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Electrogenerated base-promoted synthesis of 4-aryl-5-benzoyl-2--hydroxy-6-(trifluoromethyl)-1,4-dihydropyridine-3--carbonitriles nanoparticles by three-component condensation of aromatic aldehydes, malononitrile and 4,4,4-trifluoro-1--phenylbutane-1,3-dione

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Abstract: An electrochemical strategy to the synthesis of novel 4-aryl-5-benzoyl-2-hydroxy-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitriles nanoparticles *via* three-component reaction of aromatic aldehydes, malononitrile and 4,4,4-trifluoro-1-phenylbutane-1,3-dione in water/ethanol in an undivided cell in the presence of sodium bromide as an electrolyte is described. This method has several advantages, such as high to excellent product yields (65––85 %), atom economy, environment friendly, and no need for chromatographic separations.

Keywords: multi-component; electrosynthesis; 1,4-dihydropyridine; nanosized; aromatic aldehydes.

INTRODUCTION

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity.[1] One of the ways to fulfill these goals is the development and use of multicomponent reactions that consist of several simultaneous bond-forming reactions and allow the highly efficient synthesis of complex molecules starting from simple substrates in a one-pot manner.[2–4] The electrocatalytic multicomponent reaction is known as an important approach to address this issue, in which three or more starting materials are combined together in an electrochemical cell in the presence of an appropriate electrolyte and working electrodes to generate the target products.[5,6] The noteworthy growth in studies in organic electrochemistry during recent years has made electrosynthesis one of the most competitive protocols of modern organic chemistry and provides organic chemists with a novel and versatile synthetic

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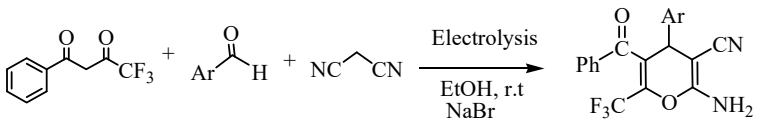
device of great promise.[7] Electrochemical procedures aimed at the synthesis of organic compounds are valuable for large-scale processes due to their catalytic nature and the use of an inexpensive and environmentally responsible chemical reagent, namely electricity.[8,9] The electrosynthesis of heterocyclic compounds can be performed at ambient temperature and pressure, which it is considered a further advantage of this approach.

Derivatives of 1,4-dihydropyridine (DHP) represent an important class of bioactive molecules, well known for their role as calcium channel modulators and used extensively for the treatment of hypertension.[10–12] Polyfunctionalized 1,4-dihydropyridines have also shown a variety of biological and pharmacological activities, such as anti-allergic, antitumor, antibacterial. anticonvulsant, anti-analgesic, anti-inflammatory, antihypertensive, cardiovascular disease and stress protective activities.[13,14] Due to their unique physical, chemical, and biological properties, fluorinated organic compounds,[15–17] have attracted much attention. Among various fluorine substituents, the trifluoromethyl group is one of the most important structural fragments, because of its important role in modulating the chemical, physical and biochemical properties of organic molecules.[18] The trifluoromethyl fragment is a part of many biologically active molecules, such as celecoxib (nonsteroidal anti-inflammatory drug),[19] efavirenz (HIV RT inhibitor),[20] mefloquine (antimalarial agent),[21] and sorafenib (oral multikinase inhibitor).[22]

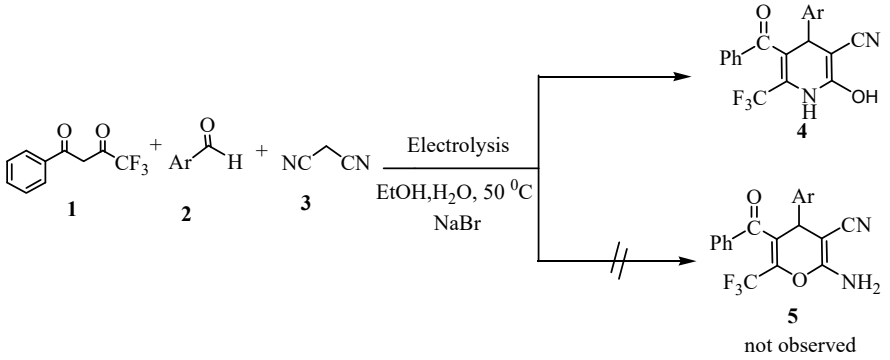
Drug structures with a high surface–volume ratio display substantial improvement of solubility, which results in stronger therapeutic effects. Thus, nano- or micro-sized drugs, due to their high surface–volume ratio, result in increases of the drug adsorption and improvement of the curative characteristics. Accordingly, the development of several new methods to synthesize nano-sized drugs is a significant challenge for both the chemist and pharmacist. Several methods, including micronization, modification of polymorphic configuration, expansion of oil-based solutions, smart application of co-solvents, application of stabilizing agents, micro-emulsions, and creation of solid dispersions, have been offered for the synthesis of nano-sized drug compounds.[23]

Recently, an electrocatalytic reaction of aromatic aldehydes, malononitrile and 4,4,4-trifluoro-1-phenylbutane-1,3-dione in alcoholic solvent to produce nano-particles of 2-amino-4-aryl-4*H*-pyran derivatives was reported[24] (Scheme 1).



