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A facile electrochemical method for the synthesis of new sulfonamide derivatives of potential biological significance

Davood Nematollahi [a,*], Saied Saeed Hosseiny Davarani [b], Pari Mirahmadpour [c], Fahimeh Varmaghani [a]

[a] Faculty of Chemistry, Bu-Ali Sina University, Hamedan 65178-38683, Iran
[b] Department of Chemistry, Faculty of Science, University of Shahid Beheshti, Tehran 19835389, Iran
[c] Department of Chemistry, Faculty of Science, Arak Branch, Islamic Azad University, Arak, Iran

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ABSTRACT

The electrochemical synthesis of some new sulfonamide derivatives was carried out *via* the electrochemical oxidation of 2,3-dihydrophthalazine-1,4-dione (**1**) in the presence of arylsulfinic acids (**2a** and **2b**) as nucleophiles. The results show that, the electrogenerated phthalazine-1,4-dione (**1ox**) participates in a Michael type addition reaction with **2a** or **2b** and *via* an *EC* mechanism to produce the corresponding sulfonamide derivatives. This method provides a one-pot procedure for the synthesis of new sulfonamide derivatives of potential biological significance in good yields without using toxic reagents at a carbon electrode in an environmentally friendly manner.

1. Introduction

The therapeutic and pharmaceutical features of sulfonamides have been reported for many years. These derivatives were intensively investigated as the first effective antibacterial agents [1]. Sulfonamides are still widely used for conditions such as acne and urinary tract infections caused by bacteria resistant to other antibiotics [2]. Sulfonamides can be carbonic anhydrase inhibitors, diuretic and hypoglycemic reagents, and pharmaceutical agents for the treatment of different diseases such as infections, Alzheimer, HIV, and cancer [3–5]. Among *N*-containing heterocyclic compounds, phthalazine has attracted scientific interest. Phthalazine derivatives were found to possess multiple biological activities such as antimicrobial, anticonvulsant, antifungal, anticancer, and anti-inflammatory activities [6–8]. Phthalazine derivatives synthesis provides an entrance to a variety of compounds with pharmacological activities. Following our experiences in electrochemical synthesis of sulfonamides based on the *in situ* generation of Michael acceptors [9–11], we envisioned that organic compounds containing both phthalazine and sulfonamide moieties might possess enhanced pharmaceutical properties and medicinal activities. This idea prompted us to investigate the electrochemical oxidation of 2,3-dihydrophthalazine-1,4-dione (**1**) in the presence of *p*-toluenesulfinic acid (**2a**) and benzensulfinic acid (**2b**) as nucleophiles and we have reported an easy and one-pot electrochemical method for the synthesis of sulfonamide derivatives (**3a** and **3b**) in good yields and purity, using environmentally friendly protocols with high atom economy.

2. Experimental

Reaction equipment was described in an earlier paper [12]. 2,3-Dihydrophthalazine-1,4-dione, toluene and benzene derivatives of sulfinic acid were obtained from commercial sources. A solution of phosphate buffer (60 mL, $c = 0.2$ mol/L, pH 2.0) in a water/acetonitrile (85/15%, v/v) solution containing 2,3-dihydrophthalazine-1,4-dione (**1**) (0.25 mmol) and 4-toluenesulfinic acid (or benzensulfinic acid) (0.25 mmol) was electrolyzed in a divided cell equipped with a carbon anode (an assembly of four rods) and a large stainless steel gauze as the cathode, at 0.85 V *vs.* Ag/AgCl, at 25 °C. The electrolysis was terminated when the current decreased by more than 95%. The process was interrupted several times during the electrolysis and the carbon anode was washed in acetone in order to reactivate the anode. At the end of the electrolysis, the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and was washed several times with water. After drying, the products were characterized by IR, NMR (^{1}H and ^{13}C) and MS.

* Corresponding author.
E-mail address: nemat@basu.ac.ir (D. Nematollahi).

