), δ_C 9.0, 26.4, 47.0, 54.8, 95.3, 108.7, 118.7, 123.3, 124.2, 129.1, 132.0, 134.8, 143.0, 155.3, 162.7, 176.4 ppm.

*6′-amino-1-benzyl-3′-methyl-2-oxo-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**3h**)*

White powder, yield 83%, 3.18 g; mp 263–265 °C. MS, *m/z* (%) = 383 (M^+, 5), 354 (6), 293 (15), 292 (76), 92 (8), 91 (100), 65 (24). Anal. Calcd. for $C_{22}H_{17}N_5O_2$ (383.4): C, 68.92%; H, 4.47%; N, 18.27%, Found C, 68.85%; H, 4.53%; N, 18.13%. ^{1}H NMR (300 MHz, [D$_6$]DMSO), δ_H 1.35 (s, 3H, CH_3), 4.91 (d, $^2J_{H,H}$ = 15.6 Hz, 1H, CH_2Ph), 5.00 (d, $^2J_{H,H}$ = 15.6 Hz, 1H, CH_2Ph), 7.00–7.14 (m, 3H, Ar), 7.23–7.36 (m, 6H. Ar, NH_2), 7.37–7.44 (m, 2H, Ar), 12.30 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO), δ_C 9.0, 43.2, 47.1, 55.0, 95.3, 109.4, 118.8, 123.4, 124.5, 127.6 (3C), 128.6 (2C), 129.0, 131.9, 134.9, 136.2, 142.1, 155.4, 162.7, 176.7 ppm.

*6′-amino-5-chloro-3′-methyl-2-oxo-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**3i**)*

Off-white powder, yield 78%, 2.56 g; mp 306–307 °C. MS, *m/z* (%) = 327 (M^+, 5), 298 (62), 66 (100), 39 (90). Anal. Calcd. for $C_{15}H_{10}ClN_5O_2$ (327.7): C, 54.97%; H, 3.08%; Cl 10.82%; N, 21.37%, Found C, 54.83%; H, 3.10%; Cl 10.78%; N, 21.22%. ^{1}H NMR (300 MHz, [D$_6$]DMSO), δ_H 1.58 (s, 3H, CH_3), 6.92 (d, $^3J_{H,H}$ = 8.2 Hz, 1H, Ar), 7.12 (s, 1H, Ar), 7.24–7.33 (m, 3H, NH_2, Ar), 10.73 (s, 1H, NH), 12.33 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO), δ_C 9.1, 47.7, 54.6, 94.8, 111.3, 118.7, 124.7, 126.6, 129.0, 134.8, 134.9, 140.4, 155.2, 162.6, 178.1 ppm.



1a-e

a $R^1 = H, R^2 = H$
b $R^1 = H, R^2 = Me$
c $R^1 = H, R^2 = Bn$
d $R^1 = Cl, R^2 = H$
e $R^1 = Me, R^2 = H$

2a,b

a $R^3 = Ph$
b $R^3 = H$

3a-i

a $R^1 = H, R^2 = H, R^3 = Ph$; **b** $R^1 = H, R^2 = Me, R^3 = Ph$;
c $R^1 = H, R^2 = Bn, R^3 = Ph$; **d** $R^1 = Cl, R^2 = H, R^3 = Ph$;
e $R^1 = Me, R^2 = H, R^3 = Ph$; **f** $R^1 = H, R^2 = H, R^3 = H$;
g $R^1 = H, R^2 = Me, R^3 = H$; **h** $R^1 = H, R^2 = Bn, R^3 = H$;
i $R^1 = Cl, R^2 = H, R^3 = H$

Scheme 1 Electrocatalytic transformation of isatins, 3-methyl-l-phenyl-2-pyrazolin-5-ones and malononitrile into spiro[indole-3,4′-pyrano[2,3-c]pyrazoles]

Results and discussion

In the present study we report our results on electrocatalytic multicomponent chain transformation of isatins **1**, 3-methyl-2-pyrazolin-5-ones **2** and malononitrile into corresponding spiro[indole-3,4′-pyrano[2,3-*c*]pyrazoles] **3** under mild conditions by the combined electrolysis in an undivided cell. The reaction is performed in ethanol in the presence of sodium bromide as an electrolyte (Scheme 1).

First, to evaluate the synthetic potential of the procedure proposed and to optimize the electrolysis conditions, the electrocatalytic multicomponent transformation of isatin **1a**, 3-methyl-1-phenyl-2-pyrazolin-5-one **2a** and malononitrile into spirocyclic [indole-3,4′-pyrano[2,3-*c*]pyrazoles] **3a** was studied (Table 1).