Scheme 1. Electrocatalytic reaction of aromatic aldehydes, malononitrile and 4,4,4-trifluoro-1-phenylbutane-1,3-dione.

Considering the above reports, and in continuation of our studies on the electro synthesis of heterocyclic compounds,[23–26] herein a convenient and facile synthesis of 4-aryl-5-benzoyl-2-hydroxy-6-(trifluoromethyl)-1,4-dihydropyridine-3--carbonitriles **4** is designed based on the electrochemically induced three-component reaction of aromatic aldehydes **1**, malononitrile 2, and 4,4,4-trifluoro-1--phenylbutane-1,3-dione **3**, in water/ethanol (1:9) solvent in an undivided cell without a base or any additive catalyst (Scheme 2).



Scheme 2. Electrocatalytic synthesis of nanoparticles of 1,4-dihydropyridine derivatives.

EXPERIMENTAL

All chemicals and solvents were purchased from Merck or Sigma–Aldrich. Melting points of the target products were measured using an IA 9100 melting point apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer. Controlled--current coulometry and preparative electrolysis were realized *via* a SAMA potentiostat/galvanoastat (Isfahan, Iran). The electrodes used in this work were an iron cathode (5 cm^2) and a graphite and magnesium anode (5 cm^2). ^{1}H-NMR spectra were achieved in DMSO-d_6 with a Bruker-Avance AQS 500 MHz spectrometer. The ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Bruker-Avance spectrometer 125 MHz. Mass spectra were determined on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV.

Analytical and spectral data of the compounds are given as Supplementary material to this paper.

General procedure for the synthesis of nanoparticle of 4-aryl-5-benzoyl-2-hydroxy-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitriles

A mixture of the required aromatic aldehyde (**1**, 1 mmol), malononitrile (**2**, 1 mmol), 4,4,4-trifluoro-1-phenylbutane-1,3-dione (**3**, 1 mmol) and sodium bromide (0.5 mmol, 0.035 g) (as the supporting electrolyte) in water/ethanol (1:9, 25 mL) was electrolyzed in an undivided cell supplied with a magnetic stirrer, a Mg anode, and a Fe cathode, at 50 °C and constant current density of 30 mA/cm^2 (I = 150 mA, electrode surface 5 cm^2). The progress of the reaction was monitored by thin layer chromatography (TLC, *n*-hexane/ethyl acetate = 3/2). After completion of the reaction, the mixture was cooled to room temperature and then concentrated to one fifth of its initial volume under reduced pressure. The solid product was

collected by filtration and washed with water (2×5 mL), ethanol (2×5 mL), cold diethyl ether (5 mL) to afford the pure product.

RESULTS AND DISCUSSION:

The reaction of 4-nitro benzaldehyde with malononitrile and 4,4,4-trifluoro-1-phenylbutane-1,3-dione in an undivided cell at a current density of 30 mA cm^{-2} (I = 150 mA, electrode surface 5 cm^2) at room temperature was selected as a model and the effects of the solvent were investigated, in order to optimize the reaction conditions. The results are summarized in Table I. As can be seen from this table, on using ethanol or methanol as the solvent, only a trace amount of the product **4** was formed and the major product was **5**[24] (entries 1 and 2). Also on using water/ethanol (1:9), the product **4** is formed in good yield, without observation of product **5** (entry 5).

TABLE I. Effect of the solvent on the electrocatalytic reaction of 4-nitrobenzaldehyde, malononitrile and 4,4,4-trifluoro-1-phenylbutane-1,3-dione. Time 90 min; for all reactions, aromatic aldehyde (1 mmol), malononitrile (1 mmol), 4,4,4-trifluoro-1-phenylbutane-1,3-dione (1 mmol), NaBr (0.5 mmol), 20 ml of solvent, iron cathode (5 cm^2), magnesium anode (5 cm^2) were used

Entry	Solvent	Yield[a], %	
		4	**5**
1	EtOH	Trace	80
2	MeOH	Trace	70
3	H_2O	30	25
4	CH_3CN	40	–
5	EtOH/H_2O[b]	85	–
6	MeOH/H_2O[b]	65	–
7	CH_3CN/H_2O[b]	45	–

[a]Isolated yield; [b]volume ratio of 1:9

Furthermore, the model reaction was examined under other factors, such as current, anode type, and temperature, and results are given in Table II.

