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Electrochemical Oxidation of 4-(Piperazin-1-yl)phenol in the Presence of Aryl Sulfinic Acids

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Electrochemical oxidation of 4-(piperazin-1-yl)phenol has been studied in the presence of aryl sulfinic acids as nucleophiles in ethanol/water mixture (10/90) using cyclic voltammetry and controlled-potential coulometry methods. The results indicate that the electrochemically generated *p*-quinone-imine participates in Michael type addition reaction with aryl sulfinic acids and via an *EC* mechanism converts to the new 2-(phenylsulfonyl)-4-(piperazin-1-yl)phenol derivatives. The present work has led to the development of a facile and environmentally friendly electrochemical method for the synthesis of some new 2-(phenylsulfonyl)-4-(piperazin-1-yl)phenol derivatives under green conditions.
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Electrochemistry has emerged as a powerful tool for the synthesis of complex organic molecules.[1] Among amines, aryl piperazines are of particular interest for the synthesis of biologically active substances since this moiety is commonly found as a key structural element in many compounds possessing broad therapeutic activities.[2] Piperazine and its derivatives especially phenylpiperazines are important pharmacores that can be found in biologically active compounds across a number of different therapeutic areas,[3] such as antifungal,[4] anti-bacterial, anti-malarial, anti-psychotic agents[5] and HIV protease inhibitor.[6]

On the other hand, diarylsulfones are important synthetic targets, and widely used synthons for synthetic organic chemists due to many applications of them.[7,8] Some of diphenylsulfones have been shown to inhibit HIV-1 reverse transcriptase and represent an emerging class of substances able to address toxicity and resistance problems of nucleoside inhibitors.[9,10] They are useful in the practice of medicinal chemistry because the sulfone functional group is found in numerous drugs.[11] For example, diphenylsulfone is used as an intermediate for the synthesis of 4,4-diaminodiphenylsulfone (*dapsone*) (Fig. 1a).[12] The importance of phenylpiperazine derivatives has prompted many workers to synthesize these compounds by various chemical methods.[13–17] Following our experience in electrochemical synthesis of organic compounds based on the in-situ generation of Michael acceptor,[18–20] we thought that synthesis of organic compounds with both structures of diphenylsulfone and piperazine would be useful from pharmaceutical properties point of view. This idea prompted us to investigate electrochemical oxidation of 4-(piperazin-1-yl)phenol (**1**) (Fig. 1b) in the presence of aryl sulfinic acids (**3a-c**) as nucleophiles and represent a facile and one-pot electrochemical method for the synthesis of some new 2-(phenylsulfonyl)-4-(piperazin-1-yl)phenol derivatives (Fig. 1c). This reaction proceeds in a single step with an environmentally friendly method in ethanol/water mixture (10/90), in ambient conditions in a divided cell using a carbon electrode.

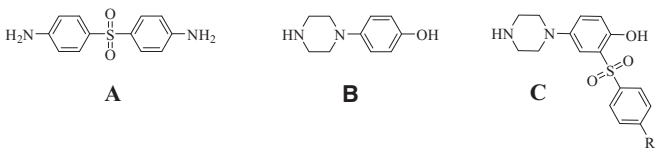


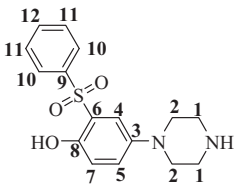
Figure 1. The structures of dapsone (**A**), 4-(piperazin-1-yl)phenol (**B**) and synthesized compounds (**C**).

