Journal of Electroanalytical Chemistry 760 (2016) 1–5

Contents lists available at ScienceDirect

Journal of Electroanalytical Chemistry

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

An environmentally friendly electrochemical method for synthesis of pyrazole derivatives

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ARTICLE INFO

Article history:
Received 1 July 2015
Received in revised form 1 November 2015
Accepted 23 November 2015
Available online 24 November 2015

Keywords:
Electrooxidation
Catechol
3-methyl-1-phenyl-1H-pyrazol-5(4H)-one
ECEC mechanism
Michael addition
Pyrazole derivative

ABSTRACT

Electrochemical oxidation of catechol and some of 3-substituted catechols (**1a–c**) has been studied in the presence of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**3**) as the nucleophile at various pH values in aqueous solution using cyclic voltammetric and controlled-potential coulometric methods. The results revealed that the products derived from catechols (**1a–c**) participate in Michael addition reactions with 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**3**) via an ECEC mechanism, converts it to form the corresponding pyrazole derivatives (**8a–c**). The electrosynthesis of these products was carried out at the surface of carbon electrode in an undivided cell under controlled-potential conditions which is an environmentally friendly method.

1. Introduction

Pyrazoles and related heterocycles are widely used in medicinal chemistry as they possess wide range of biological and pharmacological activities such as antibacterial, antifungal, anti-inflammatory, antidiabetic, analgesic, antipyretic, immunosuppressive agents, hypoglycemic, antiviral, antineoplastic antiarthritic, uricosuric, and antiphlogistic properties [1–4]. These compounds have also found applications in transition-metal chemistry as an analytical reagent [3]. Catechol is a compound with different applications. It has been used as a reagent for photography, dyeing fur, rubber and plastic production and in the pharmaceutical industry [5].

The synthesis of pyrazole and its derivatives have engrossed substantial attention from organic and medicinal chemists for many years as they belong to a class of compounds with proven utility in medicinal chemistry. Hence, this encourages us to synthesize a novel heterocyclic compounds with a pharmacological profile using electrochemical technology which is environmentally friendly because it uses only electricity and the obtained product needs less posterior purification. It is known that cyclic voltammetry is a powerful technique for investigation of electrochemical reactions that are coupled with chemical reactions [6]. The electrochemical oxidation of *o*-dihydroxybenzenes has been described and shown that these compounds can be oxidized to *o*-benzoquinones [7,8]. The formed *o*-benzoquinones are quite reactive and can be attacked by a variety of nucleophiles that undergo various mechanisms such as EC [9,10], ECE [11,12], ECEC [13,14], ECECE [15], dimerization [16], and trimerization [17]. The mechanism depends on some parameters such as, nature of nucleophile (electron with drawing or donating), electrolysis medium (solvent, acidity or pH) and catechol type. Therefore, there are many works in the study of the reactions between *o*- and *p*-quinones produced from the oxidation of *o*- and *p*-diphenols and other nucleophiles [9,16]. The main purpose of the present work is the investigation of the mechanistic aspect and synthesis of pyrazole derivatives with pharmaceutical profile and medicinal activity from the electrochemical oxidation of catechols in the presence of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one as the nucleophile by an easy and one-pot electrochemical. The pyrazole derivatives (**8a–c**) as the final products were obtained in high yield and purity. (Scheme 1).

2. Experimental

2.1. Apparatus

Cyclic voltammetry (CV) was performed using a μAutolab III (Eco Chemie B.V.) potentiostat/galvanostat by NOVA 1.8 software. Controlled-potential coulometry and preparative electrolysis were performed using a Behpajoh model BHP-2062 potentiostat/galvanostat. The working electrode (WE) used in the voltammetry experiment was a glassy carbon disc (1.8 mm diameter) and platinum wire (2 mm diameter and 1.6 cm length) was used as the counter electrode (CE). The working electrode (WE) used in controlled-potential coulometry and

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http://dx.doi.org/10.1016/j.jelechem.2015.11.030
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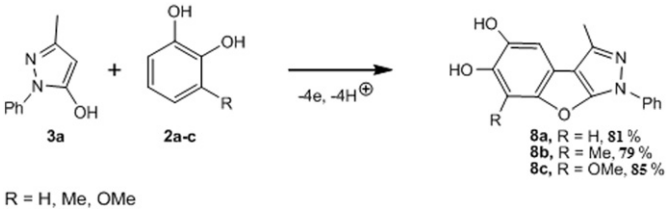

Scheme 1. Synthesis of pyrazole compounds.

macroscale electrolysis was an assembly of four ordinary carbon rods (6 mm diameter and 4 cm length from KIGCO, Mashhad, Iran), placed as single rods in the edges of a square with a distance of 3 cm and a large platinum gauze cylinder (25 cm^2 area) constituted the counter electrode. The electrochemical oxidations were performed under constant- potential conditions in a cell and equipped with a magnetic stirrer. The working electrode potentials were measured versus SCE (all electrodes from AZAR Electrode). JENWAY pH metre (model 3345) was also applied for pH measurements. All experiment was carried out at a temperature of 25 ± 1 °C. Melting points of all synthesized compounds were determined in open capillary tubes. IR spectra (KBr) were recorded on PerkinElmer GX FT-IR spectrometer. ^1H and ^{13}C, NMR spectra were recorded on a Bruker DRx-400 Avance Instruments.

2.2. Reagents

Catechol, 3-methoxycatechol, 3-methylcatechol, phenyl hydrazine and ethyl acetoacetate were reagent-grade material from Aldrich. KH_2PO_4 and other acids and bases were of analytical grade and were purchased from Merck. These chemicals were used without further purification.

