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Electrocatalytic Aldol Addition of Cyclic 1,3-Ketoesters to Isatins: Acetone as a Solvent for the Efficient and Facile Electrochemically Induced Way to 3-Substituted-3-Hydroxyindol-2-One Scaffold

M. N. Elinson,[a,z] V. M. Merkulova,[a] A. I. Ilovaisky,[a] A. O. Chizhov,[a] F. Barba,[b] and B. Batanero[b]

[a]*N. D. Zelinsky Institute of Organic Chemistry, 119991 Moscow, Russia*
[b]*Department of Organic Chemistry, University of Alcalá, 28871 Alcalá de Henares, Madrid, Spain*

The electrolysis of isatins and cyclic 1,3-ketoesters in acetone in an undivived cell results in the formation of the previously unknown 3-substituted-3-hydroxyindol-2-ones in 80–95% yields and 800–950% current efficiency. Thus, this simple electrocatalytic system can produce in aprotic solvent in an undivided cell, under mild conditions the new electrochemically induced aldol reaction of isatins and cyclic 1,3-ketoesters with the formation of 3-substituted-3-hydroxyindol-2-ones – promising synthons for different biomedically active compounds.
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The carbon – carbon bond formation is a fundamental process in organic synthesis and numerous methods have been developed for achieving it. One of the most powerful methods is the reaction of the carbonyl groups with a variety of carbon nucleophiles. Thus, the aldol reaction is very useful carbon-carbon bond forming reaction[1,2] of the latter type. In its usual form, it involves the nucleophilic addition of an aldehyde or a ketone enolate to a carbonyl group to form a β-hydroxycarbonyl compound, which is called an aldol, a structural unit occurring in many natural molecules and pharmaceuticals.[3–8] In recent years, many research efforts has been invested in the development of the direct catalytic aldol reaction, which is generally considered as one of the most powerful reactions for achieving C–C bond formation.[9]

In an aldol condensation and in a Knoevenagel condensation a nucleophilic addition of an CH-acid anion to a carbonyl group is followed by a dehydration step.[10–13]

One of the important examples of aldol type reactions is the Henry reaction, namely a base-catalyzed reaction between nitroalkanes and aldehydes or ketones.[14,15] The Henry reaction is also a very useful carbon-carbon bond forming reaction and has wide synthetic application in organic synthesis.[16]

But examples of the aldol reaction of cyclic 1,3-ketoesters with carbonyl group yielding aldols (β-hydroxyketoesters) are yet not known in the literature.

The indole nucleus is a common and important structural functionality of a variety of both natural and synthetic products.[17] The indole scaffold represents an important structural subunit for the discovery of new drug candidates. Many alkaloids and plant hormones contain the indole ring. The massive search on indole chemistry in recent years led to a vast number of biologically active compounds with a wide range of therapeutic targets, such as anti-inflammatory drugs, phosphodiesterase inhibitors and HMG-CoA reductase inhibitors and also to a great number of drugs that contain the indole substructure, such as indomethacin, ergotamine, frovatriptan, ondansetron, tadalafil.[18]

Isatin (1*H*-indole-2,3-dione) and its derivatives have also many application in medicinal chemistry.[19–21] In particular, 3-substituted-3-hydroxyindolin-2-ones, compounds bearing the indole skeletal structure, are found in several biologically active alkaloids and pharmacological agents.[22–25]

Within the context of *green chemistry*, electrochemical and especially electrocatalytic technology can provide a valuable alternative for the usual chemical synthesis.[26] Due to the electron transfer between an electrode and the substrate the formation of highly reactive intermediates is achieved under mild conditions, avoiding reductive or oxidant agents as well as acids, bases and related waste by-products.

In the course of our study on the electrochemical transformation of organic compounds, we have found a new type of electrochemical transformation induced by a catalytic amount of an electrogenerated base in an undivided cell.[27]

Recently, we have published the electrocatalytic addition of nitromethane and cyclic 1,3-diketones to carbonyl compounds in methanol solution in an undivided cell.[28,29]

Considering our preliminary results on the electrocatalytic chain transformation of aldehydes and CH-acids[28–31] as well as the certain biomedical applications of 3-substituted-3-hydroxyindolin-2-ones derivatives, we were prompted to design a convenient and facile electrocatalytic methodology for the efficient synthesis of functionalized 3-substituted-3-hydroxyindolin-2-one scaffold from 1,3-ketoesters and isatins.

