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PII: S1572-6657(16)30420-9
DOI: doi: 10.1016/j.jelechem.2016.08.023
Reference: JEAC 2797

To appear in: *Journal of Electroanalytical Chemistry*

Received date: 28 June 2016
Revised date: 11 August 2016
Accepted date: 17 August 2016

Please cite this article as: Fructuoso Barba, Belen Batanero, Isidoro Barba, Electrogenerated Superoxide anion: Hydroxylation of Electroreducible Substrates in Aprotic solvent, *Journal of Electroanalytical Chemistry* (2016), doi: 10.1016/j.jelechem.2016.08.023

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Electrogenerated Superoxide anion: Hydroxylation of Electroreducible Substrates in Aprotic solvent†

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Abstract

2-Hydroxy-1,4-naphthoquinone, 2-hydroxy-3-methyl-1,4-naphthoquinone, 3-hydroxy-2,3-diphenylindan-1-one, 3,4-diphenyl-1*H*-isochromen-1-one and benzoic acid are prepared in good yield by radical coupling reaction of the electrogenerated radical anion of 1,4-naphthoquinone, 2-methyl-1,4-naphthoquinone, 2,3-diphenyl-1-*H*-inden-1-one or phenylacetylene respectively, with simultaneously electrogenerated superoxide anion.

Keywords: Cathodic C-O bond formation, Lawsones, Isocoumarin, Oxidative reduction, Oxygen

1. Introduction

The anodic hydroxylation of aromatic hydrocarbons at platinum or at PbO_2 anodes in aqueous media generally leads to complex mixtures of products [1,2]. Hydroxylation of quinones substituted at the 2-position with an electron-withdrawing group may be achieved at the anode working at low potentials in aqueous solution [3]. In most cases acidic electrolytes are employed, and acetone, an alcohol or AcOH is added as a cosolvent to obtain a homogeneous medium. In nonaqueous solvents water is an impurity that on a preparative scale even rigorous drying fails to remove completely. Hydroxylation products are therefore common by-products.

Effective nuclear hydroxylation has been achieved indirectly by trifluoroacetoxylation with subsequent hydrolysis [4,5].

In the absence of an efficient protonating reagent, oxygen is cathodically reduced giving a quasi-reversible system at -0.85V, versus SCE, at commonly used cathodes (Hg, Ag, Pt, graphite or glassy carbon). The relatively long half-life of superoxide (about 40 min. at room temperature[6]) allows reactions to occur *in situ* in the catholyte solution with continuous generation of the reagent.

Superoxide anion may act either as a nucleophile or as a base. Due to this fact and to the already reported problems in anodic hydroxylation, we attempt in this work the cathodic hydroxylation of some carbonyl compounds (such as 1,4-naphthoquinones or 2,3-diphenylindenone) as well as phenylacetylene. The concommitant reduction of these electroactive substrates together with oxygen present in solution allowed the achievement of hydroxylated and other interesting products which formation is rationalized and discussed.

2. Experimental Section

2.1 General Remarks

The electrolyses were carried out using an Amel potentiostat Model 552 with electronic integrator Amel Model 721. IR spectra of the products were recorded as dispersions in KBr or NaCl films on a Perkin-Elmer spectrometer Spectrum 2000. All melting points were measured with a Reichert Thermovar microhot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ solutions with a Varian Unity 300 (300 MHz) spectrometer. Chemical shift values are given in ppm and

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δ scale relative to tetramethylsilane (TMS) as the internal standard. Mass spectra (EI, ionizing voltage 70 eV) were determined using a THERMOFISHER ITQ-900 DIP/GC-MSn mass-selective detector, and GC-MS (HP-5 cross linked 5% PhMe silicone) 30m-0,25mm-0.25μm chromatographic column. All starting materials were obtained from commercial sources and used without purification.

