Electrochimica Acta 178 (2015) 533–540

Contents lists available at ScienceDirect

Electrochimica Acta

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

Chemo and regioselective serendipitous electrochemically initiated spirocyclization of caffeic acid esters with barbituric acid derivatives

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ARTICLE INFO

Article history:
Received 20 April 2015
Received in revised form 2 August 2015
Accepted 4 August 2015
Available online 12 August 2015

Keywords:
Electrosynthesis
Spirocyclization
Caffeate esters
Cyclic Voltammetry
Barbituric acids

ABSTRACT

An interesting sequence of oxidation/Michael addition/oxidation/spirocyclization is observed in the electrolysis of caffeic acid esters in the presence of barbituric acid derivatives leading to the synthesis of a series of novel spirocycles. In an experimentally simple and clean procedure, the electrolyses proceed via a domino of electrochemical (E) and chemical (C) events with employing electrons as the only reagents in aqueous solution without introducing any catalyst or oxidant. From mechanistic point of view, a new type of domino mechanism ($ECEC_i$, C_i = spirocyclization) is proven with a unique C_i phenomenon at final step. Also, in light of experimental and theoretical NMR investigations, highly chemo and regioselectivities have been detected in these synthetic electrolyses.

1. Introduction

First “spiran” structure was described by Bayer in 1900 as a bicyclic hydrocarbon connected by a single carbon with a tetrahedral nature. Later on, the term “spirocyclanes” was used to describe the family of such hydocarbons. Spirocyclic compounds occupy a key position in modern synthetic organic chemistry and various useful synthetic methods for the synthesis of spiro cyclic compounds have been developed [1–4]. Moreover, phenolic compounds are secondary metabolites and also the largest class of phytochemicals distributed in plants. In nature, they usually participate in the defense role and exhibit antioxidant and other biological properties [5]. Phelligridin G **1** (Scheme 1) showed antioxidant activity inhibiting rat liver microsomal lipid peroxidation and moderate selective cytotoxic [6] also Compounds **2** exhibit enhanced hydrogen bonding capacity with diacetyldeoxyadenosine as compared to the reference diacetylthymidine [7].

Caffeic acid and their analogues which are widely distributed in the plant kingdom, are potential natural antioxidants with multiple mechanism involving free radical scavenging [8], metal ion chelation [9], and inhibitory actions on specific enzymes that induce free radical and lipid hydroperoxide formation [10,11]. In addition, cyclic β-diketones such as barbituric acid derivatives [12,13] have been shown to exhibit various biological activities. Blizzard and coworkers in 2002 reported a series 2-phenylspiroindenes such as **3** as estrogen receptor ligands [14]. By considering all of the unique synthetic and biomedical potentials of caffeic acid esters and pharmaceutically important barbituric acid derivatives, we anticipated that cross-combination of these moieties through biocompatible approach might lead to the formation of novel compounds possessing dual synthetic and biological potential functionalities.

Recent advances in electroorganic synthesis because of being green and simplicity of these methods [15,16]. Through these electrochemical processes, highly reactive intermediates (i.e., cation-radicals, anion-radicals, . . .) can be generated under ambient temperatures, normal pressure, and often in aqueous solvents. More importantly, in these protocols the electrons are used as the only reagents in synthetic organic reactions [17]. Considering above facts and in continuation of our research in the field of green electrochemical synthesis of organic structures [18–21], herein we report an experimentally clean and feasible procedure for the synthesis of a new series of spiro derivatives of various caffeates and barbituric acid derivatives. All reactions were done in mild conditions with good yields as well as electrochemical efficiencies.

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http://dx.doi.org/10.1016/j.electacta.2015.08.014
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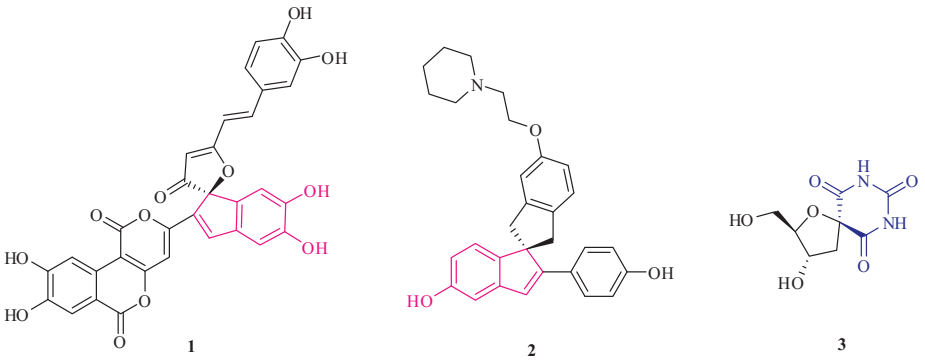


Scheme1. Structure of various spiro systems with biological activities.