Experimental

Apparatus and reagents.— Cyclic voltammetry, controlled-potential coulometry and preparative electrolysis were performed using an Autolab model PGSTAT 30 potentiostat/galvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disk (1.8 mm^2 area) and a platinum wire was used as a counter electrode. The working electrode used in controlled-potential coulometry and macro-scale electrolysis was an assembly of four carbon rods (31 cm^2) and a large steel sheet constitute the counter electrode. The working electrode potentials were measured *versus* Ag/AgCl (from AZAR electrode and Metrohm). 4-(piperazin-1-yl)phenol, benzenesulfinic acid, 4-chlorobenzenesulfinic acid and 4-toluenesulfinic acid were reagent-grade materials from Aldrich. Phosphoric acid, perchloric acid, acetic acid, sodium bicarbonate and other solvents were of pro-analysis grade from E. Merck. These chemicals were used without further purification.

Synthesis of compounds 5a-c.— A solution of perchloric acid (ca. 80 mL; $c = 0.1$ M) in ethanol/water mixture (10/90) solutions containing 4-(piperazin-1-yl)phenol (**1**) (0.25 mmol) and aryl sulfinic acids sodium salt (**3a–c**) (0.25 mmol) was electrolyzed in a divided cell at 0.45 V vs. Ag/AgCl. The electrolysis was terminated when the current decreased by more than 95% (after consumption of about 50 coulombs). At the end of electrolysis, after neutralizing the solution with saturated solution of sodium carbonate, the precipitated solids were collected by filtration and washed several times with cold water. After washing and drying, products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS. These spectra are presented in the Supplementary Material.[28] The isolated yields of **5a–c** are reported in Scheme 3.

2-(Phenylsulfonyl)-4-(piperazin-1-yl)phenol (5a).—



M.p.: 237–238°C (Dec.). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 4H, aliphatic), 2.95 (s, 4H, aliphatic), 5.71 (d, $J = 8.9$ Hz, 1H, aromatic), 6.07 (dd, $J = 2.9$ and 8.9, 1H, aromatic), 6.29 (d, $J = 2.9$, 1H, aromatic), 6.49 (t, $J = 7.8$, 2H, aromatic), 6.56 (t, $J = 7.4$, 1H, aromatic), 6.8 (d, $J = 7.4$, 2H, aromatic). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 45.46 (C-1), 50.48 (C-2), 114.7 (C-4), 118.2 (C-7), 124.5 (C-5), 125.8 (C-10), 127.7 (C-11), 128.7 (C-6), 133.0 (C-9), 141.4 (C-8), 144.5 (C-3), 148.9 (C-12). IR (KBr) ν (cm^{-1}): 3438 (broad, O-H), 3010 (weak, C-H), 2925, 2813 (weak, C-H), 1465 (strong C=C), 1455 (strong, C=C), 1288 (strong, S=O), 1288 (strong C-O), 1142 (strong, S=O), 1087, 830, 688, 593. MS (EI, 70 eV)

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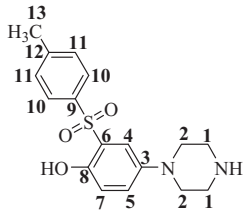
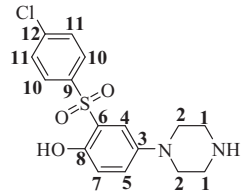
m/z (relative intensity): 318 (M^{+}., 25), 276 (100), 77 (44), 56 (73), 30 (56).

4-(Piperazin-1-yl)-2-tosylphenol (5b).—



M.p.: 246–247°C (Dec.). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 2.35 (s, 3H, methyl), 2.83 (s, 4H, aliphatic), 2.92 (s, 4H, aliphatic), 6.74 (d, $J = 8.7$ Hz, 1H, aromatic), 7.10 (d, $J = 6.6$ Hz, 1H, aromatic), 7.34 (d, $J = 7.7$ Hz, 3H, aromatic), 7.76 (d, $J = 8.0$ Hz, 2H, aromatic). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 20.9 (C-13), 45.4 (C-1), 50.4 (C-2), 114.7 (C-4), 118.2 (C-7), 124.3 (C-5), 126.1 (C-10), 127.8 (C-11), 129.1 (C-6), 138.6 (C-9), 143.4 (C-8), 144.3 (C-3), 148.9 (C-12). IR (KBr) ν (cm^{-1}): 3444 (broad, O-H and N-H), 3043 (weak, C-H), 2948 (weak, C-H), 1631 (medium C=C), 1453 (strong, C=C), 1302 (strong, S=O), 1284 (strong, C-H, methyl), 1139 (strong, S=O), 1090, 942, 828, 742, 709, 657, 593. MS (EI, 70 eV) *m/z* (relative intensity): 332 ($M^{+\cdot}$, 21), 290 (97), 124 (42), 109 (71), 91 (100).