Experimental

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance II-300 at ambient temperature in DMSO-d_6 solutions. Chemical shifts values are given in δ scale relative to Me_4Si. IR spectra were registered with a SPECORD M82 spectrometer in KBr pellets. HRMS (ESI) were measured on a Bruker micrOTOF II instrument; external or internal calibration was done with Electrospray Calibrant Solution (Fluka). All starting materials were obtained from commercial sources and used without purification. Methanol was distilled over $Mg(OMe)_2$; MeCN and acetone were distilled over P_2O_5 prior to use. Ethanol with less than 1% of water content was obtained from commercial sources and used without further purification.

Typical electrolysis procedure.— A mixture of 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** or 4-hydroxycoumarin **2** (5 mmol), isatin **3** (5 mmol), and sodium bromide (0.1 g, 1 mmol) in acetone (20 mL) was electrolyzed in undivided cell equipped with a magnetic stirrer, a graphite anode and an iron cathode at 20°C under a constant current density of 5 mA/cm^2 (I = 25 mA, electrodes square 5 cm^2) until the catalytic quantity of 0.1 F mol^{-1} of electricity was passed. After the electrolysis was finished, the reaction mixture was concentrated at 20°C /10 mm Hg. Water (10 mL) and ether (for 3-substituted-3-hydroxyindolin-2-ones **4**, 10 mL) or chloroform (for 3-substituted-3-hydroxyindolin-2-ones **5**, 10 mL) were added to the residue; the mixture was stirred for 30 min, the solid product was filtered, washed with ether or chloroform (2 × 10 mL) and dried at 20°C/0.1 mm Hg.

*3-Hydroxy-3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-1,3-dihydro-2H-indol-2-one (**4a**).*— white solid; yield 1.16 g (85%); mp 179–180°C; δ_H (300 MHz) 2.16 (s, 3H, CH_3), 3.0−4.0 (br s, 1H, OH), 6.08 (s, 1H, CH), 6.80 (d, J = 7.7, 1H, Ar), 6.91 (t, J = 7.0, 1H, Ar), 7.16 (d, J = 7.3, 1H, Ar), 7.21 (t, J = 7.7, 1H, Ar), 9.0−11.0 (br s, 1H, OH), 10.34 (s, 1H, NH); δ_C (75 MHz) 19.0, 77.5, 98.4, 101.0, 109.6, 121.6, 123.6, 129.6, 131.1, 142.8, 161.7, 162.1, 169.1, 175.7;

[z]E-mail: elinson@ioc.ac.ru

IR (KBr): ν = 3148, 3092, 3036, 1732, 1684, 1584, 1476, 1336, 912, 756; HRMS (ESI) 296.0538 $[M+Na]^+$, calcd for $C_{14}H_{11}NO_5Na$: 296.0529.

*3-Hydroxy-3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-1-methyl-1,3-dihydro-2H-indol-2-one (**4b**).*— white solid; yield 1.18 g (82%); mp 140−141°C; δ_H (300 MHz) 2.15 (s, 3H, CH_3), 3.0−4.0 (br s, 1H, OH), 3.12 (s, 3H, CH_3), 6.08 (s, 1H, CH), 6.92−7.06 (m, 2H, Ar), 7.22 (d, *J* = 7.3, 1H, Ar), 7.32 (t, *J* = 7.3, 1H, Ar), 9.0−11.0 (br s, 1H, OH); δ_C (75 MHz) 19.0, 26.1, 77.0, 98.4, 101.1, 108.4, 122.3, 123.2, 129.7, 130.5, 144.1, 161.7, 162.2, 169.1, 174.2; IR (KBr): ν = 3272, 3124, 1700, 1600, 1584, 1464, 1372, 1216, 900, 752; HRMS (ESI) 310.0684 $[M+Na]^+$, calcd for $C_{15}H_{13}NO_5Na$: 310.0686.

*1-Ethyl-3-hydroxy-3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-1,3-dihydro-2H-indol-2-one (**4c**).*— white solid; yield 1.35 g (90%); mp 116−118°C; δ_H (300 MHz) 1.17 (t, *J* = 7.3, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.0−4.0 (br s, 1H, OH), 3.57−3.80 (m, 2H, CH_2), 6.07 (s, 1H, CH), 6.97 (t, *J* = 7.3, 1H, Ar), 7.01 (d, *J* = 7.3, 1H, Ar), 7.22 (d, *J* = 7.3, 1H, Ar), 7.30 (t, *J* = 7.3, 1H, Ar), 9.0−11.0 (br s, 1H, OH); δ_C (75 MHz) 11.9, 19.1, 34.1, 76.9, 98.5, 101.1, 108.4, 122.1, 123.4, 129.7, 130.7, 143.2, 161.9, 162.1, 169.0, 173.8; IR (KBr): ν = 3384, 3252, 1712, 1664, 1612, 1584, 1408, 1372, 1200, 760; HRMS (ESI) 324.0841 $[M+Na]^+$, calcd for $C_{16}H_{15}NO_5Na$: 324.0842.

