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Electrochemically induced aldol reaction of cyclic 1,3-diketones with isatins

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ABSTRACT

The electrolysis of isatins and cyclic 1,3-diketones in alcohol in an undivided cell results in the formation of the previously unknown substituted 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)cyclohexane-1,3-diones in 70–85% substance yields and 700–850% current efficiency. Thus, the simple electrocatalytic system can produce, under mild conditions the new electrochemically induced aldol reaction of isatins and cyclic 1,3-diketones.

1. Introduction

The aldol reaction is a well-known carbon–carbon bond forming reaction [1,2]. In its usual form, it involves the nucleophilic addition of aldehyde or ketone enolate to carbonyl group to form β-hydroxycarbonyl compound, which is called aldol, a structural unit occurring in many natural molecules and pharmaceuticals [3–8].

In aldol condensation and in Knoevenagel condensation a nucleophilic addition of an active hydrogen compound anion to a carbonyl group is followed by a dehydration reaction [9–12].

One of the important examples of aldol type reaction is Henry reaction, namely a base-catalyzed reaction between nitroalkanes and aldehydes or ketones [13,14]. The Henry reaction is also very useful carbon–carbon bond forming reactions and has wide synthetic applications in organic synthesis [15].

But examples of the aldol reaction of cyclic 1,3-dicarbonyl compounds with carbonyl group yielding aldol (β-hydroxyketones) are very rare. As to our knowledge, there are only two papers which describes two rare examples where the second step, i.e. Knoevenagel condensation was avoided. One of them is the addition of dimedone to N-acetyl-2-aminobenzaldehyde in ethanol with 2-(2′-acetylamino-1-hydroxybenzyl)-5,5-dimethylcyclohexane-1,3-dione **1** formation [16]; the second is the procedure when piperonal together with dimedone were melted, then adsorbed on neutral chromatographic alumina and shaken at room temperature for 18 h [17]. 2-(Benzo[1,3]dioxol-5-yl-hydroxymethyl)-5,5-dimethylcyclohexane-1,3-dione **2** was then extracted by CH_2Cl_2 [17]. For compound **1** only melting point is known [16]. Any characteristics of compound **2** in the short communication are absent [17].

Within the domain of the *green chemistry*, electrochemical technology can provide a valuable alternative to the use of the conventional reagents for fine chemical synthesis [18]. Due to the electron transfer between an electrode and the substrate molecules 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.

Recently, we have published the electrochemically induced addition of nitromethane to carbonyl compounds in methanol solution in an undivided cell [19].

Now we wish to report the electrochemically induced addition of cyclic 1,3-dicarbonyl compounds **3a**,**b** to isatins **4a**–**f** in alcohol solution in an undivided cell (Scheme 1 and Table 1).

2. Experimental

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra

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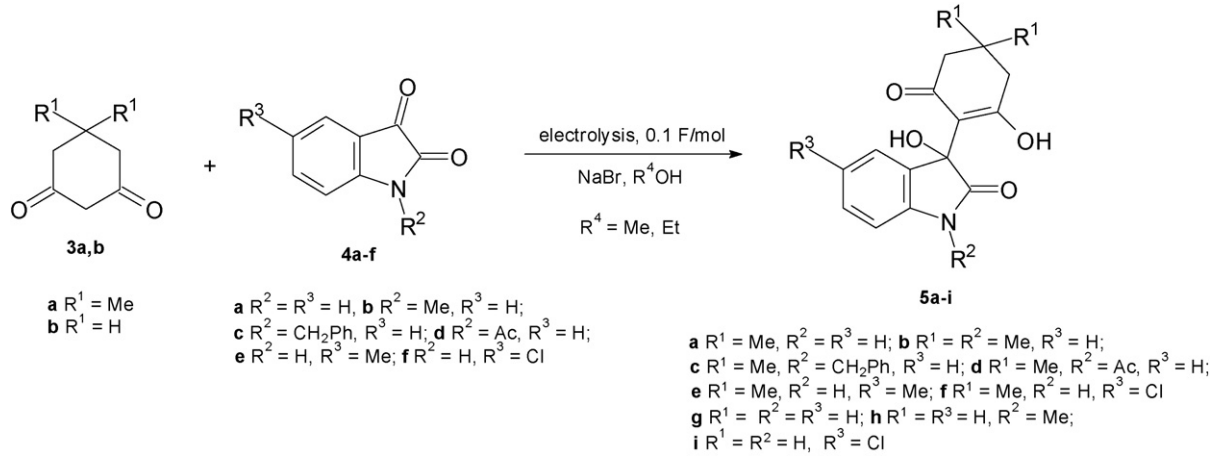