2-(4-Chlorophenylsulfonyl)-4-(piperazin-1-yl)phenol (5c).—



Mp.: 229–230°C (Dec.). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 2.88 (s, 4H, aliphatic), 2.97 (s, 4H, aliphatic), 5.38 (broad, 2H, OH, NH), 6.73 (s, 1H, aromatic), 7.15 (s, 1H, aromatic), 7.36 (s, 1H, aromatic), 7.66 (s, 2H, aromatic), 7.92 (d, 2H, aromatic). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 45.8 (C-1), 50.8 (C-2), 115.2 (C-4), 119.0 (C-7), 125.5 (C-5), 125.6 (C-10), 129.4 (C-11), 130.3 (C-6), 138.4 (C-9), 140.9 (C-8), 144.3 (C-3), 150.7 (C-12). IR (KBr) ν (cm^{-1}): 3454 (broad, O-H), 3274 (medium, N-H), 2952 and 2923 (weak, C-H, aliphatic), 2820 (weak, C-H), 1625 and 1582 (medium C=C), 1474 (strong, C=C), 1303 (strong, S=O), 1278 (medium C-O), 1147 (strong, S=O), 1087, 1011, 943, 827, 769, 705, 591. MS (EI, 70 eV) *m/z* (relative intensity): 352 ($M^{+\cdot}$, 28), 310 (100), 135 (7), 119 (7), 111 (7), 91 (14), 65 (9.3), 56 (21.7).

Results and Discussion

The effect of pH.— Electrochemical generation of *p*-quinone-imine (**2**) and using it as a Michael acceptor for the synthesis of 2-(phenylsulfonyl)-4-(piperazin-1-yl)phenol derivatives on the one hand, and minimizing its participation in other possible reactions, on the other hand, are the main goal of this work. Therefore, electrochemical oxidation of **1** has been studied in various pHs.

Cyclic voltammograms of 1.0 mM solution of 4-(piperazin-1-yl)phenol (**1**) in ethanol/water mixture (10/90) solution at pH = 1.5 are shown in Fig. 2. In this pH value, cyclic voltammograms exhibit one anodic (A_1) and two cathodic peaks (C_1 and C_0). A_1 and C_1 Peaks are related to the transformation of **1** to *p*-quinone-imine **2** and vice versa within a reversible two-electron process. In the second cycle, a new anodic peak (A_0) appears at less positive potential (Fig. 2). These peaks (A_0 and C_0) show the occurrence of some reactions such as hydroxylation on the electrochemically generated to *p*-quinone-imine **2**, and/or coupling of **1** (as a nucleophile) with *p*-quinone-imine **2** (dimerization reaction), under the experimental conditions.

Cyclic voltammograms of 4-(piperazin-1-yl)phenol **1** (1.0 mM) in ethanol/water (10/90) solution at various pH values are shown in Fig. 3. The peak current ratio (I_{pC1}/I_{pA1}) decreases with increasing pH as well as decreasing potential sweep rate. The cathodic peak C_1 disappears in basic solutions and/or in low potential sweep rates. Also, the cathodic peak current ratio (I_{pC1}/I_{pC0}) is pH dependent and decreases with increasing pH. This shows that the rate of above mentioned reactions (hydroxylation and dimerization) is pH dependent and enhances by increasing pH (Fig. 3).[21–25]