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2,3-Dihydro-2-tosylphthalazine-1,4-dione ($C_{15}H_{12}N_2O_4S$) (**3a**): Isolated yield: 75%. Mp. >270 °C (dec.), yellow. IR (KBr, cm^{-1}): ν 2512, 1738, 1672, 1495, 1298, 1255, 1208, 1115, 1073, 1022, 825, 784, 679, 618, 559, 380, 230. ^1H NMR (300 MHz, DMSO-d_6): δ 1.7 (s, 3H), 6.8 (d, 2H), 7.5 (d, 2H), 7.8 (d, 2H), 8.1 (d, 2H), 11.9 (NH, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.2, 120.1, 126.4, 126.5, 128.4, 128.5, 130.1, 135.6, 136.7, 153.1, 157.2. MS (*m*/*z*) (relative intensity): 317 $[M+H]^+$ (80), 252 (50), 221 (25), 163 (100), 132 (25), 104 (75), 76 (35), 50 (20).

2-(Phenylsulfonyl)-2,3-dihydrophthalazine-1,4-dione ($C_{14}H_{10}N_2O_4S$) (**3b**): Isolated yield: 70%. Mp. >270 °C (dec.), yellow. IR (KBr, cm^{-1}): ν 2906, 1659, 1493, 1335, 1308, 1241, 1208, 1083, 1030, 824, 778, 672, 619, 486, 440. ^1H NMR (300 MHz, DMSO-d_6): δ 6.9 (d, 2H), 7.9 (m, 3H), 7.8 (d, 2H), 8.3 (d, 2H) 10.7 (NH, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 120.1, 126.3, 128.2, 128.5, 128.7, 130.7, 131.1, 134, 156.1, 163.1. MS (*m*/*z*) (relative intensity): 303 $[M+H]^+$ (35), 239 (30), 221 (100), 163 (100), 132 (20), 104 (60), 76 (35), 50 (20).

3. Results and discussion

Cyclic voltammogram of a 1.0 mmol/L solution of 2,3-dihydrophthalazine-1,4-dione (**1**) in a water (0.2 mol/L phosphate buffer, pH 2.0)/acetonitrile (85/15%, v/v) is shown in Fig. 1, curve a. As can be seen, one anodic (A_1) and a cathodic peak C_1 were obtained at 1.0 and 0.78 V ($E_{1/2}$ = 0.89 V) *versus* Ag/AgCl. The anodic and cathodic peaks are counterpart and correspond to the transformation of **1** to phthalazine-1,4-dione (**1ox**) and *vice versa* within a *quasi*-reversible two-electron process. The peak current ratio (I_{pC1}/I_{pA1}) is less than unity and decreases with the reduction of the potential sweep rate indicating that the generated phthalazine-1,4-dione (**1ox**) is not stable. This instability is related to the oxidative ring cleavage of **1**, as discussed in details in our previously published paper [12]. The oxidation of **1** in the presence of *p*-toluenesulfinic acid (**2a**) as nucleophile was studied using cyclic voltammetry. Fig. 1, curve b, shows the cyclic voltammogram obtained for a 1.0 mmol/L solution of **1** in the presence of 1.0 mmol/L of **2a**. It is clear that the cathodic peak (C_1) disappeared and a new anodic peak (A_2) appeared with a more positive potential. In this Figure, the cyclic voltammogram of **2a** is shown in curve c. A close analysis of these three voltammograms (curves a–c) suggested that A_2 corresponds to **1ox**, which is bonded to **2a**. A similar observation was made in the case of **1** in the presence of **2b**.

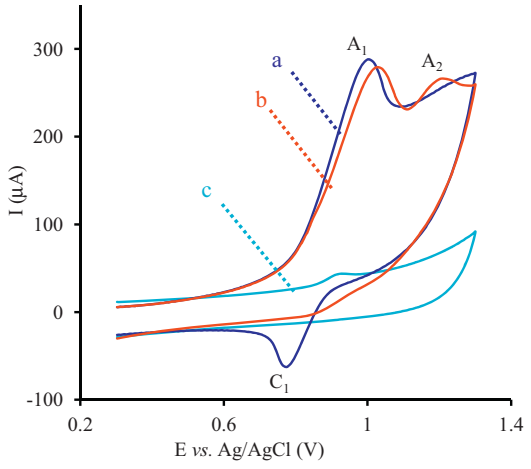


Fig. 1. A cyclic voltammogram of **1** (1.0 mmol L^{-1}) in the absence of **2a** (a), in the presence of **2a** (1.0 mmol L^{-1}) (b), **2a** (1.0 mmol L^{-1}) in the absence of **1**, in a water/acetonitrile (85/15%, v/v) solution containing phosphate buffer (c = 0.2 mol L^{-1}, pH 2.0) (c). Scan rate: 800 mV s^{-1}, temperature = (25 ± 1) °C.

