Monatsh Chem (2012) 143:1157–1160
DOI 10.1007/s00706-011-0693-1

ORIGINAL PAPER

Electro-organic synthesis of nanosized particles of 3-hydroxy-3-(1*H*-indol-3-yl)indolin-2-one derivatives

S. Makarem · A. R. Fakhari · A. A. Mohammadi

Received: 11 May 2011 / Accepted: 22 November 2011 / Published online: 13 December 2011

Abstract This article describes an electrochemical method for preparation of nanosized particles of 3-hydroxyoxindoles. The method is based on the reaction of isatins with indoles in propanol employing an undivided cell in the presence of NaBr as an electrolyte. The product was characterized after purification using infrared (IR), ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, mass spectrometry (MS), and scanning electron microscopy (SEM).

Keywords Indole · Isatin · Electrosynthesis · Nanosized particles

Introduction

Isatins are known for their manifold biological activities. Some isatin derivatives are key intermediates in synthesis of natural products [1]. Different derivatives of isatin have been synthesized to study their bioactivity. Oxindoles are well known among these compounds and are useful as antibacterials, anti-inflammatories [2], laxatives [3], growth hormone secretagogues [4], and new targets for cancer chemotherapy [5]. These intermediates are also useful in synthesis of chiral ligands to obtain high enantioselectivities in numerous catalytic reactions [6]. Oxindole derivatives have been prepared by reaction of isatins with alkylbenzenes or halobenzenes [7], diphenyl urea [8], barbituric acid [9], and indole [10], and other routes [11].

The basis of nanotechnology is the ability to form nanosized particles, for example, nanopowders, which are solid particles with nanoscale size. Many pharmaceutical companies are performing research to decrease particle size. Drugs with smaller particle size would be better absorbed by the digestive tract lining, thus reducing the amount necessary and making medicines more affordable [12]. The ability to deliver antibiotics in aerosol form to the lungs would provide an easier way of treating infections such as tuberculosis [13]. Decreasing particle size could increase bioavailability drastically, producing faster-reacting drugs with diverse applications in the health industry [14]. Until now, nanosized organic compounds have been prepared through different methods in which organic compounds are first synthesized and only then can be transformed into nanosized particles using modern high technology, for example, particle production of progesterone and medroxyprogesterone using supercritical fluid, 1,3,5-trinitroperhydro-1,3,5-triazine using the ultrahigh-pressure rapid expansion of supercritical solutions (RESS) system, and hydrocortisone using supercritical antisolvent with enhanced mass transfer [15–17]. However, we have directly synthesized nanosized particles in only one step through an electrochemical reaction. Electrochemical synthesis of nanosized organic compounds is an innovative method which has not been previously reported. In connection with the authors' ongoing work on electro-organic synthesis, benzofurans [18], 2-amino-4*H*-chromenes [19], and preparation of oxindoles [20, 21], this report describes a new electrochemical procedure for preparation of nanosized particles of 3-hydroxyoxindoles in an undivided cell in the presence of NaBr as an electrolyte.

S. Makarem · A. R. Fakhari (✉)
Department of Chemistry, Faculty of Sciences,
Shahid Beheshti University, G.C., Evin, Tehran, I.R. Iran
e-mail: a-zavareh@sbu.ac.ir

A. A. Mohammadi (✉)
Chemistry and Chemical Engineering Research Center of Iran (CCERCI), PO Box 14335-186, Tehran, I.R. Iran
e-mail: aliamohammadi@ccerci.ac.ir

Results and discussion

The reaction of indole (1 mmol) and 5-bromoisatin (1 mmol) was completed within 1 h, and 3-hydroxyoxindole **3a** was prepared in 90% yield (Scheme 1). In almost all previously reported works on the reaction of indole with isatins, one isatin molecule reacted with two molecules of indole, with rare reports in which the reaction ceased after addition of only one indole molecule to the isatin molecule [20, 22]. Interestingly, it was found that this reaction produced 3-hydroxyoxindole, since there was no evidence of formation of 3,3′-bisindolyloxindoles **4**. All 3-hydroxyoxindoles **3** were attributed based on one peak observed close to 6.30–6.60 ppm for their OH protons.