2. Experimental

2.1. Apparatus and Reagents

All experiments were carried out in a conventional electrochemical cell using traditional three-electrode system. The working electrode used in voltammetry experiments was a glassy carbon disc (1.8 mm diameter) and platinum wire was used as the counter electrode. The working electrode used in controlled-potential coulometry and bulk electrolysis (using an electronic potentiostat) was an assembly of four rods, 6-mm diameter, and ~10-cm length and large platinum gauze constituted the counter electrode. The working electrode potentials were measured versus Ag/ AgCl. ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer operating at 400 MHz and 100 MHz for proton and carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm).

^{1}H NMR spectra are reported as follows: chemical shift (δ) [multiplicity (where multiplicity is defined as: br = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant(s) J (Hz), relative integral, and assignment].Mass spectra and exact masses were recorded on a 5973 Network Mass Selective Detector, Agilent Technology (HP), (EI, 70 eV) high resolution mass spectrometer. Infrared spectra were recorded neat and are reported in wave numbers (cm^{-1}). All chemicals were reagent-grade materials and solvents and reagents were of pro-analysis grade. These chemicals were used without further purification.

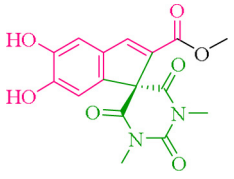
Cyclic voltammetric experiments were performed with a Voltametric Analyzer Model BHP2063 and controlled potential coulometry and preparative electrolysis were performed using a coulometry BHP2050 potentiostat/galvanostat. A conventional three electrodes system was used with a glassy carbon (GC) disc (1.8 mm diameter) as working electrode, a saturated Ag/AgCl as reference electrode, and a platinum wire as the counter electrode. The working electrode used in controlled potential coulometry and preparative electrolysis was an assembly of four carbon rods (an assembly of four rods, 6-mm diameter, and 10 cm length) and large platinum gauze constitute the counter electrode. The potential of working electrode was monitored *vs.* Ag/AgCl reference electrode (from Azar electrode, Iran).

All chemicals (caffeic acid, barbituric acid, 1,3-dimethyl barbituric acid) were reagent-grade materials., dihydrogene phosphate sodium, monohydrogene phosphate sodium acetic acid, acetate sodium, solvents and reagents were of pro-analysis. These chemicals were used without further purification. Throughout all experiments distilled water was used and all experiments were performed at room temperature.

2.2. General procedure for electrosynthesis of spirobarbiturates ***6a-6f***

In a typical procedure, 100 mL of suitable buffer solution in water/acetonitrile mixture containing 0.5 mmol of caffeic acid derivatives (**1a-c**) and 0.5 mmol of C-H acid (barbitiric acid derivatives) (Table 1), was electrolyzed in an undivided cell equipped with a carbon anode (an assembly of four rods, 6-mm diameter, and 10-cm length) and a large platinum gauze at suitable potential vs.Ag/AgCl (Table 1), at ambient condition. The electrolysis was terminated when the current decreased by more than 95%. The process was interrupted during the electrolysis and the graphite anode was washed in acetone in order to reactivate it. At the end of electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. Then pure product was obtained from aqueous solution with ethylacetate extraction followed by a recrystallization process using ethylacetate/*n*-hexane (1/2). The proper structure of the product was confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and MS.

2.2.1. Methyl 5,6-dihydroxy-1′,3′-dimethyl-2′,4′,6′-trioxo-1′,3′,4′,6′-tetrahydro-2′H-spiro[indene-1,5′-pyrimidine]-2-carboxylate ($C_{16}H_{14}N_2O_7$) (***6a***)



The product was isolated as an amorphous white solid, m.p: 265-267 °C; IR, ν (cm^{-1}): 3460, 3200, 1691, 1440, 1581; ^{1}H NMR, (DMSO-d_6, 200 MHz), δ (ppm): 3.21 (s, 6H, $2CH_3$), 3.67 (s, 3H, CH_3), 6.84 (s 1H, H_{ar}), 7.01 (s, 1H, H_{ar}), 7.86 (s, 1H, benzylic H), 9.54 (br, OH); ^{13}C NMR (DMSO-d_6, 50 MHz), δ (ppm): 29.4, 52.4, 65.7, 110.3, 112.5, 133.7, 135.5, 137.6, 142, 147.2, 147.9, 151.4, 156.7, 163.3, 166.3, 170.9; MS (EI) m/z: 346 (M^+), 232, 57, 43.

2.2.2. Ethyl 5,6-dihydroxy-1′,3′-dimethyl-2′,4′,6′-trioxo-1′,3′,4′,6′-tetrahydro-2′H-spiro[indene-1,5′-pyrimidine]-2-carboxylate ($C_{17}H_{16}N_2O_7$)(***6b***)