Organic Electrosynthesis as a New Facile and Green Method for One-pot Synthesis of Nanosized Particles of Octahydro-imidazo[1,2-*a*]quinolin-6-one Derivatives *via* a Multicomponent Reaction

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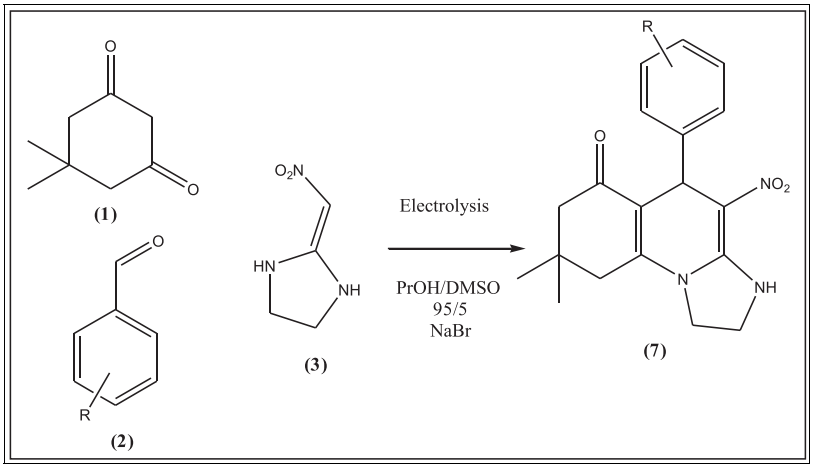


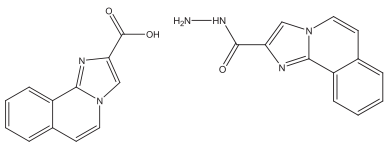
Organic electrosynthesis as a new facile and green method was applied for one-pot synthesis of octahydro-imidazo[1,2-*a*]quinolin-6-one derivatives, *via* a three component condensation of a dimedone, an aldehyde and 2-(nitromethylene)imidazolidine in propanol in an undivided cell in the presence of sodium bromide as an electrolyte at room temperature. In this study, the anion of dimedone that was produced on the cathode reacted with aromatic aldehydes through the Knoevenagel reaction and then the product condensed with 2-(nitromethylene)imidazolidine that resulted in a highly efficient formation of octahydro-imidazo[1,2-*a*]quinolin-6-one with 50–96% substance yields.

INTRODUCTION

Imidazoquinolines are classified as diverse and interesting heterocyclic systems that showed significant biological and pharmaceutical properties depending on the position of the fusion and the nature of the substituents [1,2]. A literature survey has revealed that different imidazoquinolines have been reported to act as antimalarial [3], antimicrobial [4], antitumor, and anticancer agents [5,6]. Some imidazoquinoline derivatives such as imidazo[2,1-*a*]isoquinoline-2-carboxylic acid hydrazide (1) as an inhibitor and imidazo[2,1-*a*]isoquinoline-2-carboxylic acid (2) with antiallergic activity are shown in Figure 1 [7,8].

Considering nanoscale materials, the physical, chemical, and biological properties differ in fundamental and valuable ways from the properties of individual atoms and molecules or the bulk matter. Nanotechnology R&D is directed toward understanding and creating improved materials and systems that exploit these new properties, and these unique phenomena enable novel applications. Currently, nanoparticle applications in medicine are geared toward drug discovery and drug delivery because applying nanotechnology in drug delivery enhanced drug properties such as solubility, rate of dissolution, oral bioavailability, targeting ability, enhanced dosing requirements, lower dosed administered, and a better side effect profile. The goal is to make the nanoparticles multifunctional and controllable by external signals or local environments in the future [9].

Nowadays, electrosynthesis is used as a new green methodology for the elimination of hazardous reagents, green environmental applications, the elimination of dangerous substances, treatment of pollutions, and atom economy. In this method, electrons act as catalysts, and because electrons are clean and renewable reagents, this methodology can be used to replace toxic or dangerous oxidizing or reducing reagents. Electro-organic syntheses have some advantages such as its reaction rate, the nature of the electrode that can be controlled, reaction conditions that are mild, and electrolysis that is performed at room temperature and atmospheric pressure [10]. Many reactions have been reported using organic electrosynthesis method such as the synthesis of N-



(1) (2)