2.3. Preparation of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (3)

To a magnetically stirred solution of the ethyl acetoacetate (1.91 mL, 15 mmol) and dry ethanol (4 mL), phenyl hydrazine (1.48 mL, 15 mmol) was added drop wise at room temperature. The reaction mixture was then heated in an oil bath under reflux condition for 5.5 h. After completion of reaction the reaction mixture was cooled in ice bath to precipitate. The precipitates obtained were filtered, dried and recrystallized from ethanol to give the product **3**. Yield: 85%; m.p. 128–130 °C [18].

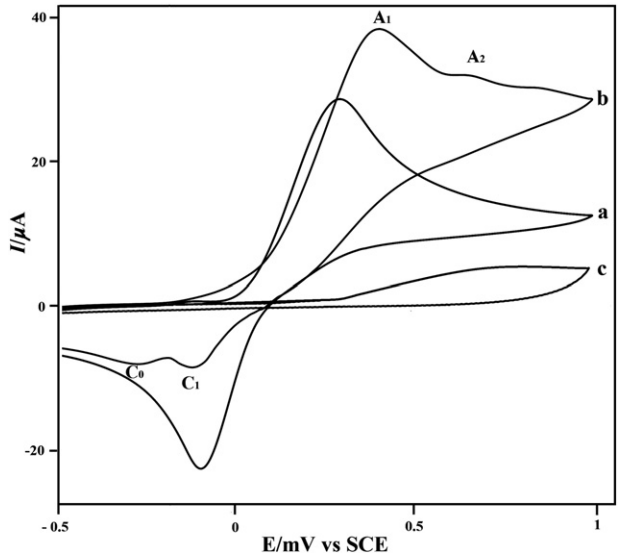

Fig. 1. Cyclic voltammograms of 1 mM catechol (1a) in the absence (a) and presence (b) of 1 mM 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (3) and 1 mM 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (3) alone (c), at glassy carbon electrode in 0.2 M phosphate buffer (pH 6.8). Scan rate = 100 mVs^{-1}. T = 25 ± 1 °C.

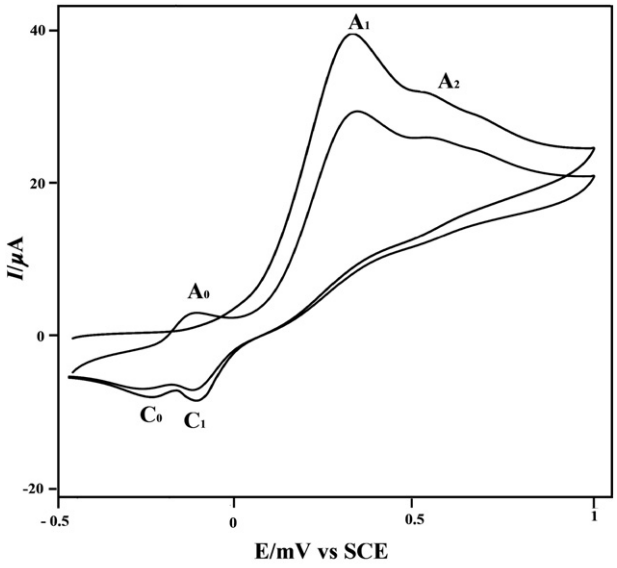

Fig. 2. Multi-cyclic voltammograms of 1 mM catechol (1a) in the presence of 1 mM 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (3), at glassy carbon electrode in 0.2 M phosphate buffer (pH 6.8). Scan rate = 100 mVs^{-1}. T = 25 ± 1 °C.

2.4. Electroorganic synthesis of 8a–c

In a typical procedure, 80 ml of a phosphate buffer solution (c = 0.2 M, pH 6.8) was pre-electrolyzed at 0.4 V versus the SCE in a two-compartment cell, and then 1 mmol of catechols (**1a–c**) and 1 mmol of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**3**) were added to the cell. The electrolysis was terminated when the current decayed to 5% of its original value. The process was interrupted during electrolysis and the graphite anode was washed with acetone to reactivate it. At

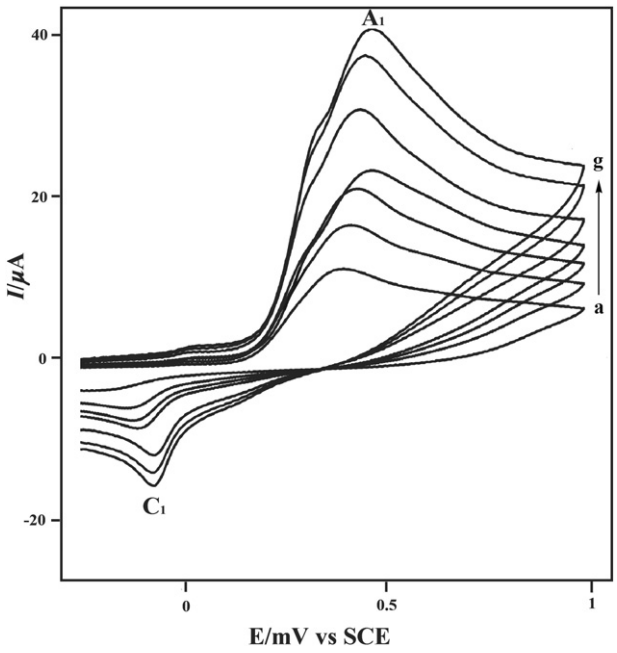

Fig. 3. Typical voltammograms of 0.2 mM catechol (1a) in the presence of 0.2 mM 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (3) in 0.2 M phosphate buffer (pH 6.8) solution at a glassy carbon electrode. Scan rates from (a) to (g) are: 50,100,200,300,500,800 and 1000 mVs^{-1}, respectively, T = 25 ± 1 °C.