Scheme 1.

Table 1
Electrocatalytic addition of dimedone **3a** to isatin **4a** with the formation of 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-5,5-dimethylcyclohexane-1,3-dione **5a**[a].

Electrolyte	*I* (mA)	Current density (mA cm^{-2})	Time (min)	Electricity passed (F mol^{-1})	Yield of **5a** (%)[b]
NaBr	25	5	32	0.1	79 (790)
NaBr	50	10	16	0.1	82 (820)
NaBr	100	20	8	0.1	84 (840)
NaBr	200	40	4	0.1	85 (850)
NaBr	400	80	2	0.1	87 (870)
NaBr	800	160	1	0.1	74 (740)
NaI	400	80	2	0.1	81 (810)
KI	400	80	2	0.1	79 (790)
NaBr[c]	400	80	2	0.1	82 (820)

[a] **3a** (5 mmol), **4a** (5 mmol), electrolyte (0.5 mmol), EtOH (20 mL), iron cathode (5 cm^2) graphite anode (5 cm^2), 20 °C.
[b] Yield of isolated **5a**, in parentheses, current efficiency is given.
[c] MeOH as a solvent.

were recorded with a Bruker Avance II-300 spectrometer 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. The ESI mass spectra were recorded with a Finnigan MAT LCQ instrument with spray capillary voltage 4530 V. A methanolic solution of the sample was injected by syringe at 10 μL/min; MS spectra were measured at positive or negative mode (registration range from *m*/*z* 100 to *m*/*z* 2000); for MS^2, helium was used as a collision gas. Interface capillary temperature was 220 °C, sheath gas flow (nitrogen) 19.4 a.u., auxiliary gas flow 0.4 a.u. Activation time was 30 ms. Activation energy was 30% from relative max. collision energy. Methanol and ethanol with less than 1% of water content were used without further purification.

2.1. Typical electrolysis procedure

A solution of isatin (5 mmol), cyclic 1,3-diketone (5 mmol) and sodium bromide (0.05 g, 0.5 mmol) in alcohol (20 mL) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode and an iron cathode at 20 °C under a constant current density of 80 mA cm^{-2} (*I* = 400 mA, electrodes square 5 cm^2) until indicated in Tables 1 and 2 quantity of electricity was passed. After the electrolysis was finished, the reaction mixture was evaporated to dryness at 10 mm Hg; evaporation time 30 min, bath temperature 20 °C. The residue obtained was triturated with water (10 mL) and filtered to isolate the solid product, which was then washed with water (3 × 10 mL) and dried under reduced pressure.

Table 2
Electrocatalytic transformation of cyclic diketones (**3a**,**b**) and isatins (**4a**–**f**) into substituted 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)cyclohexane-1,3-diones (**5a**–**i**)[a].