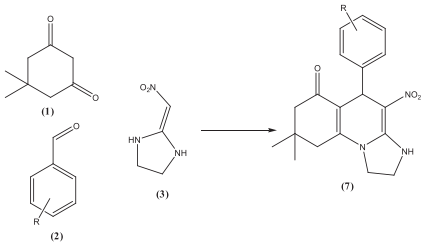
Figure 1. Examples of imidazoquinoline derivatives as biological active agents.

heterocyclic carbenes precursors [11], 1*H*-indole [12], amidation [13], imidazolium carboxylates [14], electro-oxidation of alcohols [15], bromination reaction [16], cyclic carbonates [17,18], oxidative esterification [19–21], N-functionalization [22,23] and recently, synthesizing the nanoparticles of 3-hydroxy-3-(1*H*-indol-3-yl)indolin-2-one [24], 2-amino-pyranes, [25] and spirooxindoles [26]. Based on our strong literature survey, the synthesis of octahydro-imidazo[1,2-*a*] quinolin-6-one derivatives through electro-organic methods has not been reported until now. We first investigated the reaction of dimedone (**1**), 4-nitrobenzaldehyde (**2a**) with 2-(nitromethylene) imidazolidine under various reaction conditions (Table 1). The ^{1}H and ^{13}C NMR and IR spectra of product showed the formation of 8,8-dimethyl-4-nitro-5-(4-nitro-phenyl)-2,3,5,7,8,9-hexahydro-1*H*-imidazo[1,2-*a*]quinolin-6-one.

RESULT AND DISCUSSION

In this study, we tried to design and introduce a new green methodology for the synthesis of octahydro-imidazo[1,2-*a*]quinolin-6-one derivatives by the reaction of dimedone, aldehydes, and 2-(nitromethylene) imidazolidine in an alcoholic solvent and an undivided cell in the presence of NaBr as the electrolyte (Scheme 1).

Scheme 1. General schematic for the preparation of octahydro-imidazo[1,2-*a*]quinolin-6-one derivatives.



In order to optimize the synthesis conditions, several parameters such as solvent, anode, temperature, and current were studied (Table 1).

It can be seen from Table 1 that increasing the current to amounts more than 400 mA decreased the yield of the reaction (entry 1–6). We also investigated the effect of temperature on the reaction and found that increasing the temperature also decreased the reaction yields (entry 7). Subsequently, several solvents such as propanol, ethanol, and propanol/dimethylsolfoxide were used to find the best solvent for the reaction (entry 9). Effect of anode on time and yield of the reaction was also checked (entry 10). It was found that the best condition for minimizing the synthesis time and higher production yield is dry propanol/dimethylsolfoxide (95:5, PrOH/DMSO) at a current density of 80 mA cm^{-2} (I = 400 mA, electrode surface = 5 cm^2) on magnesium anode and at room temperature (entry 9).

The scope and generality of this protocol was next examined by employing dimedone, various aromatic aldehydes, and 2-(nitromethylene)imidazolidine. Conscionably, under the optimized condition, a variety of octahydro-imidazo[1,2-*a*]quinolin-6-ones (7a–7f) were obtained in a good to excellent yield (Table 2).

Table 1

Optimization of reaction conditions and effect of solvents, anode, temperature, and current in this procedure.

Entry	Current (mA)	Temperature °C	Solvent	Passed current (F/mol)	Time (min)	Yield[c]
1[a]	100	r.t	*n*-PrOH	15.2	240	30
2[a]	200	r.t	*n*-PrOH	30.3	240	34
3[a]	300	r.t	*n*-PrOH	45.4	240	38
4[a]	400	r.t	*n*-PrOH	26.2	105	86
5[a]	500	r.t	*n*-PrOH	33.4	105	83
6[a]	600	r.t	*n*-PrOH	50.1	135	40
7[a]	400	50	*n*-PrOH	26.2	105	65
8	400	r.t	EtOH	37.6	150	33
9[a]	400	r.t	*n*-PrOH/DMSO 95/5	26.2	105	96
10[b]	400	r.t	*n*-PrOH/DMSO 95/5	26.2	105	87

Reaction conditions: dimedone (**1**, 1.0 mmol), 4-nitro benzaldehyde (**2a**, 1.0 mmol), 2-(nitromethylene)imidazolidine (**3**, 1.0 mmol), 0.5-mmol NaBr, and iron cathode (5 cm^2).
[a]Magnesium (5 cm^2) was used as anode.
[b]Graphite (5 cm^2) was used as anode.
[c]Isolated yield.