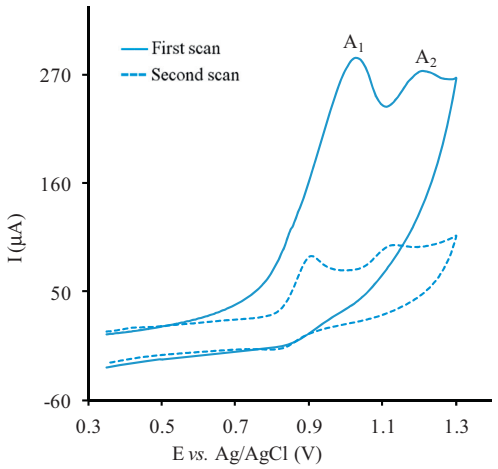


Fig. 2. Multi-cyclic voltammograms of **1** (1.0 mmol/L) in the presence of **2a** (1.0 mmol/L) at glassy carbon electrode in an aqueous phosphate buffer (0.2 mol L^{-1}, pH 2.0)/acetonitrile (85/15, v/v) solution. Scan rate: 800 mV s^{-1}, temperature = (25 ± 1) °C.

The multi-cyclic voltammograms of 1.0 mmol/L **1** in the presence of 1.0 mmol/L **2a** are shown in Fig. 2. The reduced height of the anodic peak (A_1) in the second scan is probably due to the formation of a thin film of product at the surface of the electrode, inhibiting to a certain degree the performance of the electrode process that was enhanced during the repetitive cycling of the potential.

Controlled-potential coulometry was performed in water (0.2 mol/L phosphate buffer, pH 2.0)/acetonitrile (85/15, v/v) containing 0.25 mmol of **1** and 0.25 mmol of **2a** at 0.85 V *versus* Ag/AgCl. The electrolysis progress was monitored using cyclic voltammetry (Fig. 3). It was found that, proportional to the advancement of electrolysis, the anodic peak A_1 decreased.

Diagnostic criteria of cyclic voltammetry, accompanied by spectroscopic data (IR, ^1H NMR, ^{13}C NMR and MS) of the final products allow us to propose the mechanistic pathway in Scheme 1 for the electrochemical oxidation of **1** in the presence of **2a** and **2b**. According to our results, it seems that a 1,4-Michael type addition reaction of **2a** and **2b** with **1ox** is faster than other secondary reactions, leading to the formation of **3a** and **3b**. The oxidation of

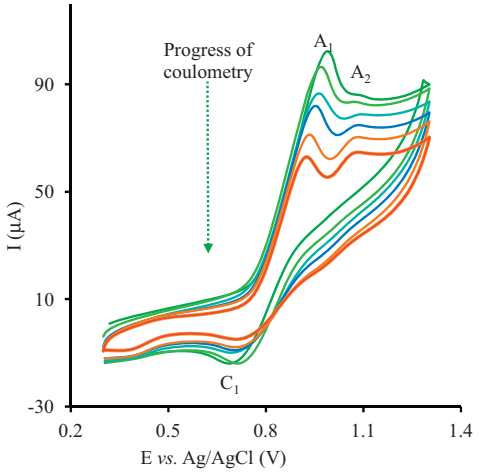
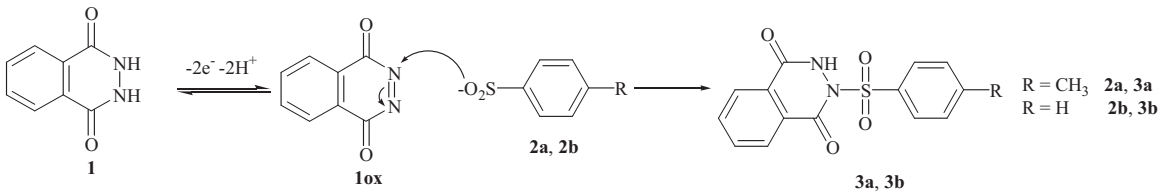


Fig. 3. Cyclic voltammograms of **1** (0.25 mmol) in the presence of **2a** (0.25 mmol), at a glassy carbon electrode in an aqueous phosphate buffer (0.2 mol L^{-1}, pH 2.0)/acetonitrile (85/15, v/v) solution during controlled-potential coulometry at 0.85 V *versus* Ag/AgCl. Scan rate: 100 mV s^{-1}, temperature = (25 ± 1) °C.