2.2 General Electrochemical Procedure.

The electrochemical reductions were performed under potentiostatic conditions in a concentric beaker-type cell with two compartments separated by a porous (D4) glass frit diaphragm and equipped with a magnetic stirrer. A mercury pool was used as the cathode (18 cm^2), a platinum plate (6 cm^2) as the anode, and a Ag/AgCl (sat) electrode as the reference. The solvent-supporting electrolyte system SSE was acetonitrile (ACN) containing 0.3 M $LiClO_4$.

1	**Substrate**	**E (V)**
a	1,4-Naphthoquinone	-0.85
b	2-Methyl-1,4-naphthoquinone	-0.85
c	2,3-Diphenyl-1*H*-inden-1-one	-1.2
d	Phenylacetylene	-1.0

Table 1. Applied reduction potentials *E* (V, *vs. Ag/Ag*$^+$). Simultaneous reduction of compounds **1(a-d)** and O_2 takes place in ACN/0.3 M $LiClO_4$ as SSE. Cathode: Hg, Anode: Pt.

A solution of the electroactive carbonyl compound **1**(**a-c**) or phenylacetylene (**1d**) (2.0 mmol in 60 ml of SSE) was electrolyzed under oxygen atmosphere at the constant potential value indicated in Table 1. The substrate consumption was followed by TLC. Once the reduction was finished the solvent in the cathodic solution was removed under reduced pressure. The residue was three times extracted with ether/water and the organic phase dried over Na_2SO_4 and concentrated by evaporation. In order to isolate the water-soluble products, the aqueous phase (slightly alkaline from the catholyte) was neutralized, ether extracted and dried.

The resulting solids were chromatographed, when needed, on silica gel (24 x 3cm) column, using CH_2Cl_2/EtOH or hexane/EtOAc (5/1) as eluents. The products were identified by their spectroscopic data and are given below.

2-Hydroxy-1,4-naphthoquinone (*Lawsone*, 2a):[7] Mp 188-190 °C, (Lit.[8] 192 ºC). ^{1}H RMN (300 MHz; $CDCl_3$) δ (ppm): 6.32 (s, 1H), 7.69 (td, J_1=7.5 Hz, J_2= 1.55 Hz, 1H), 7.78 (td, J_1=7.5 Hz, J_2= 1.25 Hz, 1H), 8.06 (t, J=1.55 Hz, 1H), 8.1 (t, J=1.25 Hz, 1H). ^{13}C RMN (75,4 MHz, $CDCl_3$) δ (ppm): 110.7, 126.5, 126.7,129.4, 132.8, 133.1, 135.2, 158.2, 156.4, 181.9, 182.1 MS m/z (relative intensity) EI: 174(M^+, 100), 146(61), 118(10), 105(92), 90(10), 89(18), 77(50), 51(14), 50(24).

1,2,4(3*H*)-Naphthalenetrione (2´a): IR (KBr) ν/cm^{-1} = 3087, 2923, 1694, 1594, 1324, 1294, 983, 857, 720. ^{1}H RMN (300 MHz; $CDCl_3$) δ (ppm): 4.01 (s, 2H), 7.7-7.8 (m, 2H), 7.9-8.0 (m, 2H). ^{13}C RMN (75,4 MHz, $CDCl_3$) δ (ppm): 55.3, 127.2, 131.7, 134.7, 190.7. MS m/z (relative intensity) EI: 174(M^+, 27), 173(M^+-1, 27), 146(95), 105 (10), 89(44), 77(50), 63(21), 50(28).

2-Hydroxy-3-methyl-1,4-naphthoquinone (*Phthiocol*, 2b): [9] Mp 168º C. (Lit.[10] 168-170 ºC). ^{1}H RMN (300 MHz; $CDCl_3$) δ (ppm): 2.09 (s, 3H), 7.28 (bs, 1H), 7.68-8.12 (m, 4H). MS m/z (relative intensity) EI: 188(M^+, 100), 160(31), 132(29), 131(47), 105(18), 104(13), 103(15), 77(20), 50(15).

3-Methyl-1,2,4(3*H*)-Naphthalenetrione (2´b): MS m/z (relative intensity) EI: 189(M^++1, 10), 188(M^+, 14), 160(100), 132(25), 131(42), 105(25), 103(26), 77(26), 76(17), 51(12), 50(27).