Table 2

Electro-organic synthesis of octahydro-imidazo[1,2-*a*]quinolin-6-ones derivatives.

Products[a]	R_1	Time (min)	Yield (%)[a]	Lit. m.p (°C)	m.p (°C)
7a	4-Nitro	105	96	265 dec.[27]	258–260 dec.
7b	4-Hydroxy	120	95	—	274–276
7c	2,4-Dimethoxy	150	63	—	260–262
7d	4-Chloro	135	70	254 dec.[27]	248–250 dec.
7e	3,4,5-Trimethoxy	120	50	—	240–242
7f	4-Methoxy	135	94	—	200–202

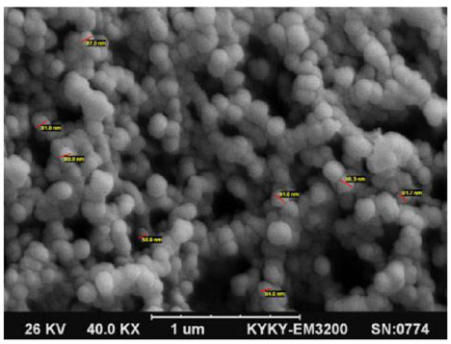
[a]Reaction conditions: an iron cathode (5 cm^2), a magnesium anode (5 cm^2), current (0.4 A), electrolyte (NaBr), and *n*-PrOH/DMSO 95/5 (25 mL), an undivided cell, and room temperature.

For investigating the effect of anode material on the size of product, under the optimized condition, we synthesized 7a with both a magnesium and a graphite anode. SEM images of the template-synthesized nanoparticles, obtained from powder, are shown in Figure 2.

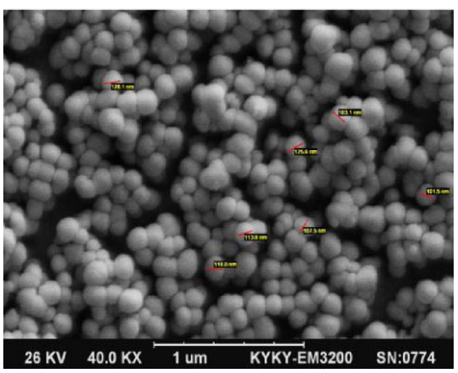
It is obvious that using magnesium as the anode decreases the size of product in nanometer. The average particle size using a magnesium anode (d_{SEM}) is $<$100 nm. Based on our previous report [23], we believed that the existence of Mg^{2+} ions in the solution might prevent the coagulation of the product molecules in the medium.

A proposed mechanism for the synthesis is depicted in Scheme 2. Deprotonation of an alcohol on the surface of the cathode leads to the formation of an alkoxide anion. The subsequent reaction between the alkoxide anion and dimedine (**1**) gives rise to the dimedone anion (**1**), and then, the reaction of aldhyde (**2**) and dimedone anion (**1**) obtains product (**5**) *via* Knoevenagel reaction. This product would undergo the condensation with ketene diaminal (**3**) giving intermediate (**6**). Intermediate (**6**) would dehydrate spontaneously to achieve products (**7**) [26–28].

The spectral data of products confirmed structure 7. The IR spectrum of compound (**7**) exhibited peaks at 3363–3700 (NH) and 1655–1725 (C═O) for the carbonyl functional group. The ^{1}H NMR spectrum showed one singlet at 4.57–5.07 ppm for the hydrogen of CH and one hydrogen of NH at 9.19–9.32.



(a)



(b)

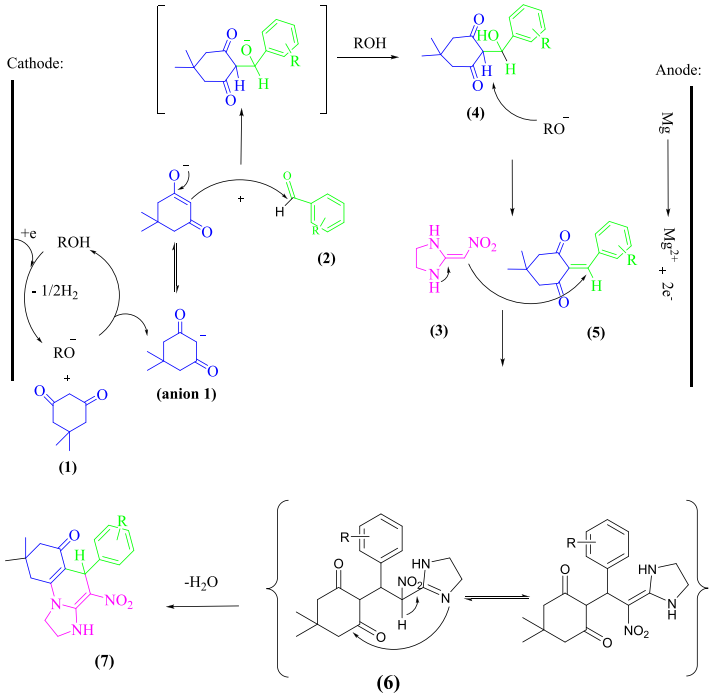
Figure 2. SEM images of 7a compound used (a) magnesium (b) graphite as anode. [Color figure can be viewed at wileyonlinelibrary.com]

