Electrochimica Acta 248 (2017) 376–387

Contents lists available at ScienceDirect

Electrochimica Acta

journal homepage: www.elsevier.com/locate/electacta

A comprehensive study on electrochemical oxidation of 2-acetamidophenol (*ortho*-acetaminophen). A green galvanostatic method for the synthesis of di-arylsulfonyl-2-acetamidophenol derivatives

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ARTICLE INFO

Article history:
Received 29 March 2017
Received in revised form 17 July 2017
Accepted 19 July 2017
Available online 27 July 2017

Keywords:
2-Acetamidophenol
Electrochemical oxidation
Bis(arylsulfonyl)acetamidophenol
Green synthesis
Cyclic voltammetry

ABSTRACT

Electrochemical oxidation of 2-acetamidophenol (*ortho*-acetaminophen) in water/ethanol (50/50, v/v) mixture, with different pH values was studied by potential sweep methods (CV and LSV), potential step methods (chronoamperometry and chronocoulometry) and controlled-potential coulometry. The cyclic voltammograms of 2-acetamidophenol show a well-defined anodic peak with different potentials, over the studied pH range (1-13). The Pourbaix diagram for 2-acetamidophenol comprises three linear segments which indicates the occurrence of different anodic reactions. In addition, the results indicate that electrochemically generated *ortho*-benzoquinoneimine can be successfully employed as a Michael acceptor in addition reactions with arylsulfinic acids to produce the corresponding bis(arylsulfonyl) acetamidophenols. In this work, some new bis(arylsulfonyl)acetamidophenol derivatives in water/ethanol (50/50, v/v) mixture, with high yields, under green conditions using an environmentally friendly galvanostatic method, are provided.

1. Introduction

It is found that the isomers of acetaminophen due to their properties as analgesics and antipyretics drugs (similar to acetaminophen) [1] and their side effects on the rates of metabolism and liver (different to acetaminophen) [2] are interest. One of these isomers is, 2-acetamidophenol which also known as 2′-hydroxyacetanilide, *N*-(2-hydroxyphenyl)acetamide), *N*-acetyl-*o*-aminophenol, *ortho*-acetaminophen and orthocetamol. A literature survey shows that 2-acetamidophenol can be considered potentially useful for medicinal application [3–9]. It is found that it has more potent anti-platelet and antiarthritic activities than aspirin and it may be a drug candidate for the incidence of rheumatoid arthritis and cardiovascular diseases [7]. In addition, it has been demonstrated that 2-acetamidophenol suppresses inflammation and inhibits the progression of arthritis in rats [5,6]. It has also been suggested that 2-acetamidophenol is effective in preventing the chronic inflammation and controlling the nociception associated with the arthritis in rats [8,9]. In addition to the mentioned cases, the antitubercular activity of 2-acetamidophenol was recently investigated and was found that, this compound has a potent inhibitory effect against mycobacterium tuberculosis H37Rv [10]. In describing the medicinal properties of 2-acetamidophenol, it has even been claimed that, this compound has a less toxicity than compared to acetaminophen [11].

It is reported that, diphenylsulfone derivatives possess antibacterial activity [12]. For example, 4,4-diaminodiphenylsulfone which also known as dapsone, with antiinflammatory and bacteriostatic activities is the major antileprosy drug [13]. A literature survey shows that the synthesis of sulfone derivatives are often performed by four methods including: alkylation of sulfinate salts, oxidation of sulfoxides or sulfides by hydrogen peroxide or peracids, Friedel–Crafts-type sulfonylation of arenes in the presence of catalysts and addition reactions to alkenes and alkynes [14]. However, these methods have some disadvantages such as harsh reaction conditions, excess oxidizing agent, high

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http://dx.doi.org/10.1016/j.electacta.2017.07.115
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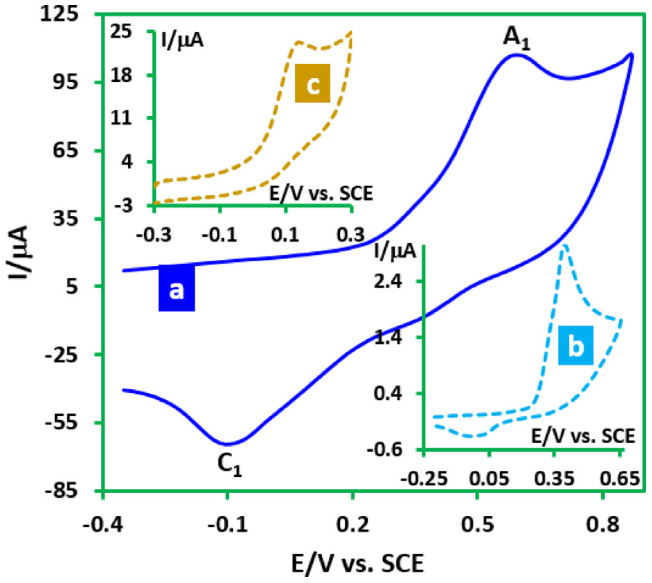


Fig. 1. Cyclic voltammograms of **2AP** (1.0 mM) (a) scan rate = 10 V s^{-1} (b) scan rate = 0.01 V/s in water (phosphate buffer, c = 0.2 M, pH 7.0)/ethanol (50:50, v/v) mixture. (c) In NaOH 1 M and scan rate = 1.0 V/s. Working electrode: GCE. Temperature = 25 ± 1 °C.

temperatures, need for stoichiometric amounts of the catalyst, generation of hazardous waste, formation of a mixture of isomers and low regioselectivity [15–20].