3-Hydroxy-2,3-diphenylindan-1-one (**2c**): Mp 127-129 °C, (Lit.[11,12] 126-128 ºC. IR (KBr) ν/cm^{-1} =3435, 3060, 2982, 1719, 1602, 1273, 1091, 698. ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm): 3.28 (bs, 1H, OH), 4.8 (s, 1H), 6.7-7.0 (m, 9H), 7.30-7.37 (m, 2H), 7.54 (t, J= 7.47 Hz, 1H), 7.67 (t, J= 7.47 Hz, 1H), 7.98 (d, J= 7.47 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm): 59.2, 82.7, 86.5, 124.0, 126.4, 126.9, 127.2, 127.4, 127.5, 127.8, 128.6, 129.6, 135.7, 136.2, 137.6, 140.7, 153.7, 207.3. MS m/z (relative intensity) EI: 300 (M^+, 48), 282 (M^+-18, 6), 195 (100), 177(14), 165(16), 152(5), 105(14), 77(15).

3,4-Diphenyl-1*H*-isochromen-1-one *or* 3,4-diphenyl-iso coumarin (**3c**): Mp 169-171 °C, (Lit.[13] 172-174 ºC. IR (KBr) ν/cm^{-1} = 3027, 2960, 1736, 1604, 1318, 1192, 1081, 766, 703. MS m/z (relative intensity) EI: 298 (M^+, 100), 270 (21), 239(6), 221(25), 193(6), 165(10), 105(18), 77(16).

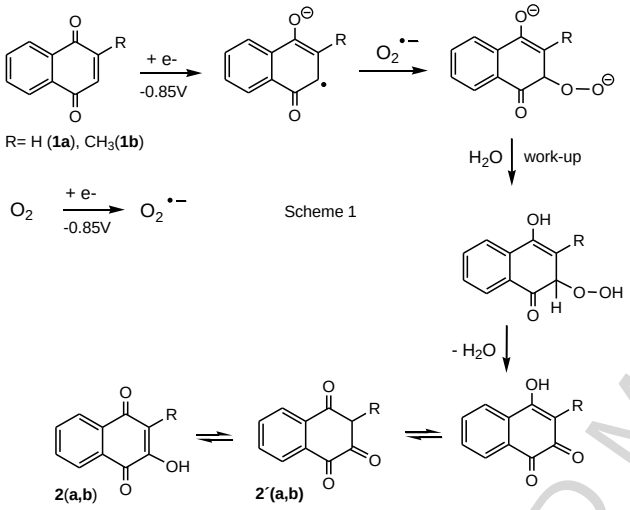
3. Results and discussion

The cathodic reduction of electroactive 1,4-naphthoquinone (**1a**) or 2-methyl-1,4-naphthoquinone (**1b**) in acetonitrile was carried out in the presence of bubbled oxygen, at a constant potential value of -0.85V. The simultaneous reduction of **1** and oxygen produces naphthoquinone radical anion and superoxide anion respectively at time. Further coupling of both intermediates affords the main reaction products. In the reduction of **1a** the corresponding 2-hydroxy-1,4-naphthoquinone (**2a**) is obtained in 70% yield together with its tricarbonyl tautomer **2´a** in 12% yield. The compound **2a** (Lawsone, CAS83-72-7) is the main dye ingredient found in the natural plant of *Henna* (*Lawsonia inermis*). It was found that 2-hydroxy-1,4-naphthoquinone is a specific inhibitor of aldehyde oxidase in vitro.[14]

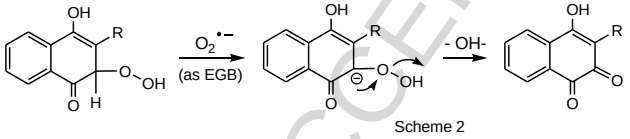
When menadione **1b** was reduced, 2-hydroxy-3-methyl-1,4-naphthoquinone (**2b**) was the main obtained

product, in 62% yield. Only traces of **2´b** were formed. Analogues of Lawsone were synthesized and tested as inhibitor against the human pathogen *Helicobacter pylori* and *Campylobacter jejuni*.[15]

The formation of these hydroxylated quinones is rationalized, as indicated in Scheme 1, through a radical coupling of superoxide anion and the quinone radical anion, followed by protonation during the work-up and final water elimination.