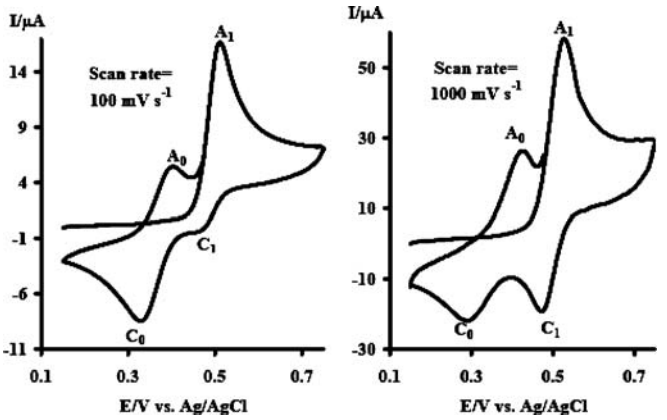


Figure 2. First and second cyclic voltammograms of 1.0 mM 4-(piperazin-1-yl)phenol (**1**) in ethanol/water mixture (10/90) with pH = 1.5, at glassy carbon electrode at various scan rates. $T = 25 \pm 1$°C.

In this work, with the aim of decreasing in the rate of introduced hydroxylation and/or dimerization reactions**,** a solution containing perchloric acid (pH = 1.0) has been selected as a suitable solution for the electrochemical study of 4-(piperazin-1-yl)phenol (**1**) in the presence of aryl sulfinic acids, and synthesis of 2-(phenylsulfonyl)-4-(piperazin-1-yl)phenol derivatives.

The E-pH diagram.— It was found that the peak potential for A_1 (E_{pA1}) shifted to the negative potentials by increasing in pH. This is expected because of the participation of proton(s) in the oxidation reaction of **1** to *p*-quinone-imine **2**. The half-wave potential ($E_{1/2}$), is given by:[26,27]

$$E'_{1/2} = E_{1/2} - (2.303\, m\mathrm{RT}/2\mathrm{F})\mathrm{pH}$$

where *m* is the number of involved protons in the reaction and $E_{1/2}$ is the half-wave potential at pH = 0.0, R, T, and F have their usual meanings. The half-wave potentials ($E_{1/2}$) were calculated as the average of anodic and cathodic peak potentials of the cyclic voltammograms $\{(E_{pA1} + E_{pC1})/2\}$. A potential-pH diagram is constructed for compound **1** by plotting the calculated $E_{1/2}$ values as a function of pH (Fig. 4). The $E_{1/2}$-pH diagram comprises two linear segments with

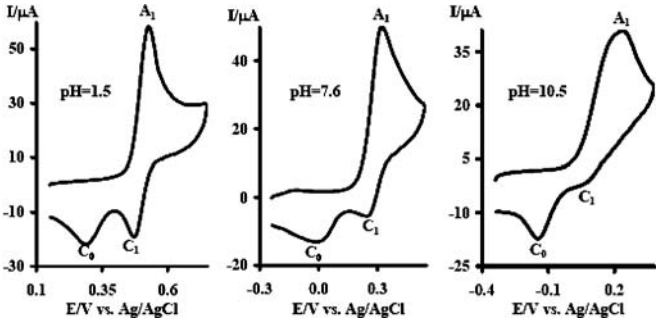


Figure 3. Cyclic voltammograms of 1.0 mM 4-(piperazin-1-yl)phenol (**1**) at a glassy carbon electrode, in buffered solutions {ethanol/water mixture (10/90)} with various pHs and same ionic strength. Scan rate: 1000 mV s^{-1}. $T = 25 \pm 1$°C.