*1-Benzyl-3-hydroxy-3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-1,3-dihydro-2H-indol-2-one (**4d**).*— white solid; yield 1.47 g (81%); mp 138−139°C; δ_H (300 MHz) 2.17 (s, 3H, CH_3), 3.0−4.0 (br s, 1H, OH), 4.84 (d, *J* = 16.1, 1H, $C\underline{H}_aH_bPh$), 4.96 (d, *J* = 16.1, 1H, $CH_a\underline{H}_bPh$), 6.11 (s, 1H, CH), 6.75 (d, *J* = 7.7, 1H, Ar), 6.98 (t, *J* = 7.3, 1H, Ar), 7.15−7.40 (m, 5H, Ar), 7.49 (d, *J* = 7.3, 2H, Ar), 9.0–11.0 (br s, 1H, OH); δ_C (75 MHz) 19.0, 43.0, 77.0, 98.2, 101.2, 109.1, 122.4, 123.4, 127.2, 127.3 (2CH), 128.4 (2CH), 129.6, 130.6, 136.2, 143.3, 161.9, 162.2, 169.3, 174.4; IR (KBr): ν = 3410, 3248, 3060, 1696, 1656, 1616, 1588, 1492, 1220, 760; HRMS (ESI) 386.0981 $[M+Na]^+$, calcd for $C_{21}H_{17}NO_5Na$: 386.0999.

*3-Hydroxy-3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-5-methyl-1,3-dihydro-2H-indol-2-one (**4e**).*— white solid; yield 1.19 g (83%); mp 125−127°C; δ_H (300 MHz) 2.16 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.0−4.0 (br s, 1H, OH), 6.08 (s, 1H, CH), 6.69 (d, *J* = 7.3, 1H, Ar), 6.98 (s, 1H, Ar), 7.02 (d, *J* = 7.3, 1H, Ar), 9.0−11.0 (br s, 1H, OH), 10.23 (s, 1H, NH); δ_C (75 MHz) 19.0, 20.5, 77.6, 98.5, 101.0, 109.3, 124.2, 129.8, 130.41, 131.1, 140.3, 161.6, 162.0, 169.1, 175.6; IR (KBr): ν = 3256, 1712, 1680, 1576, 1496, 1452, 1320, 1220, 1124, 996; HRMS (ESI) 310.0690 $[M+Na]^+$, calcd for $C_{15}H_{13}NO_5Na$: 310.0686.

*5-Chloro-3-hydroxy-3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-1,3-dihydro-2H-indol-2-one (**4f**).*— white solid; yield 1.31 g (85%); mp 139−141°C; δ_H (300 MHz) 2.15 (s, 3H, CH_3), 3.0−4.0 (br s, 1H, OH), 6.07 (s, 1H, CH), 6.81 (d, *J* = 8.0, 1H, Ar), 7.18 (s, 1H, Ar), 7.26 (d, *J* = 7.3, 1H, Ar), 9.0−11.0 (br s, 1H, OH), 10.46 (s, 1H, NH); δ_C (75 MHz) 19.0, 77.3, 97.8, 101.2, 111.0, 123.7, 125.4, 129.3, 133.2, 141.7, 161.9, 162.2, 169.4, 175.6; IR (KBr): ν = 3256, 1716, 1684, 1576, 1480, 1448, 1320, 1224, 1184, 812; HRMS (ESI) 330.0140 $[M+Na]^+$, calcd for $C_{14}H_{10}ClNO_5Na$: 330.0140.

*5-Bromo-3-hydroxy-3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-1,3-dihydro-2H-indol-2-one (**4g**).*— white solid; yield 1.40 g (80%); mp 143−146°C; δ_H (300 MHz) 2.15 (s, 3H, CH_3), 3.0−4.0 (br s, 1H, OH), 6.05 (s, 1H, CH), 6.76 (d, *J* = 8.0, 1H, Ar), 7.28 (s, 1H, Ar), 7.38 (d, *J* = 7.3, 1H, Ar), 9.0−11.0 (br s, 1H, OH), 10.45 (s, 1H, NH); δ_C (75 MHz) 19.0, 77.2, 97.6, 101.3, 111.5, 112.9, 126.3, 132.1, 133.7, 142.1, 161.9, 162.1, 169.6, 175.5; IR (KBr): ν = 3392, 3250, 1728, 1680, 1580, 1476, 1448, 1320, 1224, 1180; HRMS (ESI) 373.9626 $[M+Na]^+$, calcd for $C_{14}H_{10}BrNO_5Na$: 373.9635.