It can not be discarded an ionic route in the decomposition of the hydroperoxide anion (as indicated in Scheme 2) due to the nucleophile and base character of the superoxide anion.



Scheme 2

When this cathodic hydroxylation was attempted with 2,3-diphenyl-1*H*-inden-1-one (**1c**), under similar experimental conditions, the expected 3-hydroxy-2,3-diphenyl-indan-1-one (**2c**) was formed (35% yield) together with 3,4-diphenyl-1*H*-isochromen-1-one (isocoumarin) (**3c**) obtained in 44% yield. However in this case, the applied reduction potential to generate the radical anion of indenone was more negative (-1.2V vs Ag/Ag^+) than that of **1a** or **1b**, as expected from the cyclic voltammetry of this compound, showed in Figure 1.

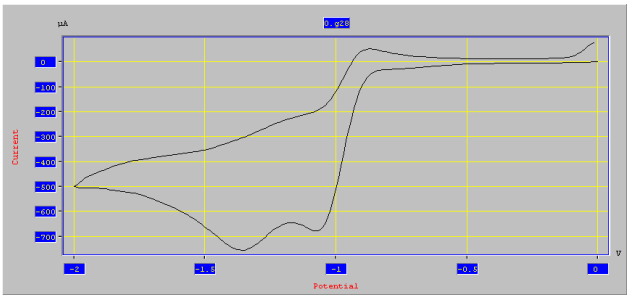
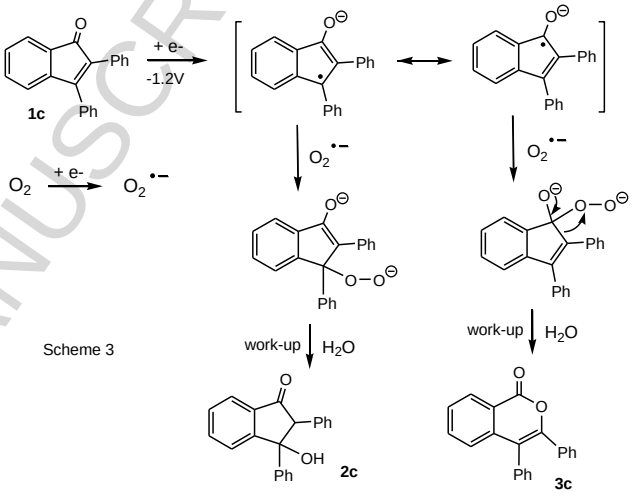


Figure 1. Cyclic voltammetry of **1c** in ACN/0.1M $LiClO_4$ as SSE. Graphite as cathode, Pt as anode. *E* (V, *vs.* Ag/Ag^+). Scan rate: 50mV/s.

The reaction takes place, once more, through a concomitant reduction of oxygen and **1c**, the first to superoxide anion that couples with the radical anion of the α,β-unsaturated carbonyl group of indenone (see Scheme 3). This coupling reaction can provide **2c** or **3c**, depending on the resonance form that is being attacked by superoxide specie.