Diketone	R^1	Isatin	R^2	R^3	*I* (mA)	Current density (mA cm^{-2})	Time (min)	Electricity passed (F mol^{-1})	Product, yield (%)[b]
3a	Me	**4a**	H	H	400	80	2	0.1	**5a**, 87 (870)
3a	Me	**4b**	Me	H	400	80	2	0.1	**5b**, 85 (850)
3a	Me	**4c**	CH_2Ph	H	400	80	2	0.1	**5c**, 86 (860)
3a	Me	**4d**	Ac	H	400	80	2	0.1	**5d**, 71 (710)
3a	Me	**4e**	H	Me	400	80	2	0.1	**5e**, 86 (860)
3a	Me	**4f**	H	Cl	400	80	2	0.1	**5f**, 83 (830)
3b	H	**4a**	H	H	400	80	2	0.1	**5g**, 72 (720)
3b	H	**4b**	Me	H	400	80	2	0.1	**5h**, 76 (760)
3b	H	**4f**	H	Cl	400	80	2	0.1	**5i**, 73 (730)

[a] 5 mmol of diketones (**3a**,**b**), 5 mmol of isatins (**4a**–**f**), 0.5 mmol of NaBr, 20 mL of ethanol, iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C.
[b] Yield of isolated product, in parentheses, current efficiency is given.

2-(3-Hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-5,5-dimethylcyclohexane-1,3-dione (**5a**): white solid; yield 1.25 g (87%); mp 166 °C; δ_H (300 MHz) 0.98 (s, 6H), 2.15–2.25 (m, 4H), 6.77 (d, *J* 7.7 Hz, 1H, Ar), 6.87 (t, *J* 7.5 Hz, 1H, Ar), 7.07 (d, *J* 7.3 Hz, 1H, Ar), 7.16 (t, *J* 7.5 Hz, 1H, Ar), 7.50–8.80 (br s, 1H, OH), 10.14 (s, 1H, NH), 10.50–12.00 (br s, 1H, OH); δ_C (75 MHz) 27.5, 31.8, 47.0 (br), 77.8, 109.4, 110.6, 121.2, 123.1, 129.1, 132.3, 142.7, 176.3, 184.0 (br); MS (+): *m/z* 310 $[M+Na]^+$, 270 $[M+H-H_2O]^+$; MS (–): *m/z* 286 $[M-H]^-$; MS^2 (+) (*m/z* 310): *m/z* 292 $[M+Na-H_2O]^+$; IR (KBr): ν_{max} 3168, 3088, 2960, 1736, 1624, 1472, 1368, 1244 cm^{-1}. Anal. Calcd. for $C_{16}H_{17}NO_4$ (%): C, 66.89; H, 5.96; N, 4.88. Found (%): C, 66.95; H, 6.09; N, 4.75.

2-(3-Hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-5,5-dimethylcyclohexane-1,3-dione (**5b**): white solid; yield 1.28 g (85%); mp 156–158 °C; δ_H (300 MHz) 0.97 (s, 6H), 2.15–2.25 (m, 4H), 3.10 (s, 3H), 6.95 (d, *J* 8.0 Hz, 1H, Ar), 6.97 (t, *J* 7.5 Hz, 1H, Ar), 7.13 (d, *J* 7.3 Hz, 1H, Ar), 7.28 (t, *J* 7.5 Hz, 1H, Ar), 9.00–11.00 (br s, 2H, OH); δ_C (75 MHz) 26.0, 27.5, 31.8, 46.6 (br), 77.5, 108.3, 110.6, 122.1, 122.8, 129.4, 131.7, 144.1, 175.0, 186.0 (br); MS (+): *m/z* 324 $[M+Na]^+$, 284 $[M+H-H_2O]^+$; MS (–): *m/z* 300 $[M-H]^-$; MS^2 (+) (*m/z* 324): *m/z* 306 $[M+Na-H_2O]^+$; IR (KBr): ν_{max} 3192, 2992, 1720, 1604, 1472, 1360, 1304, 1240 cm^{-1}. Anal. Calcd. for $C_{17}H_{19}NO_4$ (%): C, 67.76; H, 6.36; N, 4.65. Found (%): C, 67.85; H, 6.47; N, 4.48.

