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Pulsed Fe Electro-Oxidation for Catalytic Synthesis of Hydantoin Derivatives

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This paper presents an original and practical organic electrochemical/chemical (EC/C) synthesis to prepare hydantoin derivatives from N-Alkyl-piperidin-4-ones. The electrochemical assisted process is an alternative to the traditional Bucherer-Bergs method. The main contribution is the *in-situ* production of Fe (III), by pulsed electro-oxidation of an iron wire, in a methanol-water (1:1) mixture at 58°C. The oxidized iron, on the wire surface, served as catalyst in the traditional synthetic path of hydantoin derivatives, and the KCN and $(NH_4)_2CO_3$ aided as supporting electrolyte for the electrolytic process. EC/C prepared hydantoins were characterized by IR, NMR (^{1}H, ^{13}C), and MS. The pulsed potential applied to the iron wire was $0.9V/Ag/AgCl/Cl^-_{sat\ KCl(MeOH)}$ during 300s, alternated with $-0.1V/Ag/AgCl/Cl^-_{sat\ KCl(MeOH)}$ during 60s. The electrode potential program attempted to avoid electrode surface passivation. After identifying the produced hydantoins by a thin-layer chromatography, electric charge corresponding to the current integration during the pulses of 300 s (10 cycles) gave a total oxidation charge density of $5.57C/cm^2$ for hydantoin 8-(3-nitrobenzyl(-1,3,8-triazaespyrodecane-2,4-dione) and $2.68C/cm^2$ for 8-(4-nitrobenzyl(-1,3,8-triazaespyrodecane-2,4-dione),. The EC/C synthesis was compared with the traditional Bucherer-Berg method, resulting in an increase of 12-fold more hydantoins in 60 min.

Keywords: hydantoins, N-piperidone, Fe electro-oxidation in metanol-water, organic electrochemical/chemical synthesis**.**

1. INTRODUCTION

The application of electrochemical techniques in organic synthesis has become a tool, turning out to be innovative and attractive to traditional methods. The organic synthetic path involving charge transfer from a heterogeneous electrode has been reported, in particular those steps depending on adsorbed in an electrode surface [1,2,3]. Furthermore, if the synthetic path only need an applied electric current, which might even originate from renewable resources, no reagent waste should be considered [4,5]. The organic synthesis path assisted by an electrochemical method has been applied in several cases as the reductive dimerization of acrylonitrile, hydrogenation of heterocycles, pinacolization, reduction of nitro aromatics, the Kolbe reaction, synthesis of benzimidazoles derivatives, and oxidation of aromatic hydrocarbons, among others [2 ,6, 7].

Further studies show that organic electrosynthesis is characterized by those pathways using the *in-situ* electrochemical preparation of metallic catalyst by a controlled anodic dissolution. In this context, the *in-situ* formation of Fenton reagent with Fe and Cu [8, 9, 10], are used as a powerful oxidation agent. However, those applications do not deal with a controlled generation of a catalyst by electro-oxidation. This means that electrode oxidation may be used to produce a surface catalyst but it may risk to destroy the electrode or lose its activity. To prevent electrode passivation or destruction, this paper proposes to use pulsed potential signals to renew the catalyst to its initial state.

On the other hand, the electrochemical assisted organic synthesis is currently recognized as one of the innovative methodologies that can be counted among eco-friendly procedures, since it can be used to replace toxic, or hazardous oxidizing or reducing reagents. As well, the electrochemical methods may be used for the *in situ* production of unstable and dangerous reagents. All the above mentioned are some of the most outstanding qualities that make electrochemical methods a useful tool to assist organic synthetic paths, protecting the environment [2,11].

Concerning 2,4-Imidazolidinediones, best-known as hydantoins, are privileged scaffolds that have a wide range in their biological activities [11,12], which are used as anticonvulsant drugs [13], anti-ulcer [14], diabetes treatment [15], anti-tuberculosis [16], antiproliferatice activity [17], anti-tumor [18], antiviral [19], antimicrobial [20], antiandrogenic [21], anti-arrhythmic [22], antifungal activities [23], anti-HIV agents [24], likewise can be used for agrochemical applications [25]. Several alkaloid compounds from marine organisms or bacteria contain also a hydantoin core [26].