Surprisingly, it was found that these products were nanosized particles. An SEM image of the template-synthesized nanoparticles, obtained from powder, is shown in Fig. 1. The average particle size (d_{SEM}) is <100 nm. The size and form of the aggregates depended upon the conditions in which the sample was prepared.

After screening several parameters such as solvents, temperature, and current, it was found that dry propanol at current density of 10 mA cm^{-2} at 40 °C promotes the reaction of 5-bromoisatin (**1a**) and indole (**2a**) to afford 3-hydroxyoxindole **3a** efficiently (Table 1).

Initially, we used graphite and platinum as anode and cathode instead of magnesium and iron. Our experiments showed that these electrodes elongate the reaction time and reduce the yield of products, while using graphite or platinum as anode leads to production of Br_2 at the surface of the anode, making product separation difficult. Thus, despite the loss of magnesium electrodes during the reaction, this electrode was used as anode due to advantages such as shorter reaction time, higher yield, and production of nontoxic Mg^{2+}. In addition, reduction of alcohol on iron was mentioned in previous reports [23, 24].

An attempt was made to prepare nanosized particles of 3-hydroxyoxindole derivatives from indole and isatin derivatives to extend the scope of the reaction. Hence, a number of isatin derivatives effectively participated in condensation with indole derivatives to give corresponding nanosized particles of 3-hydroxyoxindole compounds in good yields. The results are summarized in Table 2.

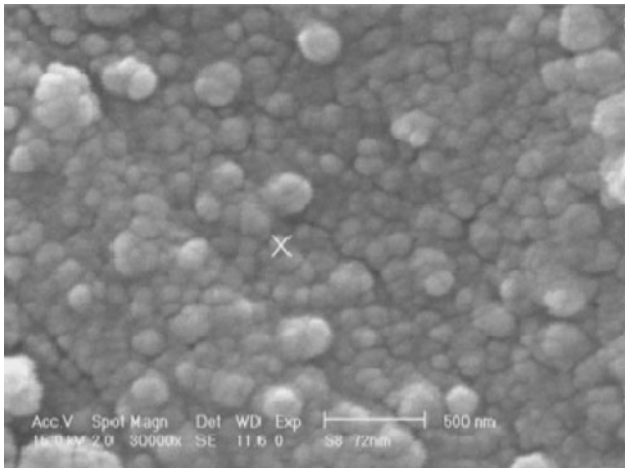


Fig. 1 Image of nanosized particles of compound **3a**

Table 1 Effect of temperature and current on reaction of 5-bromoisatin **1a** and indole **2a** to afford nanosized particles of 3-hydroxyoxindole **3a**

Entry[a]	Solvent	*t*/min	*I*/A	*T*/°C	Current passed/ F mol^{-1}	Yield/%[b]
1	Propanol	150	0.05	25	4.7	60
2	Propanol	60	0.05	40	1.9	90
3	Propanol	240	0.02	25	3.0	50
4	Ethanol	60	0.05	40	1.9	70
5	Ethanol	150	0.05	25	4.7	40

[a] For all reactions, 0.5 mmol NaBr, iron cathode (5 cm^2), and magnesium anode (5 cm^2) were used