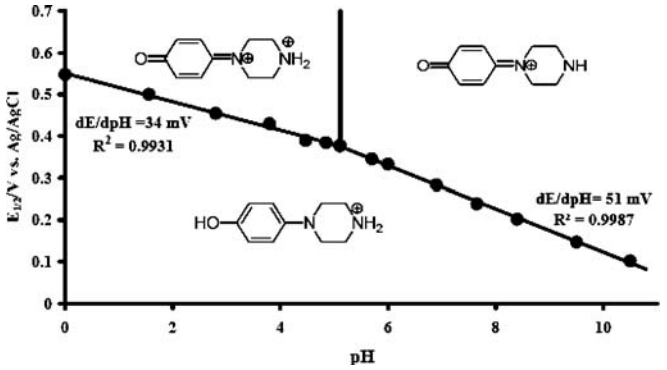


Figure 4. The potential-pH diagram of 4-(piperazin-1-yl)phenol (**1**).

different slopes, which are crossing at pH = 5.1.

$$\text{In pHs} < 5.1 : E'_{1/2} = 0.55 - 0.034\ \text{pH or slope} = 34\ \text{mV/pH}$$

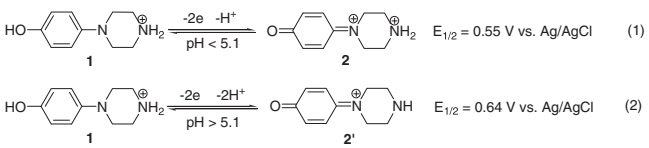
$$\text{In pHs} > 5.1 : E'_{1/2} = 0.64 - 0.051\ \text{pH or slope} = 51\ \text{mV/pH}$$

This shows that in various pHs, three different forms can be produced in diffusion layer, two in an oxidized form and another in reduced form. On the basis of the above mentioned slopes, it can be concluded that the electrode reaction occurring at the pH below 5.1 is a two-electron, one-proton process involving the oxidation of "*protonated*" **1** to the corresponding "*protonated*" *p*-quinone-imine **2** in forward scan and reduction of "*protonated*" **2** to "*protonated*" **1** in reverse scan with $E_{1/2}$ = 0.55 V vs. Ag/AgCl (Scheme 1, Eq. 1). Whereas, the electrode reaction at pH > 5.1, corresponds to the two-electron, two-proton process with $E_{1/2}$ = 0.64 V vs. Ag/AgCl (Scheme 1, Eq. 2). Also, the calculated pK_a for acid (**2**)/base (**2′**) equilibria shown in Scheme 2 is: 5.1.

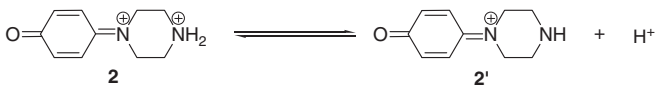
Mechanistic studies.— Cyclic voltammogram of a 1.0 mM of **1** in ethanol/water (10/90) solution containing 0.1 M perchloric acid (pH 1.0) is shown in Fig. 5 curve a. As can be seen, one anodic (A_1) and two cathodic peaks C_1 and C_0 were obtained. Anodic and cathodic peaks A_1 and C_1 are counterpart and are corresponded to the transformation of **1** to *p*-quinone-imine **2** and vice versa within a quasi-reversible two-electron process (Figure 5, curve a). The oxidation of **1** in the presence of benzenesulfinic acid (**3a**) as a nucleophile was studied in some details. Figure 5 curve b, shows the obtained cyclic voltammogram for a 1.0 mM solution of **1** in the presence of 1.0 mM benzenesulfinic acid (**3a**). Under these conditions, the cathodic peaks C_1 and C_0 disappear and a new anodic peak (A_2) appears in more positive potentials.

More studies were performed by varying the potential scan rate in a solution of **1** in the presence of **3a**. The results indicate that the peak current ratio (I_{pC1}/I_{pA1}) is dependent on the potential scan rate and increases with increasing it. The same result was obtained by decreasing the concentration of benzenesulfinic acid (**3a**).