Several methods for obtaining hydantoins cores have recently been reported [27]. The most common method is Bucherer-Bergs reaction [28, 29] involving *N*-Alkyl-piperidones with ammonium carbonate and potassium cyanide to generate the desired products. Another methodology starts with a methylene aziridine as an alternative of the carbonyl compound [30]. Other procedures for hydantoin production include the treatment of amino amides with triphosgene [31], the reaction of amino acids with acetic anhydride and ammonium thiocyanate [32]. Hydantoins can also be prepared from amino esters [33, 34]. On the other hand, the major challenge of current research dealing with organic synthesis of biologic key molecules, are the steps controlled by catalytic phenomena [35]. For example, the electron transfer to oxidize C-H bonds, as needed during the Bucherer- Bergs hydantoins synthesis. For this purpose, metallic catalysts have proved its efficiency, such the case of the Nickel-catalyzed ($Ni(cod)_2/SIPr$) for the synthesis of 1,3,5-tribustityted hydantoins from acrylates and isocyanates [36], other processes such intermolecular α-amination of esters employed CuCl as catalyst and *di-tert*-butyldiaziridinone as nitrogen source for synthesis of hydantoins under mild contidions [37]. A different metal used is Palladium (II) ($Pd(TFA)_2$), for the C-arylation of *N-N*disubstituted hydantoins by aryl iodides to obtain 5,5-disubstituted hydantoins [38]. Organic type catalysts also have been reported, as the bis (amide catalyst, $[Ae\{N(SiMe_3)_2\}_2 (THF)]$ (Ae=Mg, Ca, Sr) for preparation of imidazolidine-2-ones and thiazolidine derivatives [39]. More recently the catalytic effect of Fe(III) in the synthesis of hydantoin by Bucherer Berg method was tested by Safari et al. who proposed to add iron reactive species into the reaction flask. During the synthesis process Fe nanoparticles (Fe_3O_4) (1 mol%) were used as catalyst species. The results disclose that the use of nanoparticles of iron substantially reduces the reaction times [40].

Bringing together all the above mentioned, three contributions are presented. Fisrt of all, a new EC/C method to synthetize hydantoins serving as synthetic proteins precursors; in a second instance to control Fe (III) species generation on the electrode surface serving as a solid state catalyst; and finally. to eliminate the most time consuming process at the end of an organic synthesis, i.,e. recovery of the final product with good yield and high purity. The conjunction of these three issues create an innovative EC/C organic synthesis beginning with a pulsed *in-situ* Fe electrochemical oxidation, in a methanol-water solution of N-alkyl-piperidone with ammonium carbonate and potassium cyanide. The electrochemical assisted process should have gotten high yields in less time. To validate this proposal, the same hydantoins were synthesized using the traditional method Bucherer-Berg method.

2. EXPERIMENTAL

2.1. General Procedures

The EC/C synthetized hydantoins were detected by thin-layer chromatography (TLC) performed on silica gel F_{254} plates (Merck) using UV light. Melting points were obtained on an Electrothermal 88629 apparatus. Infrared spectra (IR) were recorded on a Perkin Elmer FT-IR 1600 spectrophotometer. ^{1}H and ^{13}C Nuclear Magnetic Resonance spectra at 200 MHz and 50 MHz, respectively, were done in a Varian Mercury 200 MHz Spectrometer using $CDCl_3$ and/or DMSO-d_6 with TMS as internal standard. Mass spectra were obtained from an Agilent Technologies 5975C MS Spectrometer at 70 eV by direct insertion. The morphology and the surface elemental composition were determined by scanning electronic microscopy (SEM) in a Tescan, VEGA3. The energy dispersive spectroscopy (EDS) was determined in a Bruker QUANTAX 200. The electrochemical analyses were performed using a postentiostat-galvanostat Autolab PGSTAT 320N and the Nova 8.1 software. All reagents were purchased at the Aldrich Company and used without purification.

2.2. General Method to prepare hydantoin derivatives.

The reaction mixture was composed by a solution of methanol-water (1:1) (10mL), ketones [1-(3-nitrobenzyl)piperidin-4-one (1a) and 1-(4-nitrobenzyl)piperidin-4-one (2a)] (0.1 g, 0.43 mmol), KCN (0.06 g, 0.89 mmol), and $(NH_4)_2CO_3$ (0.16g, 1.71 mmol). It was stirred and heated at 56 °C for 12 hours. After the reaction time, ethyl ether (20mL) was added to precipitate the product, which was washed with water (3x30mL) and ethyl ether (3x30mL). A solid white powder was obtained 2a,b without further purification [41].