It can be seen from Table II that the best conditions for minimizing the synthesis time and maximizing the yield of the nanosized particles of 1,4-dihydropyridine production is ethanol/water at a current density of 30 mA cm^{-2} (I = 150 mA, electrode surface 5 cm^2) at 50 °C. Afterwards, the synthesized products were evaluated by scanning electron microscopy (SEM), Fig. 1. Fortunately, it was found that the 1,4-dihydropyridine derivatives were of nanoscale size. The presence of Mg^{2+}in the solution may prevent the aggregation of the products and promote the formation of nanoparticles.[9,27]

To study the scope and generality of the reaction, a series of aromatic aldehydes were employed. The results are given in Table III. In all cases, the aromatic ring of the aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the res-

pective products in good yields. It could also be concluded that the aromatic ring of the aromatic aldehydes bearing electron-withdrawing groups required shorter times and gave higher yields (Table III).

TABLE II. The effect of the current used in the reaction of 4-nitrobenzaldehyde, malononitrile and 4,4,4-trifluoro-1-phenylbutane-1,3-dione in water/ethanol on the formation of 1,4-dihydropyridine (**4a**) nanoparticles; for all reactions, aromatic aldehyde (1 mmol), malononitrile (1 mmol), 4,4,4-trifluoro-1-phenylbutane-1,3-dione (1 mmol), NaBr (0.5 mmol), 20 ml water/ /ethanol (1:9), iron cathode (5 cm^2)

Entry	Temperature, °C	Current, mA	Time, min	Electricity passed, F mol^{-1}	Yield[c], %
1[a]	r.t	30	140	2.6	40
2[a]	35	30	120	2.2	50
3[a]	50	30	100	1.8	55
4[a]	r.t	50	120	3.7	50
5[a]	35	50	120	3.7	55
6[a]	50	50	100	3.1	60
7[a]	r.t	100	120	7.5	55
8[a]	35	100	120	7.5	60
9[a]	50	100	100	6.2	70
10[a]	35	150	100	9.3	70
11[a]	50	150	90	8.3	85
12[a]	60	150	100	9.3	85
13[a]	50	200	100	12.4	80
14[a]	60	200	100	12.4	80
15[b]	50	150	90	8.3	78
16[b]	60	200	100	12.4	75

[a]Magnesium anode; [b]graphite (5 cm^2) anode. [c]isolated yield

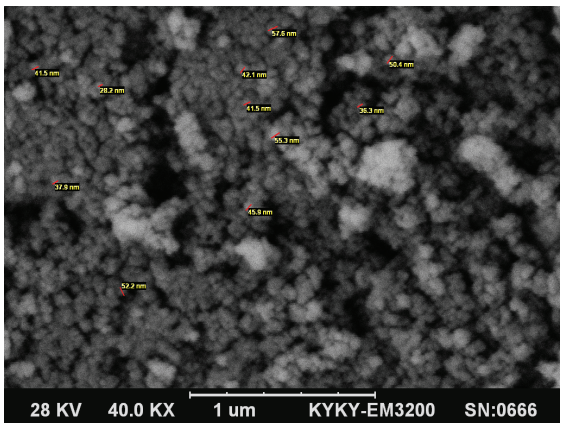


Fig. 1. SEM image of nanoparticles 1,4-dihydropyridine derivatives.

Compounds **4a**–**h** are new and their structures were deduced by elemental and spectral analysis.

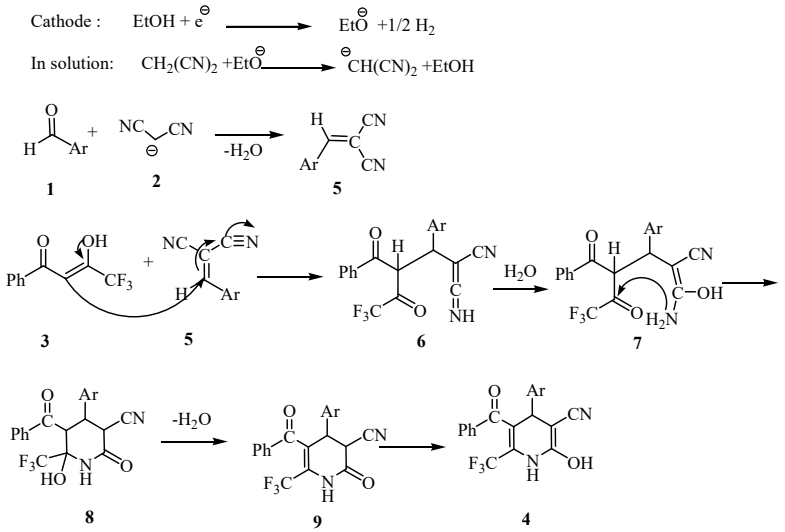
TABLE III. Results obtained from synthesis of nanoparticles of 4-aryl-5-benzoyl-2-hydroxy--6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitriles (**4a**–**h**); 0.5 mmol of NaBr, iron cathode (5 cm^2), water/ethanol (1:9) used as solvent, magnesium (5 cm^2) used as anode, and 100 mA current at r.t.