Scheme 1. Proposed mechanism for the electrochemical oxidation of **1** in the presence of arylsulfinic acids (**2a** and **2b**).

these compounds (**3a** and **3b**) is harder than the oxidation of the starting molecule (**1**) by virtue of the presence of an electron-withdrawing phenylsulfonyl group on **3a** and **3b**.

4. Conclusion

The results of this work show that 2,3-dihydrophthalazine-1,4-dione (**1**) is oxidized to phthalazine-1,4-dione (**1ox**), which is then attacked by arylsulfinic acids (**2a** and **2b**). The final products are obtained *via* an *EC* mechanism after a Michael type addition of arylsulfinic acids to the electro-generated **1ox**. According to our results, these processes lead to the formation of new sulfonamide derivatives in good yields. The presented work represents a facile and reagent-less method with high atom economy for the synthesis of sulfonamides using a carbon electrode.

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References

[1] Z. Huang, Z. Lin, J. Huang, A novel kind of antitumour drugs using sulfonamide as parent compound, Eur. J. Med. Chem. 36 (2001) 863–872.
[2] S.F. Yang, C.F. Lin, C.J. Wu, K.K. Ng, A.Y.C. Lin, P.K.A. Hong, Fate of sulfonamide antibiotics in contact with activated sludge—sorption and biodegradation, Water Res. 46 (2012) 1301–1308.
[3] K. Seri, K. Sanai, K. Kurashima, Y. Imamura, H. Akita, (R)-ACX is a novel sufonylurea compound with potent, quick and short-lasting hypoglycemic activity, Eur. J. Pharmacol. 389 (2000) 253–256.
[4] S. Bano, J. Javed, S. Ahmad, I.G. Rathish, S. Singh, M.S. Alam, Synthesis and biological evaluation of some new 2-pyrazolines bearing benzene sulfonamide moiety as potential anti-inflammatory and anti-cancer agents, Eur. J. Med. Chem. 46 (2011) 5763–5768.
[5] X.P. Hong, J.Y. Ma, Electrochemical study of sulfadiazine on a novel phthalocyanine-containing chemically modified electrode, Chin. Chem. Lett. 24 (2013) 329–331.
[6] R. Sivakumar, S.K. Gnanasam, S. Ramachandran, Pharmacological evaluation of some new 1-substituted-4-hydroxy-phthalazines, Eur. J. Med. Chem. 37 (2002) 79–8013.
[7] S.L. Zhang, Y.J. Liu, Y.F. Zhao, Q.T. Guo, P. Gong, Synthesis and antitumor activities of novel 1,4-substituted phthalazine derivatives, Chin. Chem. Lett. 21 (2010) 1071–1074.
[8] X. Zhai, J. Li, L. He, S. Zheng, Y.B. Zhang, P. Gong, Synthesis and in vitro cytotoxicity of novel 1,4-disubstituted phthalazines, Chin. Chem. Lett. 19 (2008) 29–32.
[9] D. Nematollahi, A. Maleki, Electrochemical oxidaton of N,N-dialkyl-p-phenylenediaminesin the presence of arylsulfinic acids. An efficient method for the synthesisof new sulfonamide derivatives, Electrochem. Commun. 11 (2009) 488–491.
[10] D. Nematollahi, E. Mehdipour, A. Zeinodini-Meimand, A. Maleki, Chemical and electrochemical oxidative coupling of N,N-dialkyl-p-phenylenediamines and arylsulfinic acids. Synthesis of sulfonamide derivatives, Tetrahedron Lett. 51 (2010) 6447–6450.
[11] F. Varmaghani, D. Nematollahi, S.E. Mallakpour, R. Esmaili, Electrochemical oxidation of 4-substituted urazoles in the presence of arylsulfinic acids: an efficient method for the synthesis of new sulfonamide derivatives, Green Chem. 14 (2012) 963–967.
[12] F. Varmaghani, D. Nematollahi, Electrochemical study of 1,2-dihydropyridazine-3,6-dione in protic and aprotic solvents: oxidative ring cleavage and reduction, Electrochim. Acta 56 (2011) 6089–6160.