2.2.1. Physical characteristics of synthesized hydantoins

*8-(3-nitrobenzyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (***2a***).* White solid (0.755 g, 6.79

mmol, 72 % yield). M.p. 207-209 °C. IR (ATR): 3223, 2918, 1730, 1710 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 10.63 (s, 1H), 8.43 (s, 1H), 8.15-8.08 (m, 2H), 7.80-7.58 (m, 2H), 3.63 (s, 2H), 2.76-2.67 (m, 2H), 2.41-2.29 (m, 2H), 1.92-1.77 (m, 2H), 1.53 (d, *J* =13.0 Hz, 2H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 178.2, 156.4, 147.9, 141.2, 135.3, 129.8, 122.2, 122.0, 60.7, 60.1, 48.1, 33.2. EIMS *m*/z; $C_{14}H_{16}N_4O_4$, [M] 304.

*8-(4-nitrobenzyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (***2b***).* White solid (1.21 g, 4.83 mmol, 70 % yield). M.p. 232-234 °C. IR (ATR): 3220, 3179, 1773, 1712 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.45 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 3.63 (s, 2H), 2.73-2.77 (m, 2H), 2.39-2.28 (m, 2H), 1.94-1.79 (m, 2H), 1.53 (d, *J* = 13.2 Hz, 2H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 178.1, 156.4, 147.0, 146.6, 129.6, 123.4, 61.0, 60.1, 48.2, 33.2. EIMS *m*/z; $C_{14}H_{16}N_4O_4$, [M] 304.

2.3. Electrochemical Method for synthesis of hydantoin derivatives.

The typical three electrode electrochemical cell was composed by a high purity Fe wire as working electrode (WE), Pt coil as counterelectrode (CE) and Ag/AgCl rod immersed in saturated KCl/MetOH:H_2O (1:1) solution as reference electrode (RE). Dissolution of methanol:water (1:1) was prepared with: KCN (0.06 g, 0.89 mmol), and $(NH_4)_2CO_3$ (0.16g, 1.71 mmol) and the respective 1-(4-nitrobenzyl)piperidine-4-one) derivatives (1a, 1b) (0.100 g, 0.43 mmol). To identify the onset electro-oxidation onset potential, an anodic linear sweep voltammetry at 100 mV/s was performed to oxidize Fe^o to Fe (III) according to equation 1,

$$Fe^0 \rightarrow Fe\,(III) + 3e^- \qquad (1)$$

in a solution containing only KCN and $(NH_4)_2CO_3$ (without 1-(4-nitrobenzyl)piperidine-4-one) derivatives) starting from the open circuit potential (OCP) until 1V/Ag/AgCl/ $Cl^-_{(MetOH)}$. From this result, the Fe electro-oxidation potential (considering the ionic methanol-water media) was selected as the more suitable applied oxidation potential for the following EC/C hydantoins synthesis. Finally, an alternate electrode potential signal is proposed to prevent iron wire passivation.

Figure 1 shows the potential pulsed program, composed by 10 cycles between oxidation at 0.9V/Ag/AgCl/$Cl^-_{(MetOH)}$ and rest potential at -0.1V/Ag/AgCl/$Cl^-_{(MetOH)}$. The expected result is the electrochemical formation of Fe (III) catalyst, during 300s and its recovery during 60 s [42,43]. The potential pulsed program will be applied to the iron wire immersed in the electrolytic solution containing ketones at 56°C, under constant agitation to prevent diffusion controlled steps throughout the electrode surface. All the curves in this work were normalized to the geometric area of the Fe wire (0.0347cm^2) and the progress of the hydantoins synthesis was monitored by TLC.

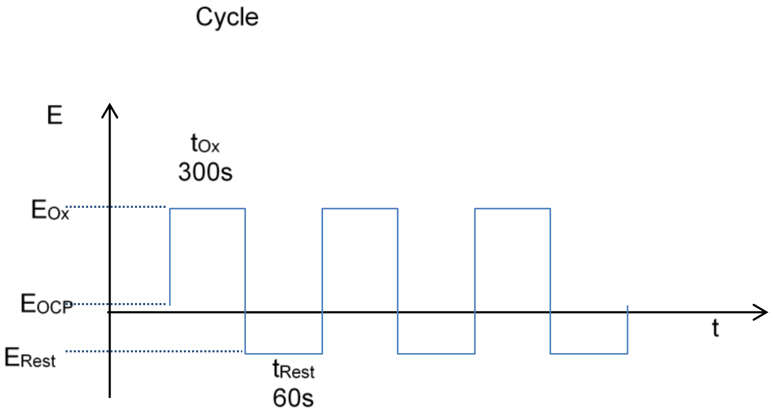


Figure 1. Potential pulsed program for the EC/C process.