2-(1-Benzyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-5,5-dimethylcyclohexane-1,3-dione (**5c**): white solid; yield 1.62 g (86%); mp 148–149 °C; δ_H (300 MHz) 0.99 (s, 6H), 2.16–2.28 (m, 4H), 4.80 (d, *J* 16.1 Hz, 1H), 4.95 (d, *J* 16.1 Hz, 1H), 6.66 (d, *J* 8.0 Hz, 1H, Ar), 6.95 (t, *J* 7.5 Hz, 1H, Ar), 7.09–7.21 (m, 2H, Ar), 7.23–7.38 (m, 3H, Ar), 7.52 (d, *J* 7.3 Hz, 2H, Ar), 8.20–9.50 (br s, 1H, OH), 10.50–12.10 (br s, 1H, OH); δ_C (75 MHz) 27.5, 31.8, 42.9, 46.8 (br), 77.5, 108.9, 110.4, 122.1, 122.9, 127.1, 127.2, 128.4, 129.2, 131.7, 136.4, 143.2, 175.0, 184.0 (br); MS (+): *m/z* 400 $[M+Na]^+$, 360 $[M+H-H_2O]^+$; MS (–): *m/z* 376 $[M-H]^-$; MS^2 (+) (*m/z* 400): *m/z* 382 $[M+Na-H_2O]^+$; IR (KBr): ν_{max} 3408, 3344, 2952, 1732, 1600, 1480, 1356, 1248 cm^{-1}. Anal. Calcd. for $C_{23}H_{23}NO_4$ (%): C, 73.19; H, 6.14; N, 3.71. Found (%): C, 73.35; H, 6.29; N, 3.58.

2-(1-Acetyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-5,5-dimethylcyclohexane-1,3-dione (**5d**): white solid; yield 1.18 g (71%); mp 178–180 °C; δ_H (300 MHz) 0.96 (s, 6H), 2.16–2.28 (m, 4H), 2.56 (s, 3H), 7.19 (t, *J* 7.5 Hz, 1H, Ar), 7.29 (d, *J* 7.3 Hz, 1H, Ar), 7.34 (t, *J* 7.5 Hz, 1H, Ar), 8.10 (d, *J* 8.1 Hz, 1H, Ar), 9.20–11.30 (br s, 2H, OH); δ_C (75 MHz) 26.0, 27.4, 32.0, 46.5 (br), 77.2, 111.3, 115.8, 123.4, 125.2, 129.5, 131.3, 139.9, 170.4, 175.7, 183.0 (br); MS (+): *m/z* 352 $[M+Na]^+$, 330 $[M+H]^+$, 312 $[M+H-H_2O]^+$; MS (–): *m/z* 328 $[M-H]^-$; MS^2 (+) (*m/z* 352): *m/z* 334 $[M+Na-H_2O]^+$; IR (KBr): ν_{max} 2968, 2704, 1776, 1712, 1600, 1468, 1364, 1252 cm^{-1}. Anal. Calcd. for $C_{19}H_{23}NO_5$ (%): C, 65.64; H, 5.81; N, 4.25. Found (%): C, 65.44; H, 5.93; N, 4.11.

2-(3-Hydroxy-5-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-5,5-dimethylcyclohexane-1,3-di-one (**5e**): white solid; yield 1.30 g (86%); mp 169–171 °C; δ_H (300 MHz) 0.98 (s, 6H), 2.13–2.25 (m, 4H), 2.25 (s, 3H), 6.65 (d, *J* 7.3 Hz, 1H, Ar), 6.88 (s, 1H, Ar), 6.96 (d, *J* 7.3 Hz, 1H, Ar), 8.00–9.00 (br s, 1H, OH), 10.00 (s, 1H, NH), 9.50–11.50 (br s, 1H, OH); δ_C (75 MHz) 20.6, 27.5, 31.7, 46.7 (br), 78.0, 109.2, 110.6, 123.7, 129.3, 130.0, 132.4, 140.2, 176.4, 184.0 (br); MS (+): *m/z* 324 $[M+Na]^+$, 284 $[M+H-H_2O]^+$; MS (–): *m/z* 300 $[M-H]^-$; MS^2 (+) (*m/z* 324): *m/z* 306 $[M+Na-H_2O]^+$; IR (KBr): ν_{max} 3192, 2960, 1728, 1596, 1496, 1368, 1248 cm^{-1}. Anal. Calcd. for $C_{17}H_{19}NO_4$ (%): C, 67.76; H, 6.36; N, 4.65. Found (%): C, 67.85; H, 6.47; N, 4.50.