*3-Hydroxy-3-(4-hydroxy-2-oxo-2H-chromen-3-yl)-1,3-dihydro-2H-indol-2-one (**5a**).*— white solid; yield 1.47 g (95%); mp 188−191°C; δ_H (300 MHz) 2.5−4.5 (br s, 1H, OH), 6.85 (d, *J* = 7.7, 1H, Ar), 6.92 (t, *J* = 7.3, 1H, Ar), 7.23 (d, *J* = 7.3, 1H, Ar), 7.25 (d, *J* = 7.0, 1H, Ar), 7.37 (d, *J* = 8.4, 1H, Ar), 7.43 (t, *J* = 7.7, 1H, Ar), 7.68 (t, *J* = 7.3, 1H, Ar), 7.93 (d, *J* = 7.7, 1H, Ar), 9.0–11.0 (br s, 1H, OH), 10.45 (s, 1H, NH); δ_C (75 MHz) 78.3, 100.9, 109.7, 115.6, 116.1, 121.6, 123.1, 123.8, 124.3, 129.9, 130.7, 132.9, 142.9, 152.2, 159.5, 164.8, 175.4; IR (KBr): ν = 3152, 3096, 3040, 1728, 1672, 1616, 1476, 1340, 1176, 755; HRMS (ESI) 332.0527 $[M+Na]^+$, calcd for $C_{17}H_{11}NO_5Na$: 332.0529.

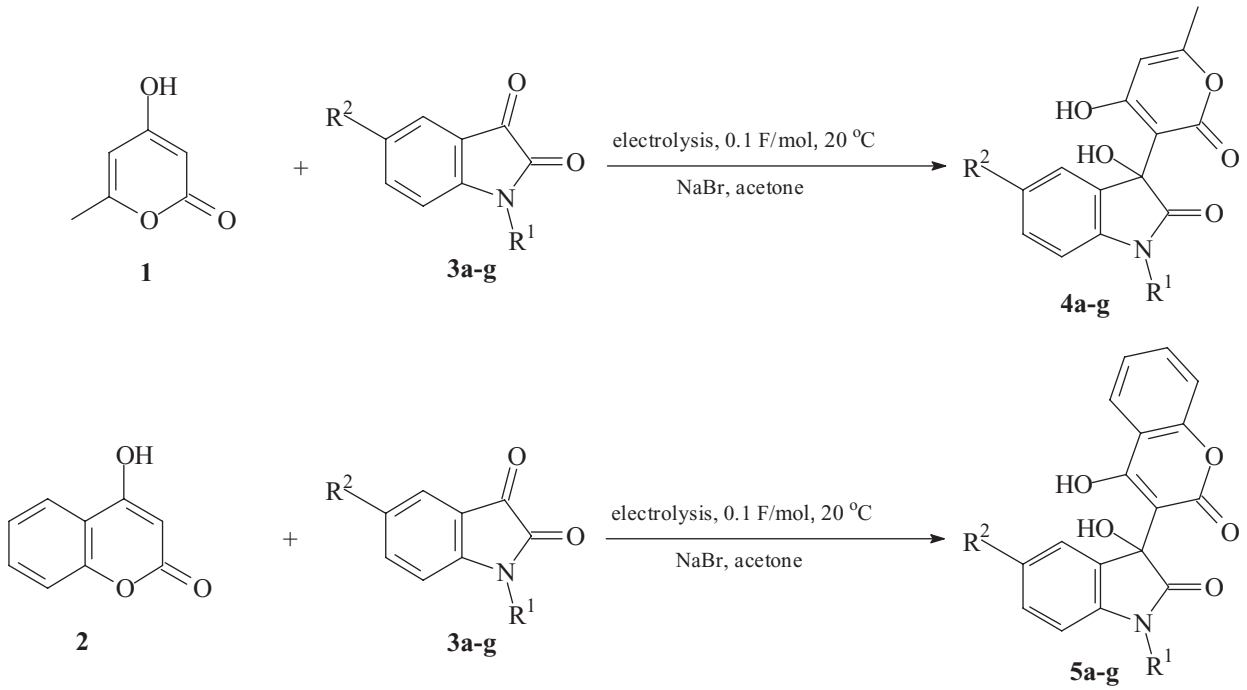
*3-Hydroxy-3-(4-hydroxy-2-oxo-2H-chromen-3-yl)-1-methyl-1,3-dihydro-2H-indol-2-one (**5b**).*— white solid; yield 1.47 g (91%); mp 129−133°C; δ_H (300 MHz) 2.5−4.5 (br s, 1H, OH), 3.17 (s, 3H, CH_3), 7.00 (t, *J* = 7.3, 1H, Ar), 7.02 (d, *J* = 7.7, 1H, Ar), 7.25−7.37 (m, 3H, Ar), 7.40 (t, *J* = 7.7, 1H, Ar), 7.65 (t, *J* = 7.7, 1H, Ar), 7.93 (d, *J* = 7.7, 1H, Ar), 9.0–11.0 (br s, 1H, OH); δ_C (75 MHz) 26.1, 77.9, 100.3, 108.4, 116.1, 116.3, 122.3, 123.2, 123.3, 124.1, 129.8, 130.6, 132.6, 144.2, 152.3, 159.7, 165.8, 174.3; IR (KBr): ν = 3250, 3110, 1712, 1696, 1628, 1496, 1472, 1340, 1092, 756; HRMS (ESI) 346.0688 $[M+Na]^+$, calcd for $C_{18}H_{13}NO_5Na$: 346.0686.