3. RESULTS AND DISCUSSION

Hydantoin derivatives synthesis are reported in two sections: (1) those obtained in presence of in-situ Fe(III) controlled by pulsed electro-oxidation of an iron wire and (2) same reaction by the Bucherer-Berg reaction without Fe catalyst.

3.1 Hydantoins prepared by pulsed electrochemical/chemical method

As a first step to elucidate the suitable conditions to perform a controlled electrolysis and get solid state catalyst (Fe(III) species), an anodic linear sweep voltammetry of pure Fe wire was done in the supported electrolyte composed by two of the key reagents for the hydantoin derivatives synthesis (KCN and $(NH_4)_2CO_3$). Electrolysis overpotential of 0.9V $Ag/AgCl/Cl^{-}_{(MetOH)}$ was selected expecting a faradaic current density around 1.5mA/cm^2 [43].

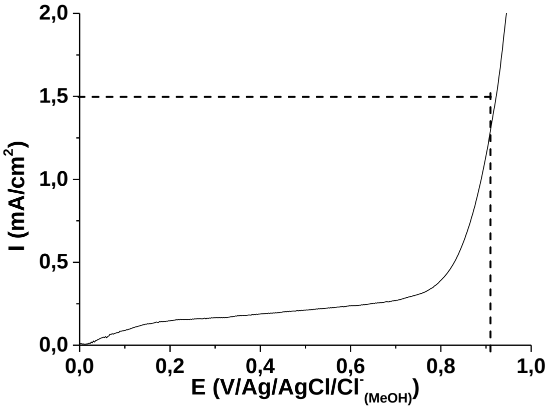


Figure 2. Anodic polarization of Fe wire in the supporting electrolyte composed by KCN and $(NH_4)_2CO_3$, v = 0.1V/s, T=58°C.

A first attempt to produce hydantoin derivatives was done by controlled potential electrolysis during 1h (not shown), the attained current density was 0.12 mA/cm^2 (12.5 times smaller than current expected by anodic polarization in Figure 2). A visible white fluff product was detected covering Fe wire, thus passivating the electrode surface. The new material was later identified as the desired product.

As an alternative to avoid Fe surface passivation, authors decided to use a pulsed potential program to maintain active surface state (Figure 1). Figure 3 presents the pulsed electrolysis results for two hydantoin derivatives. For hydantoin derivative 2a the current-time plots show a steady state pattern reached after the first 800s at a current of 1mA/cm^2 (Figure 3a); on the other hand, for hydantoin derivative 2b a peak appeared around 1600s, and then returns to the steady state at a current of 1.5mA/cm^2. These current values match with those predicted in Figure 2.

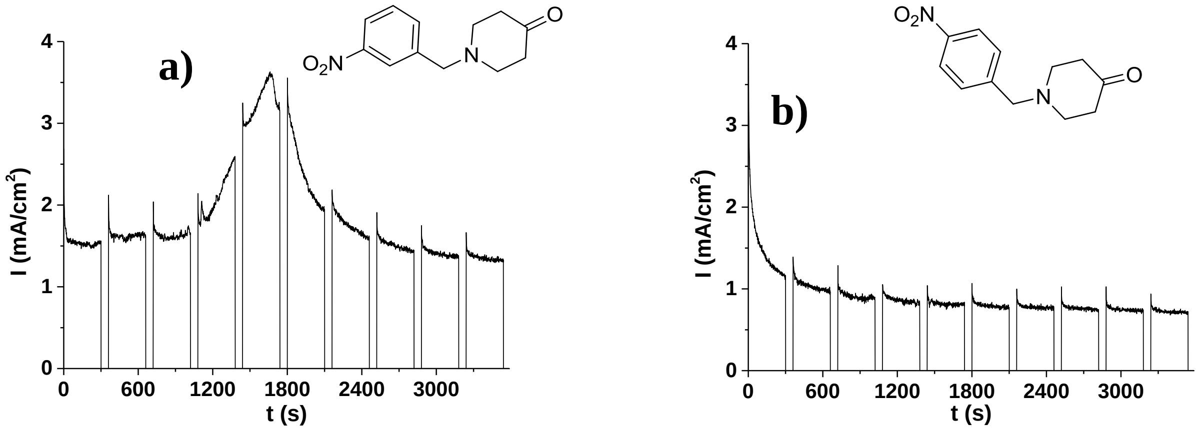


Figure 3. Pulsed electro-oxidation of Fe^0: a) hydantoin derivative **2a** and b) hydantoin derivative **2b**, 10 cycles, T = 58^{o}C.