[b] Isolated yields based on 5-bromoisatin **1a**

Scheme 1

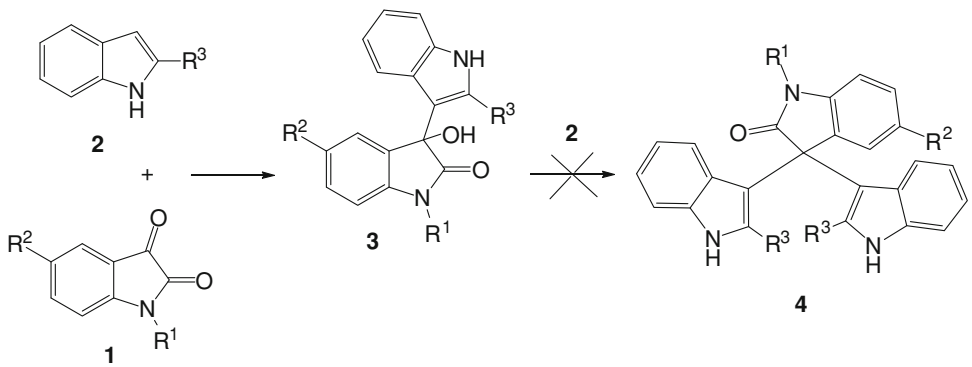


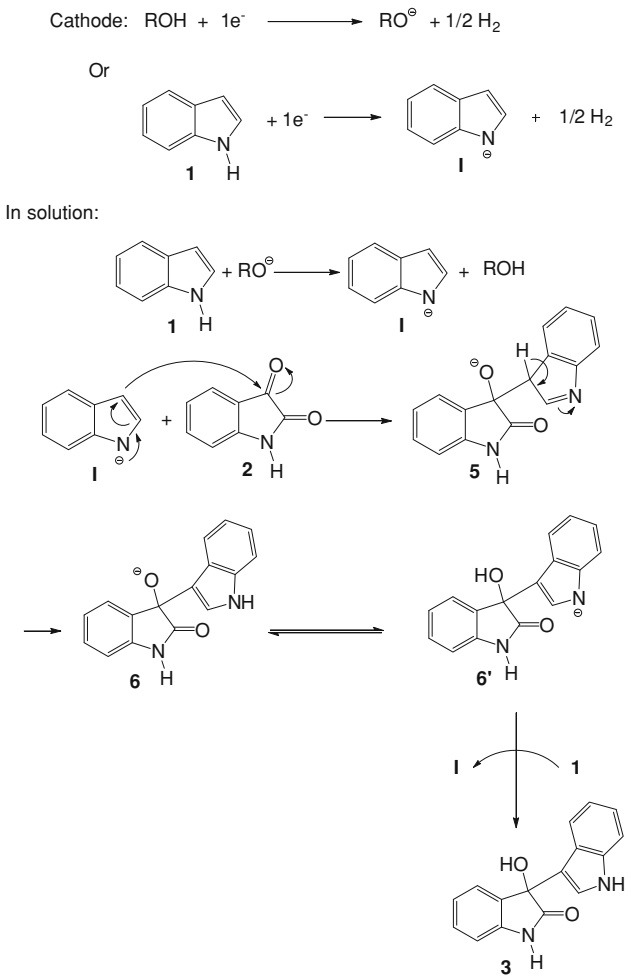
Table 2 Electrochemical condensation of isatins **1** and indoles **2** for preparation of 3-hydroxyoxindoles **3**

Comp.[a]	R^1	R^2	R^3	M.p./°C	Yield/%[b]	Ref.
3a	H	Br	H	209	90	–
3b	H	Br	Me	228	92	–
3c	Et	Br	H	80	89	–
3d	Me	H	H	52	87	–
3e	H	H	Me	160	85	[10]
3f	H	H	H	143 (dec)	94	[10]

[a] All reactions were run with 0.147 g isatin (1 mmol), 0.117 g indole (1 mmol), and 0.05 g NaBr (0.5 mmol) in 25 cm^3 propanol at 40 °C

[b] Yields based on isatins

The following mechanism is proposed to account for the reaction: Deprotonation of alcohol at the cathode led to formation of an alkoxide anion. Subsequent reaction between the alkoxide anion and indole gave rise to an indole anion. Condensation of anion **I** with **2** yielded intermediate **5**. Finally, product **3** was formed by protonation and rearrangement of **5** (Scheme 2).



Scheme 2

Conclusions

A successful new strategy for efficient, convenient, green synthesis of 3-hydroxyoxindoles via condensation reaction of indoles and isatins is described. This reaction, the first reported for preparation of nanosized particles of organic compound by electro-organic synthesis, is a useful process for synthesis of nanosized particles of 3-hydroxyoxindoles.

Experimental

Constant-current coulometry and preparative electrolysis were performed using a SAMA potentiostat/galvanostat (Isfahan, Iran). The working electrodes were an iron cathode (5 cm^2) and a magnesium anode (5 cm^2). IR spectra were recorded on a Bruker IFS-66 Fourier transform (FT)-IR spectrophotometer. NMR spectra were recorded on a Bruker DRX-300 Avance instrument. Mass spectra were obtained using a QP-1100 EX Shimadzu gas chromatography (GC)-MS [electrospray ionization (EI) at 70 eV] and an HP (Agilent Technologies) 5937 mass-selective detector. Scanning electron microscopy (SEM) was run with an axl30 scanning electron microanalyzer (Philips, The Netherlands) at acceleration voltage of 20.0 kV. Melting points were obtained using an electrothermal melting point apparatus (model 9200). All starting materials were commercially available, obtained from Merck, and used without further purification.