2-(5-Chloro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)-5,5-dimethylcyclohexane-1,3-dione (**5f**): white solid; yield 1.34 g (83%); mp 187–188 °C; δ_H (300 MHz) 0.99 (s, 6H), 2.15–2.26 (m, 4H), 6.79 (d, *J* 8.1 Hz, 1H, Ar), 7.05 (s, 1H, Ar), 7.22 (d, *J* 8.1 Hz, 1H, Ar), 9.50–11.50 (br s, 2H, OH), 10.32 (s, 1H, NH); δ_C (75 MHz) 27.5, 31.8, 46.8 (br), 77.8, 110.0, 110.9, 123.1, 125.1, 128.9, 134.4, 141.6, 176.1, 182.0 (br); MS (+): *m/z* 344, 346 $[M+Na]^+$, 304, 306 $[M+H-H_2O]^+$; MS (–): *m/z* 320, 322 $[M-H]^-$; MS^2 (+) (*m/z* 344): *m/z* 326 $[M+Na-H_2O]^+$; IR (KBr): ν_{max} 3136, 2960, 1736, 1592, 1448, 1368, 1248 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}ClNO_4$ (%): C, 59.73; H, 5.01; Cl, 11.02; N, 4.35. Found (%): C, 59.87; H, 5.26; Cl, 10.94; N, 4.23.

2-(3-Hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)cyclohexane-1,3-dione (**5g**): white solid; yield 0.93 g (72%); mp 241 °C; δ_H (300 MHz) 1.75–1.88 (m, 2H), 2.22–2.36 (m, 4H), 6.76 (d, *J* 7.3 Hz, 1H, Ar), 6.86 (t, *J* 7.5 Hz, 1H, Ar), 7.08 (d, *J* 7.5 Hz, 1H, Ar), 7.15 (t, *J* 7.5 Hz, 1H, Ar), 8.50–9.50 (br s, 1H, OH), 10.14 (s, 1H, NH), 11.20–12.50 (br s, 1H, OH); δ_C (75 MHz) 20.4, 33.0 (br), 77.9, 109.4, 112.0, 121.3, 123.3, 129.2, 132.5, 142.7, 176.5, 187.0 (br); MS (+): *m/z* 282 $[M+Na]^+$, 242 $[M+H-H_2O]^+$; MS (–): *m/z* 258 $[M-H]^-$; MS^2 (+) (*m/z* 282): *m/z* 264 $[M+Na-H_2O]^+$; IR (KBr): ν_{max} 3088, 2944, 1700, 1592, 1472, 1364, 1196 cm^{-1}. Anal. Calcd. for $C_{14}H_{13}NO_4$ (%): C, 64.86; H, 5.05; N, 5.40. Found (%): C, 64.98; H, 5.32; N, 5.29.

2-(3-Hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)cyclohexane-1,3-dione (**5h**): white solid; yield 1.04 g (76%); mp 158–160 °C; δ_H (300 MHz) 1.76–1.89 (m, 2H), 2.22–2.38 (m, 4H), 3.09 (s, 3H), 6.94 (d, *J* 8.0 Hz, 1H, Ar), 6.96 (t, *J* 7.5 Hz, 1H, Ar), 7.15 (d, *J* 7.3 Hz, 1H, Ar), 7.27 (t, *J* 7.5 Hz, 1H, Ar), 9.50–12.00 (br s, 2H, OH); δ_C (75 MHz) 20.3, 26.0, 33.0 (br), 77.5, 108.2, 112.0, 122.0, 122.9, 129.3, 131.7, 144.1, 174.9, 186.0 (br); MS (+): *m/z* 296 $[M+Na]^+$, 256 $[M+H-H_2O]^+$; MS (–): *m/z* 272 $[M-H]^-$; MS^2 (+) (*m/z* 296): *m/z* 278 $[M+Na-H_2O]^+$; IR (KBr): ν_{max} 3488, 2952, 1664, 1608, 1472, 1376, 1136 cm^{-1}. Anal. Calcd. for $C_{15}H_{15}NO_4$ (%): C, 65.92; H, 5.53; N, 5.13. Found (%): C, 66.17; H, 5.67; N, 5.02.