Table 1 presents the approached faradaic charge of the Fe oxidation process as the contribution of each cycle after integrating the area behind the plotted points in Figure 3. Then Faraday´s law (equation 2) allowed to estimate produced moles of Fe (III) catalyst.

$$m = Q/n\ F \qquad (2)$$

where: m = mass <mols>

Q = charge <C>

n = number of e$^-$

F = Faraday constant <96485C/mol>

Table 1. Summary of charge and moles of Fe (III) after 10 cycles (60min) of pulsed controlled electro-oxidation.

	2b^1	**2b^2**	**2b^3**	**2a^3**
Q/A (C/cm^2)	0.47	2.704	2.68	5.57
m Fe (III)/A (mol/cm^2)	2.41x10^{-06}	9.34x10^{-06}	9.26x10^{-06}	1.92x10^{-05}

^{1}Constant potential without rest pulses
^{2}Constant potential with rest pulses of 0V, 30s
^{3}Constant potential with rest pulses of -0.1V, 60s

Histograms for the Faradaic charge after of 10 cycles of pulsed iron electro-oxidation are shown in Figure 5. This trend in faradaic charge suggests that at least 50% of cycles guaranty a constant dosage of Fe (III) catalyst throughout the exposed wire surface.

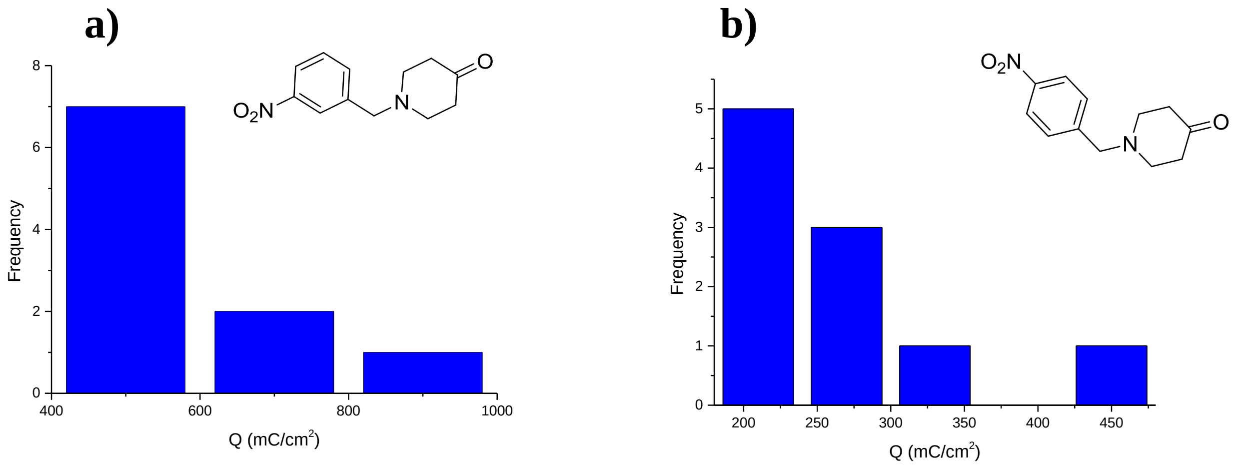


Figure 5. Histograms of charge values after 10 cycles of pulsed bulk electrolysis, a) **1a** and b) **1b**.

The morphology of Fe wire, before and after the EC/C synthesis, was evaluated by SEM and EDS elemental analysis.