5-Bromo-3-hydroxy-3-(1H-indol-3-yl)indolin-2-one (**3a**, $C_{16}H_{11}BrN_2O_2$)

A mixture of indole (1 mmol), 5-bromoisatin (1 mmol), and 51 mg NaBr (0.5 mmol) in 25 cm^3 propanol was stirred and electrolyzed in an undivided cell equipped with an iron cathode and a magnesium anode at 40 °C under constant current density of 10 mA cm^{-2} ($I = 50$ mA). After completion of the reaction [monitored by thin-layer chromatography (TLC), ethyl acetate/*n*-hexane 2:1], the solvent was evaporated under reduced pressure, ethanol (90%) was added to the reaction mixture, and the resulting solid was centrifuged. The crude products were then gathered for analysis. M.p.: 209 °C; IR (KBr): $\bar{\nu} = 3{,}414$, 3,234, 1,710, 1,615 cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta =$ 10.98 (s, 1H, NH), 10.33 (s, 1H, NH), 7.31–7.34 (m, 2H, Ar), 7.21–7.26 (m, 2H, Ar), 7.05 (d, 1H, $J = 2.2$ Hz, Ar), 6.97–7.04 (m, 1H, Ar), 6.83–6.94 (m, 2H, Ar), 6.34 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 178.9$, 142.1, 137.2, 133.9, 129.5, 125.3, 125.1, 123.9, 122.1, 121.5, 120.8, 118.9, 115.9, 111.9, 110.0, 75.3 ppm; MS: m/z (%) = 344

(M^++2, 25) 342 (M^+, 25), 264 (20), 197 (98), 180 (25), 117 (75), 90 (30), 63 (25), 44 (100).

5-Bromo-3-hydroxy-3-(2-methyl-1H-indol-3-yl)indolin-2-one (**3b**, $C_{17}H_{13}BrN_2O_2$)
M.p.: 228 °C; IR (KBr): $\bar{\nu}$ = 3,387, 2,913, 1,721, 1,614 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 10.96 (s, 1H, NH), 10.55 (s, 1H, NH), 7.44 (d, 1H, Ar), 7.20–7.25 (m, 2H, Ar), 7.87–6.98 (m, 3H, Ar), 6.75–6.80 (m, 1H, Ar), 6.48 (s, 1H, OH), 2.41 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 178.6, 141.3, 136.9, 135.3, 134.0, 132.1, 127.9, 126.8, 120.4, 119.2, 118.9, 113.8, 112.3, 110.9, 109.1, 76.4, 13.7 ppm; MS: *m/z* (%) = 358 (M^++2, 10), 356 (M^+, 10), 343 (10), 247 (30), 218 (12), 117 (50), 91 (100), 65 (27), 39 (26).

5-Bromo-1-ethyl-3-hydroxy-3-(1H-indol-3-yl)indolin-2-one (**3c**, $C_{18}H_{15}BrN_2O_2$)
M.p.: 80 °C; IR (KBr): $\bar{\nu}$ = 3,392, 2,919, 1,712, 1,607 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 11.06 (s, 1H, NH), 7.54 (d, 1H, J = 8.1 Hz, Ar), 7.33 (d, 2H, J = 7.9 Hz, Ar), 7.24 (d, 1H, J = 8.1 Hz, Ar), 7.12 (d, 2H, J = 8.3 Hz, Ar), 7.03 (t, 1H, J = 7.5 Hz, Ar), 6.87 (t, 1H, J = 7.5 Hz, Ar), 6.60 (s, 1H, OH), 3.72 (q, 2H, J = 7.0 Hz, CH_2), 1.19 (t, 3H, J = 7.0 Hz, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 176.1, 141.8, 137.2, 135.8, 132.3, 127.6, 125.0, 124.1, 121.7, 120.2, 119.2, 114.9, 114.5, 112.1, 111.3, 75.0, 34.6, 12.8 ppm; MS: *m/z* (%) = 372 (M^++2, 50), 370 (M^+, 50), 354 (35), 341 (20), 325 (100), 275 (30), 242 (50), 142 (75), 117 (30), 100 (25), 69 (30), 57 (45), 44 (65).