Controlled-potential coulometry was performed in ethanol/water (10/90) solution containing 0.25 mmol of **1** and 0.25 mmol of benzenesulfinic acid (**3a**) at 0.45 V versus Ag/AgCl. The electrolysis progress was monitored by cyclic voltammetry (Fig. 6). It is shown that, proportional to the progress of electrolysis,, and in parallel with



Scheme 1.



Scheme 2.

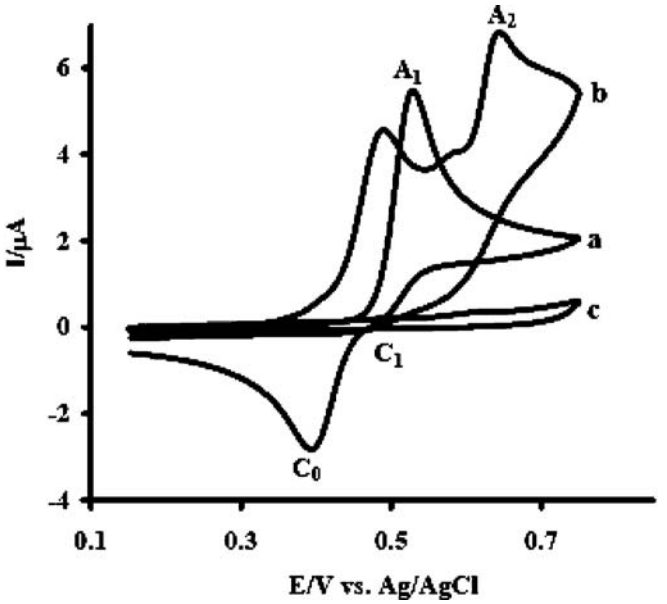


Figure 5. (a) Cyclic voltammogram of 1.0 mM 4-(piperazin-1-yl)phenol (**1**) in the absence, (b) in the presence of 1.0 mM benzenesulfinic acid (**3a**) and, (c) 1.0 mM benzenesulfinic acid (**3a**) in the absence of **1** at a glassy carbon electrode, in ethanol/water mixture (10/90) solution containing 0.1 M perchloric acid (pH 1.0). Scan rate: 10 mV s^{-1}, $T = 25 \pm 1$°C.