*1-Ethyl-3-hydroxy-3-(4-hydroxy-2-oxo-2H-chromen-3-yl)-1,3-dihydro-2H-indol-2-one (**5c**).*— white solid; yield 1.58 g (94%); mp 119−120°C; δ_H (300 MHz) 1.21 (t, *J* = 7.0, 3H, CH_3), 2.5−4.5 (br s, 1H, OH), 3.63−3.81 (m, 2H, CH_2), 6.99 (t, *J* = 7.3, 1H, Ar), 7.06 (d, *J* = 7.7, 1H, Ar), 7.26−7.39 (m, 3H, Ar), 7.43 (t, *J* = 7.7, 1H, Ar), 7.68 (t, *J* = 8.4, 1H, Ar), 7.93 (d, *J* = 7.7, 1H, Ar), 9.0−11.0 (br s, 1H, OH); δ_C (75 MHz) 11.9, 34.1, 79.1, 100.9, 108.6, 115.6, 116.1, 122.1, 123.1, 123.6, 124.3, 130.0, 130.2, 132.9, 143.3, 152.2, 159.4, 164.7, 173.5; IR (KBr): ν = 3430, 2976, 1700, 1684, 1632, 1616, 1488, 1376, 1352, 756; HRMS (ESI) 360.0830 $[M+Na]^+$, calcd for $C_{19}H_{15}ClNO_5Na$: 360.0842.

*1-Benzyl-3-hydroxy-3-(4-hydroxy-2-oxo-2H-chromen-3-yl)-1,3-dihydro-2H-indol-2-one (**5d**).*— white solid; yield 1.64 g (82%); mp 123–125°C; δ_H (300 MHz) 2.5−4.5 (br s, 1H, OH), 4.88 (d, *J* = 16.1, 1H, $C\underline{H}_aH_bPh$), 4.99 (d, *J* = 16.1, 1H, $CH_a\underline{H}_bPh$), 6.79 (d, *J* = 8.1, 1H, Ar), 6.98 (t, *J* = 7.3, 1H, Ar), 7.19−7.48 (m, 7H, Ar), 7.52 (d, *J* = 7.3, 2H, Ar), 7.69 (t, *J* = 7.3, 1H, Ar), 7.96 (d, *J* = 7.3, 1H, Ar), 9.0–11.0 (br s, 1H, OH); δ_C (75 MHz) 43.1, 77.9, 100.6, 109.2, 115.6, 116.2, 122.4, 123.2, 123.6, 124.4, 127.2, 127.3 (2CH), 128.4 (2CH), 129.9, 130.1, 133.0, 136.1, 143.4, 152.2, 159.6, 165.1, 174.2; IR (KBr): ν = 3300, 3164, 1700, 1616, 1572, 1488, 1172, 760. HRMS (ESI) 422.0989 $[M+Na]^+$, calcd for $C_{24}H_{17}NO_5Na$: 422.0999.