Excellent conversions of the starting materials were obtained under all current densities studied after 0.04 F/mol of electricity had been passed. The current density 2 mA/cm^2 ($I = 10$ mA, electrodes surface 5 cm^2) was found to be optimal for the electrochemically induced chain process and allowed for the highest yield of spiro[indole-3,4′-pyrano[2,3-*c*]pyrazoles] **3a**. An increase in the current density up to 10 mA/cm^2 ($I = 50$ mA) resulted in significant decrease in the reaction yield, and may be a result of the activation of the undesired direct electrochemical processes that lead to oligomerization of the starting material.

Under the optimal conditions (current density 2 mA/cm^2, 0.04 F/mol passed) the electrolysis of isatins **1a–e**, 3-methyl-2-pyrazolin-5-ones **2a,b** and malononitrile in an undivided cell in ethanol affords corresponding spiro[indole-3,4′-pyrano[2,3-*c*]pyrazoles] **3a–e** and **3g–i** in yields of 78–99% at ambient temperature over 64 min reaction period (Table 2). It should be mentioned that the yield of spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] **3f** under electrolysis conditions reported in Table 2 surprisingly comprised only 51%. Nevertheless,

Table 1 Electrocatalytic transformation of isatin **1a**, 3-methyl-1-phenyl-2-pyrazolin-5-one **2a** and malononitrile into spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] **3a**[a]

I (mA)	Current density (mA/cm^2)	Time (min)	Electricity passed (F/mol)	Yield of **3a** (%)[b]
50	10	13	0.04	51
25	5	26	0.04	57
10	2	64	0.04	95
5	1	128	0.04	89

[a] **1a** (10 mmol), **2a** (10 mmol), malononitrile (10 mmol), NaBr (1 mmol), EtOH (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C
[b] Yield of isolated product obtained by filtration of reaction mixture

the additional current density variation experiments in this case allowed to obtain spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] **3f** in 85% yield by increasing the electrolysis current density from 2 mA/cm^2 to 5 mA/cm^2 (Table 3).

In all performed multicomponent electrocatalytic processes spiro[indole-3,4′-pyrano[2,3-*c*]pyrazoles] **3a–i** were directly crystallized from the reaction mixture after electrolysis and did not require any further purification.

With the above results taken into consideration and the mechanistic data on the electrocatalytic chain cyclizations previously performed by us [21–23], the following mechanism for the electrocatalytic chain transformation of isatins **1**, 3-methyl-2-pyrazolin-5-ones **2** and malononitrile into substituted spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] **3** is proposed. The catalytic cycle begins with the deprotonation of a molecule of alcohol at the cathode, which leads to the formation of an ethoxide anion. The subsequent reaction between the ethoxide anion and malononitrile gives rise to the malononitrile anion (Scheme 2).

The following process in the solution represents a typical cascade reaction. Knoevenagel condensation of the malono-

Table 2 Electrocatalytic transformation of isatins **1a–e**, 3-methyl-2-pyrazolin-5-ones **2a, b** and malononitrile into spiro[indole-3,4′-pyrano[2,3-*c*]pyrazoles] **3a–i**[a]

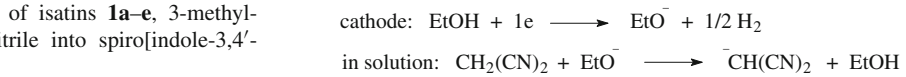
Isatin	Pirazolin-5-one	Time (min)	Electricity passed (F/mol)	Product	Yield of **3** (%)[b]
1a	**2a**	64	0.04	**3a**	95
1b	**2a**	64	0.04	**3b**	89
1c	**2a**	64	0.04	**3c**	85
1d	**2a**	64	0.04	**3d**	83
1e	**2a**	64	0.04	**3e**	98
1a	**2b**	64	0.04	**3f**	51
1b	**2b**	64	0.04	**3g**	99
1c	**2b**	64	0.04	**3h**	83
1d	**2b**	64	0.04	**3i**	78

[a] **1** (10 mmol), **2** (10 mmol), malononitrile (10 mmol), NaBr (1 mmol), EtOH (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), current density 2 mA/cm^2, 20 °C
[b] Yield of isolated product obtained by filtration of reaction mixture

Table 3 Electrocatalytic transformation of isatin **1a**, 3-methyl-2-pyrazolin-5-one **2b**, and malononitrile into spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] **3f**[a]