2-(5-Chloro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl)cyclohexane-1,3-dione (**5i**): white solid; yield 1.07 g (73%); mp 129–131 °C; δ_H (300 MHz) 1.77–1.90 (m, 2H), 2.26–2.38 (m, 4H), 6.77 (d, *J* 8.1 Hz, 1H, Ar), 7.09 (s, 1H, Ar), 7.21 (d, *J* 8.1 Hz, 1H, Ar), 9.50–12.00 (br s, 2H, OH), 10.31 (s, 1H, NH); δ_C (75 MHz) 20.3, 33.0 (br), 77.8, 110.8, 111.4, 123.4, 125.1, 128.9, 134.5, 141.6, 176.3, 188.0 (br); MS (+): *m/z* 316, 318 $[M+Na]^+$, 276, 278 $[M+H-H_2O]^+$; MS (–): *m/z* 292, 294 $[M-H]^-$; MS^2 (+) (*m/z* 316): *m/z* 298 $[M+Na-H_2O]^+$; IR (KBr): ν_{max} 3496, 3208, 1700, 1596, 1480, 1400, 1184 cm^{-1}. Anal. Calcd. for $C_{14}H_{12}ClNO_4$ (%): C, 57.25; H, 4.12; Cl, 12.07; N, 4.77. Found (%): C, 57.37; H, 4.28; Cl, 11.89; N, 4.62.