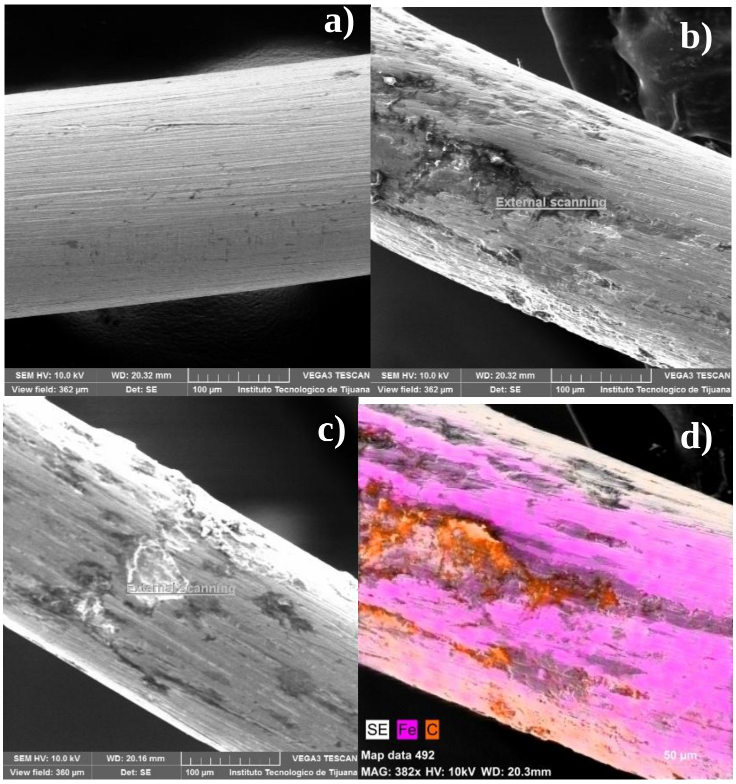


Figure 4. SEM image of Fe wire: a) before electrolysis, b) after electrolysis zone 1, c) after electrolysis zone 2, d) EDS image after electrolysis.

Figure 4 shows SEM images before and after Fe pulsed electro-oxidation: (4a) shows the clean wire before the electro-oxidation, (4b) shows the effect over the iron wire surface after pulsed electro-oxidation, (4c) shows a white powder deposit embedded on the surface, corresponding to the hydantoin derivatives, and (4d) corresponds to the image of mapping EDS showing the distribution of the Fe and white deposits containing high carbon percentage. The electrode morphology and elemental composition is in accord with EC/C synthesis of hydantoins presented by the electrochemical results. The iron wire elemental analysis is reported in table 2, showing C content after pulsed Fe electro-oxidation to produce hydantoin derivatives. The observed corrosion of the iron wire is certainly due to irreversible formation of Fe_2O_3. Moreover, this compound contains Fe(III) confirming that it is responsible of the catalytic process for the hydantoin reaction.