*3-Hydroxy-3-(4-hydroxy-2-oxo-2H-chromen-3-yl)-5-methyl-1,3-dihydro-2H-indol-2-one (**5e**).*— white solid; yield 1.41 g (87%); mp >300°C; δ_H (300 MHz) 2.19 (s, 3H, CH_3), 2.5−4.5 (br s, 1H, OH), 6.74 (d, *J* = 7.7, 1H, Ar), 7.04 (d, *J* = 7.7, 1H, Ar), 7.06 (s, 1H, Ar), 7.36 (d, *J* = 8.4, 1H, Ar), 7.42 (t, *J* = 7.7, 1H, Ar), 7.67 (t, *J* = 7.3, 1H, Ar), 7.92 (d, *J* = 7.7, 1H, Ar), 9.0−11.0 (br s, 1H, OH), 10.34 (s, 1H, NH); δ_C (75 MHz) 20.4, 78.4, 100.9, 109.5, 115.70, 116.1, 123.1, 124.3, 124.4, 130.0, 130.6, 130.8, 132.8, 140.5, 152.2, 159.5, 164.8, 175.5; IR (KBr): ν = 3360, 3024, 1716, 1672, 1628, 1576, 1492, 1344, 964, 760; HRMS (ESI) 346.0687 $[M+Na]^+$, calcd for $C_{18}H_{13}NO_5Na$: 346.0686.

*5-Chloro-3-hydroxy-3-(4-hydroxy-2-oxo-2H-chromen-3-yl)-1,3-dihydro-2H-indol-2-one (**5f**).*— white solid; yield 1.46 g (85%); mp >300°C; δ_H (300 MHz) 2.5−4.5 (br s, 1H, OH), 6.86 (d, *J* = 8.1, 1H, Ar), 7.20−7.48 (m, 4H, Ar), 7.67 (t, *J* = 7.3, 1H, Ar), 7.92 (d, *J* = 7.3, 1H, Ar), 9.0−11.0 (br s, 1H, OH), 10.59 (s, 1H, NH); δ_C (75 MHz) 78.2, 100.2, 111.2, 115.7, 116.2, 123.2, 124.1, 124.3, 125.6, 129.6, 132.8, 132.9, 141.8, 152.3, 159.7, 165.2, 175.4; IR (KBr): ν = 3408, 3208, 1724, 1672, 1620, 1576, 1480, 1308, 960, 756; HRMS (ESI) 366.0129 $[M+Na]^+$, calcd for $C_{17}H_{10}ClNO_5Na$: 366.0140.



a $R^1 = R^2 = H$; **b** $R^1 = Me$, $R^2 = H$; **c** $R^1 = Et$, $R^2 = H$; **d** $R^1 = CH_2Ph$, $R^2 = H$;
e $R^1 = H$, $R^2 = Me$; **f** $R^1 = H$, $R^2 = Cl$; **g** $R^1 = H$, $R^2 = Br$

Scheme 1. Electrochemically induced addition of cyclic 1,3-ketoesters **1**,**2** to isatins **3a**–**g**.

*5-Bromo-3-hydroxy-3-(4-hydroxy-2-oxo-2H-chromen-3-yl)-1,3-dihydro-2H-indol-2-one (**5g**).*— white solid; yield 1.55 g (80%); mp >300°C; δ_H (300 MHz) 2.5−4.5 (br s, 1H, OH), 6.71 (d, J = 8.1, 1H, Ar), 7.16−7.34 (m, 4H, Ar), 7.52 (t, J = 8.1, 1H, Ar), 7.86 (d, J = 8.1, 1H, Ar), 9.0−11.0 (br s, 1H, OH), 10.17 (s, 1H, NH); δ_C (75 MHz) 78.2, 100.1, 111.7, 113.2, 115.8, 116.2, 123.2, 124.3, 126.7, 132.4, 132.9, 133.2, 142.3, 152.3, 159.7, 165.2, 175.2; IR (KBr): ν = 3200, 1732, 1672, 1620, 1560, 1476, 1304, 956, 816, 756; HRMS (ESI) 409.9628 $[M+Na]^+$, calcd for $C_{17}H_{10}BrNO_5Na$: 409.9635.

Results and Discussion

In the present study, we report our results on the electrochemically induced addition of cyclic 1,3-ketoesters **1**,**2** to isatins **3a**–**g** in an undivided cell (Scheme 1, Tables I and II).