EXPERIMENTAL

General electro-organic synthesis procedure for the preparation of octahydro-imidazo[1,2-*a*]quinolin-6-ones derivatives. A mixture of dimedone (1 mmol), aldehyde (1 mmol), 2-(nitromethylene)imidazolidine (1 mmol), and NaBr (0.05 g, 0.5 mmol) in propanol (25 mL) was magnetically stirred and electrolyzed in a cell equipped with an iron cathode (5 cm^2) and a magnesium anode (5 cm^2) at room temperature under a constant current density of 80 mA/cm^2 (I = 400 mA). After completion of the reaction (monitored by thin-layer chromatography, ethyl acetate/n-hexane 2:1), the solvent was evaporated under reduced pressure (about 40 torr), and then, 20-ml ethanol (80%) was added to the reaction mixture. The precipitate was separated by centrifugation.

Spectral data for selected new products. ***8,8-Dimethyl-4-nitro-5-(4-nitro-phenyl)-2,3,5,7,8,9-hexahydro-1H-imidazo[1,2-a]quinolin-6-one (7a).*** Yellow crystal; mp 258–260°C; yield (96%); IR (KBr) (ν_{max}, cm^{-1}): 3343 (NH), 1725 (C═O), 1617, 1520, 1510. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm) 1.00 (3H, S, CH_3), 1.02 (3H, s, CH_3), 1.88 (1H, d, J = 12.2, CH), 1.96 (1H, d, J = 13.50, CH), 2.14 (1H, d, J = 13.8, CH), 2.43 (1H, d, J = 12.6, CH), 3.56, 3.74 (3H, m, CH), 4.41 (1H, d, J = 11.1 CH), 6.30 (1H,

Scheme 2. Plausible mechanism for the condensation of dimedone, aldehydes, and 2-(nitromethylene)imidazolidine. [Color figure can be viewed at wileyonlinelibrary.com]



s, CH_3),7.47 (1H, t, ArH), 9.20 (1H, s, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ_C (ppm) 26.0, 29.3, 31.8, 43.4, 44.8, 49.2, 106.5, 112.4, 121.2, 122.5, 129.2, 134.5, 146.4, 147.1, 149.8, 151.3, 193.3. *Anal*. Calcd for $C_{19}H_{20}N_4O_5$: C, 59.37; H, 5.24; N, 14.58%. Found: C, 59.25; H, 5.34; N, 14.40%.

5-(4-Hydroxy-phenyl)-8,8-dimethyl-4-nitro-2,3,5,7,8,9-hexahydro-1H-imidazo[1,2-a]quinolin-6-one (7b). Yellow crystal; mp 274–276°C; yield (95%); IR (KBr) (ν_{max}, cm^{-1}): 3343 (NH), 1725 (C═O), 1520, 1124. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm) 1.00 (3H, s, CH_3), 1.02 (3H, s, CH_3), 1.87 (1H, d, J = 12.6, CH), 1.96 (1H, d, J = 13.1, CH), 2.14 (1H, d, J = 13.50, CH), 2.43 (1H, d, J = 12.3, CH), 3.31 (3H, s, CH_3), 3.62–3.77 (3H, m, CH_2), 4.41 (1H, d, J = 11.4, CH), 6.27 (1H, s, CH), 7.47 (1H, t, J = 8.1, ArH), 7.69 (1H, d, J = 7.8, ArH), 7.96 (2H, d, J = 5.1, ArH), 9.19 (1H, s, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ_C (ppm) 27.5, 31.3, 32.8, 34.7, 45.6, 53.2, 59.8, 84.9, 107.2, 147.0, 147.2, 157.0, 204.5. *Anal*. Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.82%. Found: C, 64.31; H, 5.85; N, 11.70%.