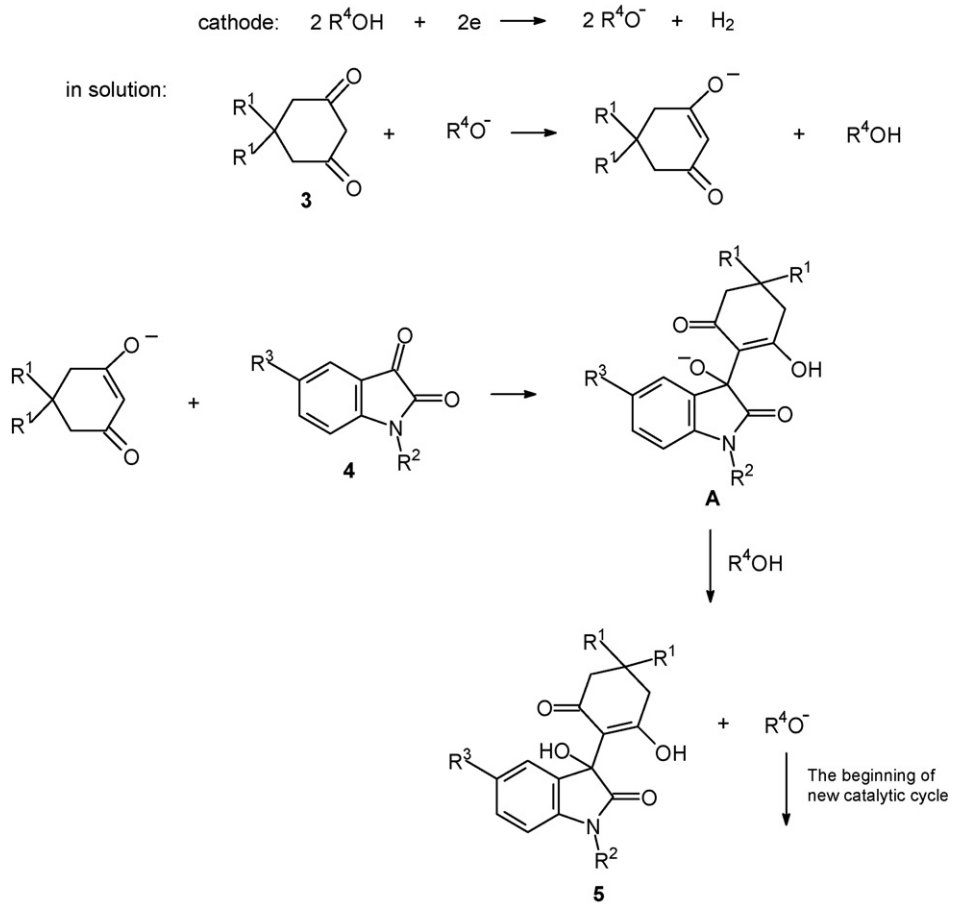
3. Results and discussion

In the present study, we report our results on the electrochemically induced addition of cyclic 1,3-dicarbonyl compounds **3a**,**b** to isatins **4a**–**f** in alcohol solution in an undivided cell (Scheme 1 and Table 1).

First, to evaluate the synthetic potential of the procedure proposed and to optimize the electrolysis conditions, the electrocatalytic addition of dimedone **3a** to isatin **4a** in alcohol solution in an undivided cell was studied (Table 1).

Under the optimal conditions (*I* = 400 mA, current density 80 mA cm^{-2}, 0.1 F mol^{-1} passed, time 2 min, NaBr as electrolyte) the electrolysis of dimedone **3a** or cyclohexane-1,3-dione **3b** with isatins **4a**–**f** in ethanol in an undivided cell resulted in the formation of corresponding substituted 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)cyclohexane-1,3-diones **5a**–**i** in 70–85% yields (Table 2).

Taking into consideration the data obtained and our previous results on the electrochemically generated base induced tandem Knoevenagel–Michael reaction with further cyclization in alcohol solution in an undivided cell [20–22] and electrochemically induced Henry reaction [19], the following reaction scheme for the electrochemically induced aldol reaction of cyclic 1,3-diketones **3a**,**b** with isatins **4a**–**f** is proposed (Scheme 2). The deprotonation of



Scheme 2.

alcohol at the cathode leads to the formation of alkoxide anion. The subsequent reaction in solution between alkoxide anion and cyclic 1,3-diketone gives rise to cyclic 1,3-diketone anion (Scheme 2).

Then addition of cyclic 1,3-diketone anion to isatin takes place in the solution with the formation of the intermediate alkoxide anion **A**. The following reaction of alkoxide anion **A** with alcohol leads to the formation of the end 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-diones **5a**–**i** with the regeneration on this stage the new alkoxide anion. This alkoxide anion continues the catalytic chain process by the interaction with the next molecule of cyclic 1,3-diketone (Scheme 2). An alternative variant of the continuation of the catalytic cycle is direct interaction of anion **A** with the cyclic 1,3-diketone with the formation of cyclic 1,3-diketone anion, and then once more addition to isatin.

The reaction at anode is usual for the system alcohol –NaBr. The anode reaction does not participate in our process and was carefully discussed earlier [23].

4. Conclusions

In conclusion, the simple electrocatalytic system can produce, under mild conditions in an undivided cell, a fast and selective previously unknown aldol reaction of cyclic 1,3-dicarbonyl compounds with isatins to form substituted 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)cyclohexane-1,3-diones in 70–85% yields and 700–850% current efficiency. This electrocatalytic chain process is an efficient and convenient way to substituted 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)cyclohexane-1,3-diones—the promising synthons for the synthesis of different biomedically active compounds. The procedure utilizes inexpensive reagents, simple equipment and an undivided cell; it is easy to carry out, the procedure of the isolation of the final aldol is very simple and is fully beneficial from the viewpoint of "green" organic synthesis and large-scale processes.

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