I (mA)	Current density (mA/cm^2)	Time (min)	Electricity passed (F/mol)	Yield of **3f** (%)[b]
100	20	6	0.04	57
50	10	13	0.04	68
25	5	26	0.04	85
10	2	64	0.04	51
5	1	128	0.04	43

[a] **1a** (10 mmol), **2b** (10 mmol), malononitrile (10 mmol), NaBr (1 mmol), EtOH (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C
[b] Yield of isolated product obtained by filtration of reaction mixture

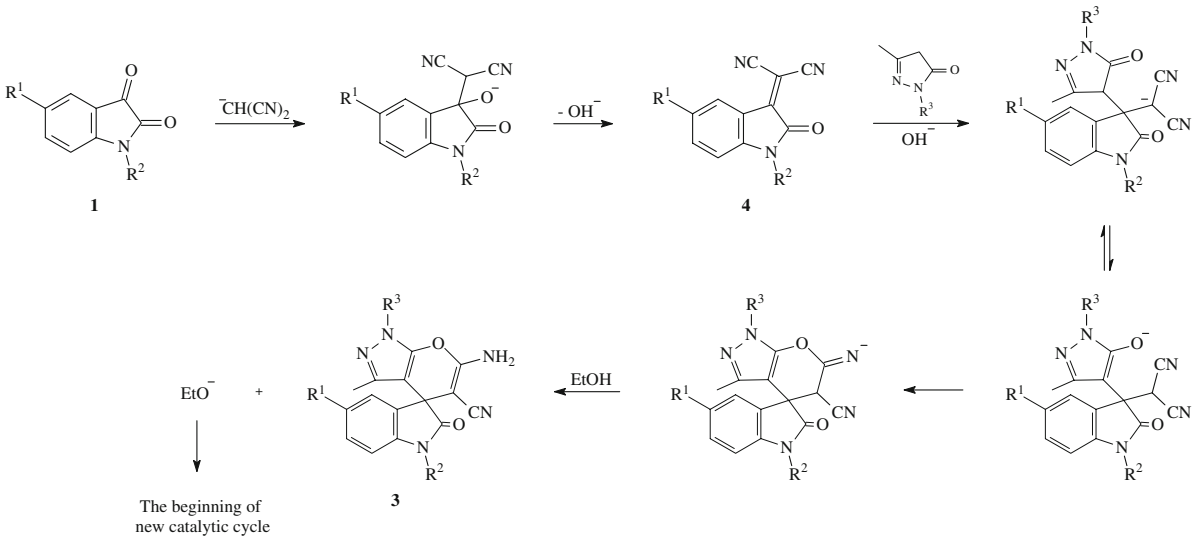


Scheme 2 Initiation step

nitrile anion with isatin **1** takes place with the elimination of a hydroxide anion and formation of isatylidenemalononitrile **4** [25]. The subsequent hydroxide-promoted Michael addition of 3-methyl-2-pyrazolin-5-ones **2** to electron deficient Knoevenagel adduct **4** followed by intramolecular cyclization leads to corresponding spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] **3** with the regeneration of the ethoxide anion as the last step. The catalytic chain process then continues by the interaction of the ethoxide with the next molecule of malononitrile (Scheme 3).

Conclusion

In conclusion, the simple electrocatalytic system can produce, under neutral and mild conditions, a fast and selective multicomponent transformaton of isatins, 3-methyl-2-pyrazolin-5-ones and malononitrile into corresponding spiro [indole-3,4′-pyrano[2,3-*c*]pyrazoles] in excellent yields. This novel electrocatalytic chain process offers an efficient and convenient way to create diverse spirocyclic oxindole systems with fused functionalized pyrano[2,3-*c*]pyrazole fragment—the promising hybridized 'privileged drug scaffold' for human cancer therapy and other biomedical applications. The developed electrocatalytic multicomponent procedure utilizes facile equipment, an undivided cell, and requires simple and reasonable starting materials. It is easily carried out, and the reaction products are directly crystallized from the



Scheme 3 The general mechanism of electrocatalytic spiro[indole-3,4′-pyrano[2,3-c]pyrazoles] formation

reaction mixture. This efficient electrocatalytic approach to spirocyclic [indole-3,4′-pyrano[2,3-*c*]pyrazole] ring system represents a novel example of synthetic concept for multicomponent reactions, and allows for the combination of the synthetic virtues of conventional MCRs with ecological benefits and convenience of facile electrocatalytic procedure.

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