First, to evaluate the synthetic potential of the procedure proposed and to optimize the electrolysis conditions, the electrocatalytic addition of 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** and 4-hydroxycoumarin **2** to isatin **3a** in alcohol solution in an undivided cell was studied (Table I). Data in Table I show that 3-substituted-3-hydroxyindol-2-one **4a** in methanol is formed only in moderate (50%) yield under conditions studied. An increase yield of **4a** was found when the electrolysis was carried out in aprotic solvents: acetonitrile (76%) and especially acetone (88%). This fact could be explained by the influence of two factors: 1) the direct reduction of 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** at the cathode in aprotic solvent; 2) the increase of CH-acidity of ketoesters in aprotic solvents compare with their acidity in alcohols.[32] A similar tendency was also found for the addition of 4-hydroxycoumarin **2** to isatin **3a**. In the latter case the yield of 3-substituted-3-hydroxyindol-2-one **5a** in acetone is also higher than in alcohols (95% and 70% respectively). Under the optimal conditions thus found (I = 25 mA, current density 5 mA cm^{-2}, 0.1 F mol^{-1} passed, time 32 min, acetone as a solvent) the electrolysis of 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** and 4-hydroxycoumarin **2** with isatins **3a**–**g** in acetone in an undivided cell resulted in the formation of the corresponding 3-substituted-3-hydroxyindol-2-ones **4a**–**g** and **5a**–**g** in 80–95% yields and 800–950% current efficiency (Table II).

Table I. Electrocatalytic addition of ketoesters 1 and 2 to isatin 3a with the formation of aldol adducts 4a and 5a[a].

Entry	Ketoester	Solvent	Current density (mA cm^{-2})	Time (min)	Electricity passed (F mol^{-1})	Product, yield (%)[b]
1	**1**	MeOH	5	32	0.10	**4a**, 50 (500)
2	**1**	EtOH	5	32	0.10	**4a**, 49 (490)
3	**1**	EtOH	5	48	0.15	**4a**, 51 (340)
4	**1**	EtOH	10	16	0.10	**4a**, 48 (480)
5	**1**	MeCN	5	32	0.10	**4a**, 76 (760)
6	**1**	Me_2CO	5	32	0.10	**4a**, 85 (850)
7	**1**	Me_2CO	5	48	0.15	**4a**, 88 (587)
8	**2**	MeOH	5	32	0.10	**5a**, 71 (710)
9	**2**	EtOH	5	32	0.10	**5a**, 75 (750)
10	**2**	Me_2CO	5	32	0.10	**5a**, 95 (950)

[a]Ketoester **1** or **2** (5 mmol), isatin **3a** (5 mmol), NaBr (1 mmol), solvent (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20°C.
[b]Yield of isolated product (in parentheses, current efficiency is given).

Table II. Electrocatalytic addition of ketoesters 1,2 to isatins 3a–g with the formation of aldol adducts 4a–g and 5a–g[a].

Ketoester	Isatin	*I* (mA)	Current density (mA cm^{-2})	Time (min)	Electricity passed (F mol^{-1})	Product	Yield (%)[b]
1	**3a**	25	5	32	0.1	**4a**	85 (850)
1	**3b**	25	5	32	0.1	**4b**	82 (820)
1	**3c**	25	5	32	0.1	**4c**	90 (900)
1	**3d**	25	5	32	0.1	**4d**	81 (810)
1	**3e**	25	5	32	0.1	**4e**	83 (830)
1	**3f**	25	5	32	0.1	**4f**	85 (850)
1	**3g**	25	5	32	0.1	**4g**	80 (800)
2	**3a**	25	5	32	0.1	**5a**	95 (950)
2	**3b**	25	5	32	0.1	**5b**	91 (910)
2	**3c**	25	5	32	0.1	**5c**	94 (940)
2	**3d**	25	5	32	0.1	**5d**	82 (820)
2	**3e**	25	5	32	0.1	**5e**	87 (870)
2	**3f**	25	5	32	0.1	**5f**	85 (850)
2	**3g**	25	5	32	0.1	**5g**	80 (800)

[a]Ketoester **1** or **2** (5 mmol), isatin **3** (5 mmol), NaBr (1 mmol), acetone (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20°C.
[b]Yield of isolated product (in parentheses, current yield is given).