3-Hydroxy-3-(1H-indol-3-yl)-1-methylindolin-2-one (**3d**, $C_{17}H_{14}N_2O_2$)
M.p.: 52 °C; IR (KBr): $\bar{\nu}$ = 3,391, 2,931, 1,713, 1,610 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 11.03 (s, 1H, NH), 7.27–7.37 (m, 4H, Ar), 6.99–7.09 (m, 4H, Ar), 6.83–6.88 (t, 1H, J = 7.5 Hz, Ar), 6.43 (s, 1H, OH), 3.15 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 177.1, 143.5, 137.2, 133.2, 129.6, 125.3, 124.8, 124.1, 122.8, 121.5, 120.7, 119.0, 115.6, 112.0, 109.0, 75.1, 31.2 ppm; MS: *m/z* (%) = 278 (10), 261 (60), 233 (35), 218 (10), 141 (10), 125 (25), 115 (30), 97 (53), 70 (73), 57 (100).

Acknowledgments Financial support from the Research Affairs of Shahid Beheshti University is gratefully acknowledged.

References

1. Garden SJ, Torres JC, Ferreira AA, Silva RB, Pinto AC (1997) Tetrahedron Lett 38:1501
2. Popp FD (1984) J Heterocycl Chem 21:1367
3. Garrido F, Ibanez J, Gonalons E, Giraldez A (1975) Eur J Med Chem 10:143
4. Tokunaga T, Hume WE, Nagamine J, Kawamura T, Taiji M, Nagata R (2005) Bioorg Med Chem Lett 15:1789
5. Yong SR, Ung AT, Pyne SG, Skelton BW, White AH (2007) Tetrahedron 63:5579
6. Berens U, Brown JM, Long J, Selke R (1996) Tetrahedron Asymmetr 7:285
7. Klumpp DA, Yeung KY, Prakash GKS, Olah GA (1998) J Org Chem 63:4481
8. Franklin DP (1973) Ger. Patent 2258505
9. Jursic B, Stevens ED (2002) Tetrahedron Lett 43:5681
10. Kumar VP, Reddy VP, Sridhar R, Srinivas B, Narender M, Rao KR (2008) J Org Chem 73:1646
11. Wright SW, McClure LD, Hageman DL (1996) Tetrahedron Lett 37:4631
12. Pison U, Welte T, Giersig M, Groneberg DA (2006) Eur J Pharmacol 533:341
13. Reverchon E, DeMarco I, Porta GD (2002) Int J Pharmaceut 243: 83
14. Azzam EMS, Kandile NG, Badawi AM, Sami RM (2011) J Dispersion Sci Technol 32:1325
15. Alessi P, Cortesi A, Kikic I (1996) Ind Eng Chem Res 35:4718
16. Cortopassi A, Kuo KK, Ferrara PJ, Wawiernia TM, Essel JT (2008) Int J Energetic Materials Chem Prop 7:39
17. Thakur R, Gupta RB (2006) Chem Eng Commun 193:293
18. Fakhari AR, Nematollahi D, Shamsipur M, Makarem S, Hosseini Davarani SS, Alizadeh AA, Khavasi HR (2007) Tetrahedron 63: 3894
19. Makarem S, Mohammadi AA, Fakhari AR (2008) Tetrahedron Lett 49:7194
20. Azizian J, Mohammadi AA, Karimi N, Mohammadizadeh MR, Karim AR (2006) Catal Commun 7:752
21. Mohammadi AA, Dabiri M, Qaraat H (2009) Tetrahedron 65: 3804
22. Paira P, Hazra A, Kumar S, Paira R, Sahu KB, Naskar S, Saha P, Mondal S, Maity A, Banerjee S, Mondal NB (2009) Bioorg Med Chem Lett 19:4786
23. Elinson MN, Ilovaisky IA, Merkulova MV, Demchuk VD, Elyakov AP, Ogibin NY, Nikishin IG (2008) Electrochim Acta 53:8346
24. Elinson MN, Dorofeev AS, Feducovich SK, Gorbunov SV, Nasybullin RF, Stepanov NO, Nikishin GI (2006) Tetrahedron Lett 47:7629