5-(2,4-Dimethoxy-phenyl)-8,8-dimethyl-4-nitro-2,3,5,7,8,9-hexahydro-1H-imidazo[1,2-a]quinolin-6-one (7c). Yellow crystal; mp 260–262°C; yield (63%); IR (KBr) (ν_{max}, cm^{-1}): 3273 (NH), 1713 (C═O), 1605, 1503, 1145. ^{1}H NMR (300 MHz, $CDCl_3$) δH (ppm) 1.01 (3H, s, CH_3), 1.92–2.07 (3H, m, CH), 2.53 (1H, m, CH), 3.38–3.47 (3H, m, CH), 3.51–3.58 (1H, m, CH), 3.68 (3H, s, CH), 3.71 (3H, s, CH_3), 5.68 (1H, s, CH) 6.30 (1H, dd, J = 6.3, 2.2, ArH) 6.45 (1H, d, J = 2.2, ArH), 6.69 (1H, d, J = 8.4, ArH), 9.32 (1H, s, NH). ^{13}C NMR 18.5, 29.8, 32.1, 32.8, 43.9, 53.3.55.0, 56.0, 58.4, 84.5, 97.8,103.7, 104.2, 123.1, 128.1, 156.8, 157.0, 158.4, 205.9. *Anal*. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.15; H, 6.31; N, 10.52%. Found: C, 63.28; H, 6.41; N, 10.39%.

8-Methyl-4-nitro-5-(3,4,5-trimethoxy-phenyl)-2,3,5,7,8,9-hexahydro-1H-imidazo[1,2-a]quinolin-6-one (7e). Yellow crystal; mp 240–242°C; yield (50%); IR (KBr) (ν_{max}, cm^{-1}): 3700 (NH), 3376, 2955, 1693 (C═O), 1590, 1505, 1123. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm) 0.91 (3H, s, Me), 1.05 (3H, s, Me), 2.03 (1H, d, J = 16, CH), 2.21 (1H, d, J = 16.1 CH), 2.52–2.58 (2H, m, CH_2), 3.57 (3H, s, CH_3), 3.78–3.83 (2H, m, CH_2), 3.98–4.01 (1H, m, CH), 4.13–4.19 (1H, m, CH), 5.07 (1H, s, CH), 6.44 (2H, s, ArH), 9.74 (1H, s, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ_C (ppm) 13.8, 39.2, 109.2, 109.8, 113.2, 120.2, 120.9, 123.1, 127.2, 135.3, 140.2, 153.3, 170.8. *Anal*. Calcd for $C_{22}H_{27}N_3O_6$: C, 61.53; H, 6.34; N, 9.78%. Found: C, 61.43; H, 6.44; N, 9.63%.

5-(4-Methoxyphenyl)-8,8-dimethyl-4-nitro-2,3,5,7,8,9-hexahydroimidazo[1,2-a]quinolin-6(1H)-one (7f). Yellow crystal; mp 200–202°C; yield (94%); IR (KBr) (ν_{max}, cm^{-1}): 3700 (NH), 3371, 3220, 2957, 1655 (C═O), 1606, 1510, 1409. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm) = 0.92 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.89–1.94 (4H, s, CH_2), 3.55 (3H, s, CH_3), 3.64–3.70 (4H, m, CH_2), 4.75 (1H, s, CH), 6.71 (2H, d, J = 6.3, ArH), 7.08 (2H, d, J = 7.08, ArH), 8.41 (1H, s, NH). ^{13}C NMR

(75.4 MHz, $CDCl_3$) δ_C = 13.8, 39.2, 109.2, 109.8, 113.2, 120.2, 120.9, 123.1, 127.2, 135.3, 140.2, 153.3, 170.8. *Anal*. Calcd for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.28; N, 11.37%. Found: C, 65.14; H, 6.40; N, 11.24%.

CONCLUSION

In conclusion, a simple electrosynthesis method has been developed to prepare nanosized particles of octahydro-imidazo[1,2-*a*]quinolin-6-ones derivatives *via* a multicomponent reaction. The electrosynthesis process is crucial for the green synthesis of inexpensive and highly electrocatalytically active intermediate for sustainable energy production. Albeit, the process can be used for a myriad of nanoparticles of organic compounds.

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