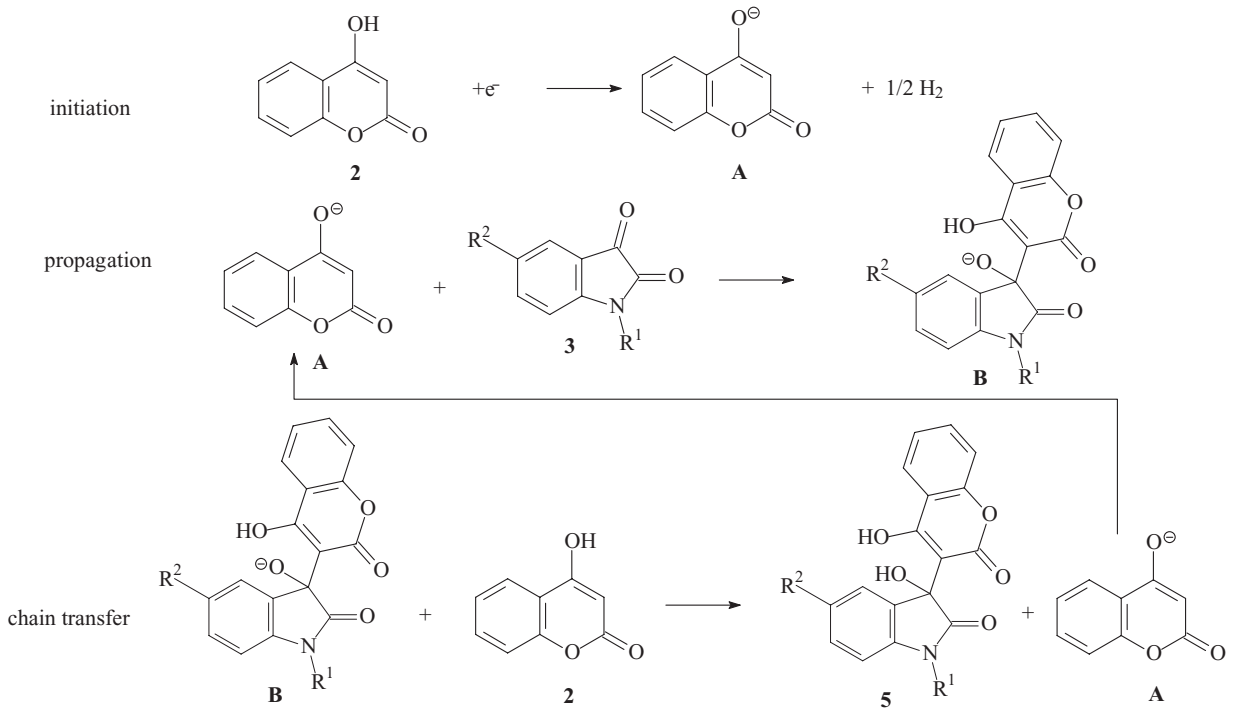
Taking into consideration the above data and our previous results[28–31] the following mechanism for the electrochemically induced aldol reaction of cyclic 1,3-ketoesters **1**,**2** with isatins **3a**–**g** in acetone is proposed (Scheme 2, example with the cyclic ketoester **2**).

The initiation step is the reduction of the O-H bond of the enol of the cyclic 1,3-ketoester, which leads to the formation of the cyclic 1,3-ketoester anion **A**. The evolution of hydrogen at the cathode is observed, especially when electrolysis is conducted without stirring of the reaction mixture.

Then the propagation step takes place, namely the addition of the cyclic 1,3-ketoester anion to isatin with the formation of the intermediate anion **B**. The chain transfer step is the subsequent reaction of anion **B** with another molecule of the ketoester **3** with the formation of the final product of the electrocatalytic process, i.e. the corresponding 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)cyclohexane-1,3-dione **5** and the regeneration of new anion **A**. Then anion **A** continues the catalytic chain process by the interaction with the next molecule of isatin. (Scheme 2).

Conclusions

In conclusion, the simple electrocatalytic system described can produce, under mild conditions in an undivided cell, and in an aprotic solvent such as acetone, a fast and selective previously unknown aldol reaction of cyclic 1,3-ketoesters with isatins to form substituted 3-hydroxy-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-1,3-dihydro-2*H*-indol-2-ones or 3-hydroxy-3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dihydro-2*H*-indol-2-ones in 80–95% yields and 800–950% current efficiency. This electrocatalytic chain process is an efficient and convenient access to substituted 3-hydroxy-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-1,3-dihydro-2*H*-indol-2-ones and



Scheme 2. Mechanism of electrochemically induced addition of cyclic 1,3-ketoesters **1**,**2** to isatins **3a**–**g**.

3-hydroxy-3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dihydro-2*H*-indol-2-ones – the promising synthons for different biomedically active compounds. The procedure utilizes inexpensive reagents, simple equipment (e.g. galvanostat), an undivided cell, and is easy to carry out. The procedure for the isolation of the final aldol is very simple and the whole process is beneficial from the viewpoint of "green" organic synthesis and large-scale processes.

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