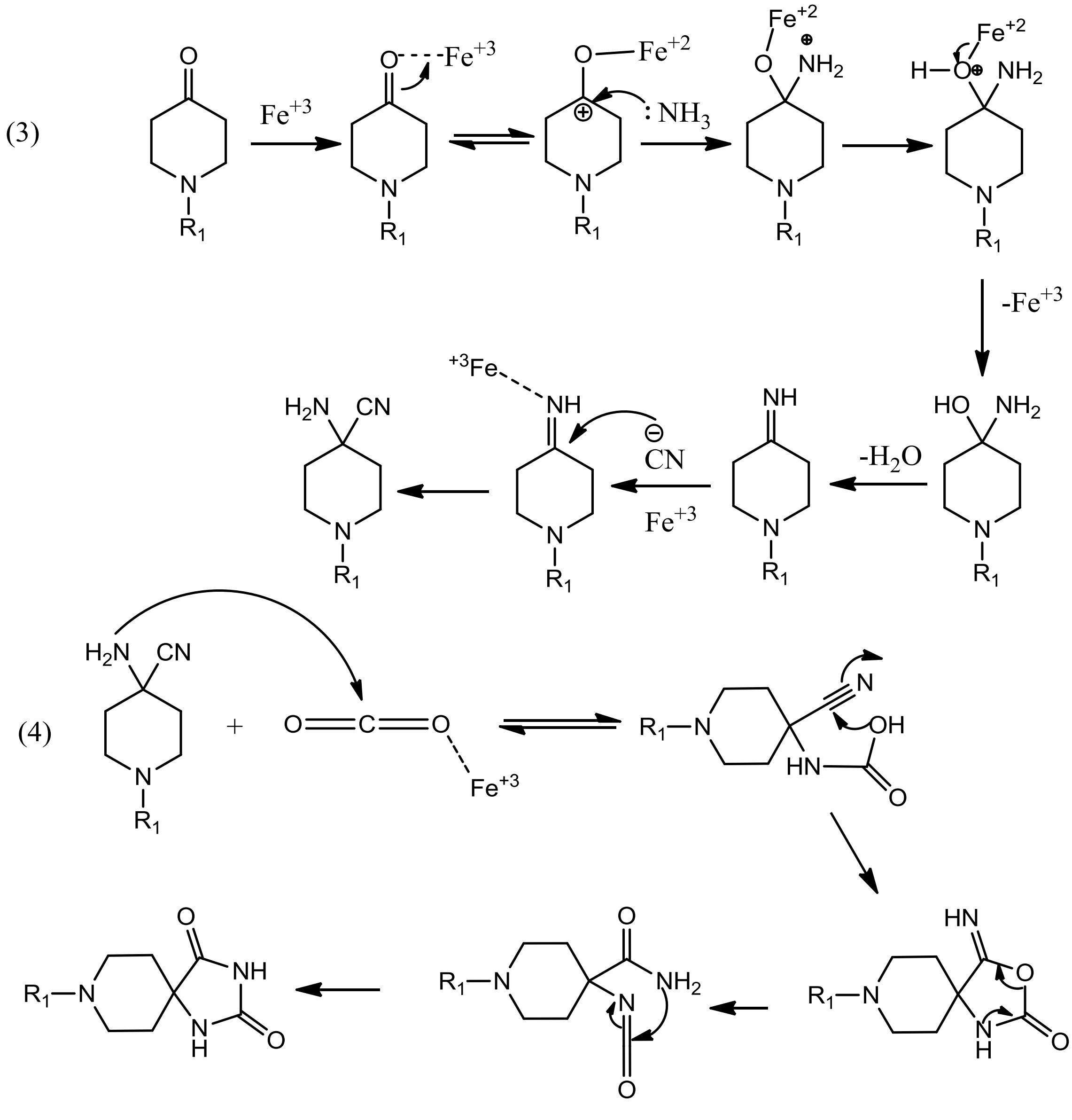
Table 2. EDS analysis of Fe wire during EC/C hydantoines synthesis.

Element	Before electrochemical oxidation (Atomic %)	After electrochemical oxidation (Atomic %)
Fe	95.84	33.94
C	4.16	42.93
O	0.0	32.13

Gathering the Fe surface characterization after the pulsed electro-oxidation and the elemental analysis after EC/C synthesis demonstrate that hydantoin derivative production is a feasible eco-friendly, since it does not require subsequent purification steps. Another important result is thee demonstration of Fe electro-oxidation in methanol media showing that electroassisted organic synthesis is challenging but possible processes. To complete the contribution of this paper, a proposal of synthetic path is described in scheme 1. The irreversible formation of Fe_2O_3 by two reactions: 1) the iron wire electro-oxidation to form Fe^{+3} and 2) the solubility product reaction in basic media to form iron oxide. The carbonyl group of *N*-alkyl-piperidin-4-one (step **3**) was activated by the interaction of Lewis acid (Fe^{+3} in very low concentrations 10^{-6} mol/cm^2). The carbonyl carbon is unprotected to increase the electrophilic character and decrease the energy of the transition state [41], thus it is more susceptible the nucleophiles attack such as ammonia, resulting in the formation of 1,1 amino alcohols (step 4), which is dehydrated to form the imine group. The above mentioned group may then be attacked by cyanide anion to form the amino-cyanide gem. The amino group attacked the CO_2 activated by the ion Fe^{+3} which was produced from ammonium carbonate to form the carbamic acid. This acid attacks the cyanide group to finally form the ring iminooxazolidinone. This ring is not stable and will open forming amide and isocyanate groups, which react *in situ* to form hydantoin as a more stable cyclical system. Finally, Fe^{+3} is reduced to Fe^{+2}, this process is reversible and depends on the formation of the amino alcohol.