In light of these data, it can be expected that sulfonylation of 2-acetamidophenol may lead to the formation of new effective drugs. Therefore, the synthesis of the compounds containing both acetamidophenol and diphenylsulfone moieties, by a simple method using a green strategy is the particular object of this paper.

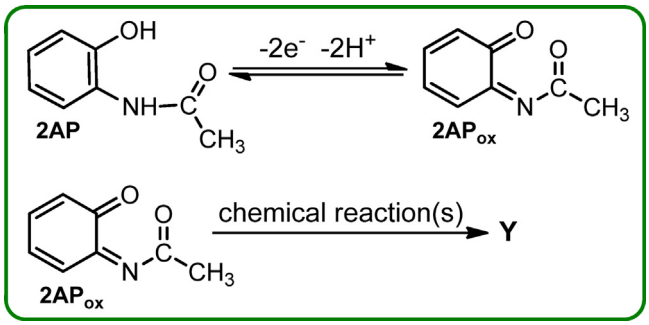
2. Experimental

2.1. Apparatus and Reagents

Cyclic voltammetry, choronoamperometry, chronocoulometry, controlled-potential cuolometry, constant current electrolysis and preparative electrolysis were performed using an Autolab model PGSTAT 20 potentiostat/galvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disc and a platinum wire was used as the counter electrode. The working electrode used in constant current electrolysis and macro-scale electrolysis was an assembly of three carbon plates (33 cm^2), while a large stainless steel gauze constitute the counter electrode. The working electrode potentials were measured vs. SCE (all electrodes from AZAR Electrodes). IR spectra (KBr) were recorded on Perkin–Elmer GX FT-IR spectrometer.^{1}H and ^{13}C NMR spectra were recorded on BRUKER Ultrashield 400 spectrometer operating at 400 and 100 MHz, respectively. Mass spectra were recorded on a HP 5973 GC-MS instrument operating at an ionization potential of 70 eV. 2-acetamidophenol (**2AP**), 4-toluenesulfinic acid (**4TS**), benzenesulfinic acid (**BS**), and 4-chlorobenzenesulfinic acid (**4CS**) were reagent grade materials from Aldrich. Phosphoric acid, and other solvents were of proanalysis grade from E. Merck. These chemicals were used without further purification.

2.2. Electroorganic synthesis of *PDS1-3*

In a typical procedure, a solution (80 mL) of water (phosphate buffer, pH = 7.0, c = 0.2 M)/ethanol mixture (50/50, v/v) containing



Scheme 1. Electrochemical oxidation of **2AP**.

0.25 mmol of 2-acetamidophenol (**2AP**) and 0.5 mmol of arylsulfinic acids sodium salt was electrolyzed in a undivided cell at 25 °C under a constant-current density of 0.3 mA cm^{-2}. The electrolysis was terminated when the decay of the current became more than 95%. Since, the reaction products are insoluble in water; separation is carried out only by filtration. The collected solids were washed on the filter with distilled water (several times). After drying, the products were characterized by FTIR, ^{1}H NMR, ^{13}C NMR and MS.

2.3. Characteristics of products

***N*-(2-hydroxy-3,6-ditosylphenyl)acetamide (PDS1),** Isolated yield: 83%. Decompose point: 147–149 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 2.11 (s, 3H, methyl), 2.36 (s, 6H, methyl), 7.31 (dd, J = 2 Hz and J = 8 Hz, 2H, aromatic), 7.40 (d, J = 8 Hz, 2H, aromatic), 7.56 (d, J = 8 Hz, 1H, aromatic), 7.69 (d, J = 8 Hz, 2H, aromatic), 7.74 (d, J = 8 Hz, 2H, aromatic), 8.15 (d, J = 8 Hz, 1H, aromatic), 9.38 (s, 1H, NH), 10.67 (s, 1H, OH).^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 20.9 (C-1), 23.9 (C-10), 112.9 (C-15), 118.5 (C-16), 121.1 (C-11), 125.4 (C-12), 126.8 (C-8), 127.0 (C-4), 130.0 (C-3), 130.8 (C-14), 130.9 (C-5), 131.4 (C-13), 135.4 (C-6), 138.7 (C-17), 143.9 (C-2), 147.2 (C-7), 169.3 (C-9). IR (KBr) ν/cm^{-1}: 3311, 3067, 2986, 1683,

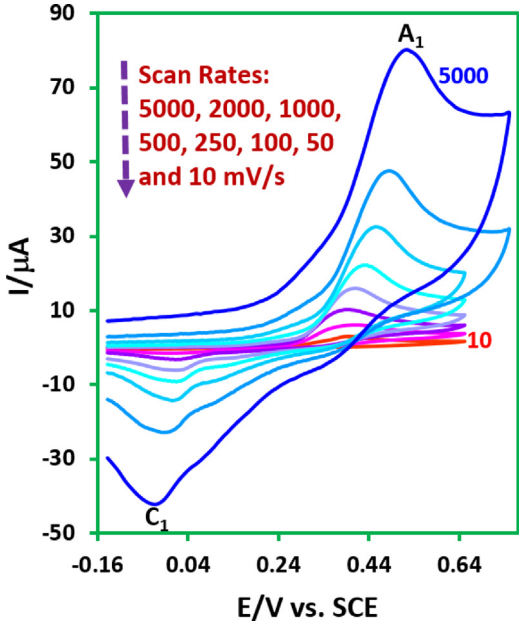


Fig. 2. Cyclic voltammograms of **2AP** (1.0 mM) in water (phosphate buffer, c = 0.2 M, pH 7.0)/ethanol (50:50, v/v) mixture, at GCE, at various scan rates. Temperature = 25 ± 1 °C.