Scheme 3

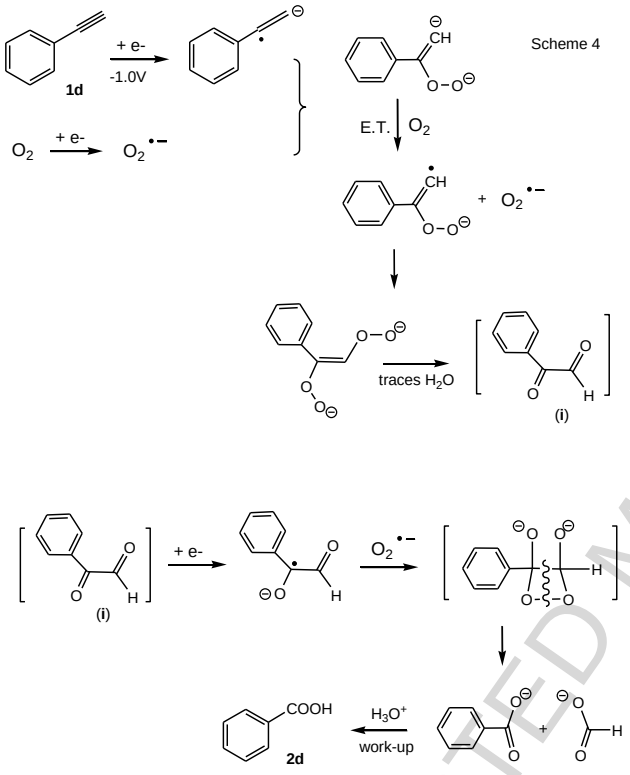
This mechanism proposal is supported by the fact that when electrolysis of **1c** was performed at -0.8 V (vs Ag/Ag^+), where only oxygen is being reduced, compounds **2c** and **3c** were not achieved. In this case the starting indenone was completely recovered.

The formation of **3c** is rationalized via a Baeyer-Villiger rearrangement. After the C-O coupling reaction, a ring expansion to the six-membered lactone (isocoumarin) is achieved. Isocoumarins are the key scaffolds of various natural products that show a wide range of exciting biological activities.[16] Recently a novel ruthenium catalyzed straighforward synthesis of isocoumarin has been accomplished by the decarbonylative addition reaction of phthalic anhydride with diphenylacetylene (tolane).[17]

Furthermore, the electrogeneration of superoxide anion was studied in the presence of phenylacetylene (**1d**), another interestig substrate. This compound, without a carbonyl group, is however electroactive at the cathode. The reported[18] reduction potential of phenylacetylene in HMPA/Bu_4NI is -0.95 V(vs SCE). The simultaneous reduction of bubbled oxygen and **1d** was performed at -1.0V (vs Ag/Ag^+). Surprisingly, the expected carbonyl derivative (acetophenone) as result of hydroxylation reaction after coupling of the radical anion with superoxide, was not obtained, instead benzoic acid was formed as the main product. The reaction mechanism is rationalized in Scheme 4.

The formation of benzoic acid (**2d**) when electrolysis is performed at -1.0V can be explained involving the a α-ketoaldehyde (**i**), easier to be reduced than

phenylacetylene, which anion radical couples with superoxide to afford a unstable dioxetane intermediate, similarly to the already reported by us in the electrochemical reduction of 1,2-quinones.[19]



The obtained result with phenylacetylene is a double hydroxylation reaction that can be used with other unsaturated, and conjugated, substrates to get stable and useful derivatives. This electrochemical hydroxylation is complementary to the aerobic carbon-carbon bond cleavage catalyzed by a transition metal polyoxometalates [20] or the iodine-mediated oxidative annulation of aryl acetylenes [21].

4. Conclusion

Contrary to the anodic hydroxylation reactions, the possibility to introduce an OH group through the concomitant cathodic reduction of electroactive organic substrates and molecular oxygen, involving the radical coupling of superoxide with the corresponding radical anion, opens a clean and good yielded route to a high variety of hydroxylated products.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

The authors gratefully acknowledge the financial support of the University of Alcala-CCG2015/EXP-031.

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Highlights:

- Use of superoxide anion in organic hydroxylations.
- Electrosynthesis of *Lawsone*, *Phthiocol*, 3-Hydroxy-2,3-diphenylindan-1-one or 3,4-diphenylisocoumarin in only one pot.
- Radical coupling mechanism pathway at the cathode.
- Concomitant cathodic reduction of oxygen and electroactive organic substrates.