(1) $Fe^0 \longrightarrow Fe^{+3} + 3e^-$ (Iron electrooxidation)

(2) $2Fe^{+3} + 6OH^- - + 2Fe(OH)_3 \longrightarrow Fe_2O_3 + 3H_2O$ (Coupled solid state formation on the anode surface)

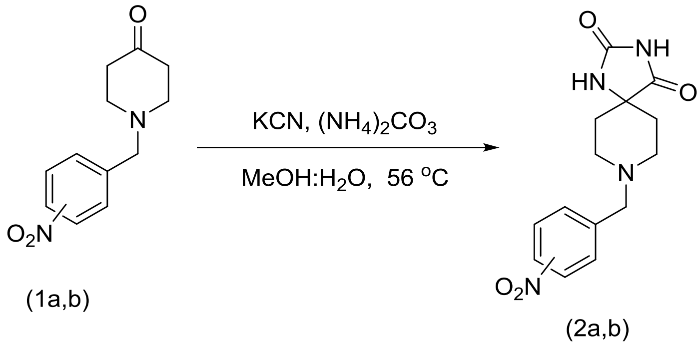


Scheme 2. Mechanism for EC/C hydantoin synthesis.

3.2 Chemical synthesis

The synthesis of two hydantoin derivatives was carried out with two different *N*- piperidin-4-ones as a starting material, using the Bucherer-Berg reaction shown in Scheme 2.

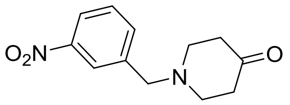
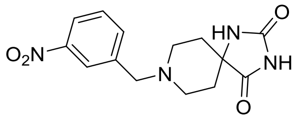
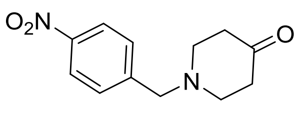
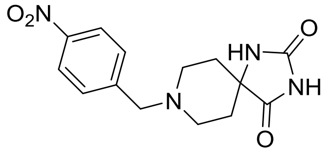
In the set of experiments, the reactions were synthetized by Bucherer-Berg reaction using *N*-piperidin-4-ones 1a and 1b respectively (Table 3). The reaction was prepared by reported method [40], under normal conditions of temperature and pressure during 8-12 h to get compounds 2a and 2b (Table 3).



Scheme 1. Synthesis of hydantoins using Bucherer-Berg reaction.

Table 3 presents a comparison between the two synthesis methods: chemical and EC/C. A considerable increase in the hydantoin yield is reached with the EC/C method, for both *N*-piperidin-4-ones, **1a** and **1b**, been 12 and 10-fold more conversion %, respectively, in 60 min, than the chemical method, Bucherer-Berg method.

Table 3. Comparison between the chemical and EC/C synthesis methods to produce hydantoins.

N-piperidin-4-one	Product (hydantoin)	Yield in 60 min	
		General Method (%)	*Electrochemical Method (%)*
 **1a**	 **2a**	8	96
 **1b**	 **2b**	10	92

4. CONCLUSION

A simple and free solid residue method for the synthesis of two hydantoin derivatives was performed. The reaction paths were through an acid catalysis induced by the presence of Fe (III) species on a pure Fe wire surface. The synthesis of 8-(3-nitrobenzyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (**2a**) and 8-(4-nitrobenzyl)-1,3,8-triazaspiro[4.5]-decane-2,4-dione (**2b**) via the pulsed electrochemical oxidation of the Fe wire was very efficient, safe and inexpensive, since the amounts of catalyst produce were in the micromols range (~50μmol/cm^2 for **2b**, and ~60μmol/cm^2 for **2a** at the end of the electrolysis) under soft reaction conditions. The synthesis method of Bucherer-Berg containing key reagents such as ammonium carbonate and potassium cyanide that resulted in good electrolytes in MeOH playing an important role during controlled Fe electro-oxidation rate and the onset potential of bulk Fe dissolution. The application of a reduction pulse improved the production of Fe (III) catalyst, going, in **2a**, from 2.9 μmol/cm^2 to 5.1μmol/cm^2, in less time (from 7000s to 5000s). SEM microscopy and EDS analysis strongly suggested that the final iron species was Fe_2O_3 on the Fe wire after its electro-oxidation. The proposed pulsed method avoids excessive amounts of Fe (III) and do not require its subsequent removal, thus it demonstrate to be an innovative eco-friendly procedure. Excellent results are obtained by the electrochemical production of Fe (III) catalyst in MeOH compared with the standard method since in 1 h, the reaction proceed at 96 and 92%, for **2a** and **2b** with a faster and more efficient process. Further investigation on the catalytic effects of Fe(III) on an anode are in course as a new proposal in challenging organic synthesis.

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Conflict of Interest

“The authors declare no conflict of interest”.

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