Entry	Ar	Time, min	Yield[a], %	M.p. / °C
4a	4-NO_2-C_6H_4	90	85	173–175
4b	3-NO_2-C_6H_4	100	70	174–176
4c	4-OH-C_6H_5	95	65	175–177
4d	4Cl-C_6H_4	110	70	182–184
4e	2,4-Dimethoxy-C_6H_3	120	72	172–174
4f	3,5-Dimethoxy-C_6H_3	115	65	165–167
4g	4-Br-C_6H_4	90	70	174–176
4h	2-CH_3-C_6H_4	100	65	171–173

[a]Isolated yield for all reactions

For example, the ^{1}H-NMR spectrum of compound **4a** exhibited a singlet signal at 4.49 ppm for CH protons. The aromatic protons and NH proton were observed at δ 7.32–7.92 ppm. In addition, the proton of the hydroxy group resonated at 9.65 ppm as a broad singlet. When the ^{1}H-NMR spectrum was recorded after addition of some D_2O to the DMSO-d_6 solution of **4a,** the signals related to NH and OH disappeared due to rapid exchange with D_2O. The ^{13}C-NMR spectrum of compound **4a** showed 16 signals, which is consistent with the proposed structure.

A possible mechanism for the formation of the products **4a–h** is proposed in Scheme 3.



Scheme 3. The mechanism proposed for the formation of 4-aryl-5-benzoyl-2-hydroxy-6-(trifluoromethyl)-1,4-dihydropyridine-3-carbonitriles.

In the first step of the catalytic condensation cycle, deprotonation of an alcohol at the cathode leads to the formation of the corresponding alkoxide anion. Its subsequent reaction in solution with malononitrile gives rise to the malononitrile anion. Then Knoevenagel condensation of aromatic aldehydes **1** with the malononitrile anion **2** occurs in the solution with the elimination of water and the formation of the corresponding arylidenemalononitrile **5**. Then the nucleophilic addition of the enolizable 4,4,4-trifluoro-1-phenylbutane-1,3-dione **3** to arylidene malononitrile **5** leads to intermediate **6** and then intermediate **6** could be hydrolyzed by water to form **7** and then through intramolecular condensation yield the cyclic product **8**. This intermediate loses a molecule of water and tautomerization to product **4** under the reaction condition.

CONCLUSIONS

In conclusion, an efficient, convenient electrochemical way to the synthesis of novel nanosized 1,4-dihydropyridine derivatives has been presented. From the green chemistry point of view, the application of electro-synthetic method has some significant advantages, *i.e.*, clean synthesis, one-step reaction, using electricity as an alternative source of energy instead of an oxidative reagent, technical feasibility, and high atom economy are prominent advantageous of this green approach.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

ЕЛЕКТРОХЕМИЈСКА СИНТЕЗА НАНОЧЕСТИЦА 4-АРИЛ-5-БЕНЗОИЛ-2-ХИДРОКСИ-6-(ТРИФЛУОРОМЕТИЛ)-1,4-ДИХИДРОПИРИДИН-3-КАРБОНИТРИЛА ПОТПОМОГНУТА БАЗОМ И ИЗВЕДЕНА ТРОКОМПОНЕНТНОМ КОНДЕНЗАЦИЈОМ АРОМАТИЧНОГ АЛДЕХИДА, МАЛОНОНИТРИЛА И 4,4,4-ТРИФЛУОРО-1-ФЕНИЛ-БУТАН-1,3-ДИОНА

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Описан је електрохемијски поступак синтезе нових наночестица 4-арил-5-бензоил-2-хидрокси-6-(трифлуорометил)-1,4-дихидропиридин-3-карбонитрила трокомпонентном реакцијом ароматичног алдехида, малононитрила и 4,4,4-трифлуоро-1-фенил-бутан-1,3-диона у смеши етанола и воде у једноделној електрохемијској ћелији у натријум-бромиду као електролиту. Ова метода има неколико предности као што су висок принос (65–85 %), висок степен конверзије атома, односно мала количина споредних производа, еколошка прихватљивост и то што нема потребе за хроматографском сепарацијом.

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