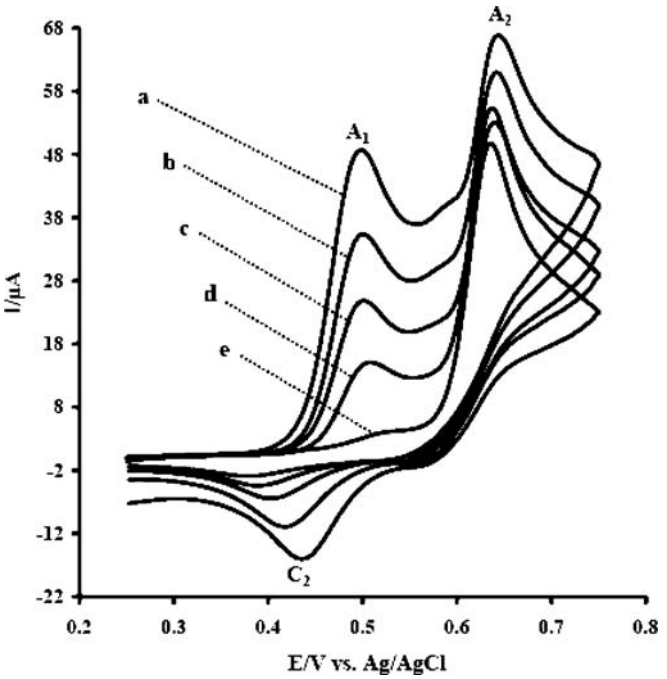
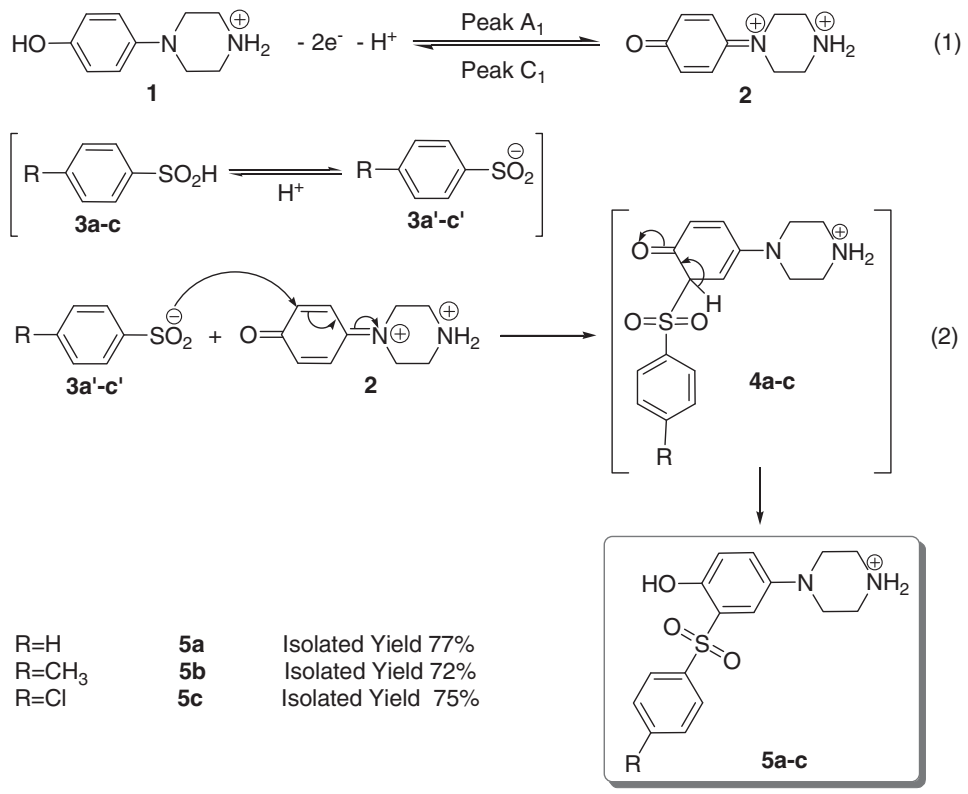
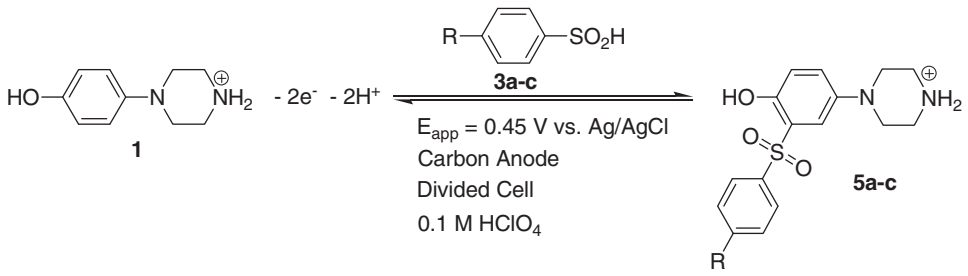


Figure 6. Cyclic voltammograms of 0.25 mmol 4-(piperazin-1-yl)phenol (**1**) in the presence of 0.25 mmol benzenesulfinic acid (**3a**) at a glassy carbon electrode in ethanol/water mixture (10/90) containing 0.1 M perchloric acid (pH = 1.0) during controlled-potential coulometry at 0.45 V versus SCE after consumption of (a) 0, (b) 12, (c) 22, (d) 32, and (e) 42 C. Scan rate: 100 mV s^{-1}. $T = 25 \pm 1$°C.



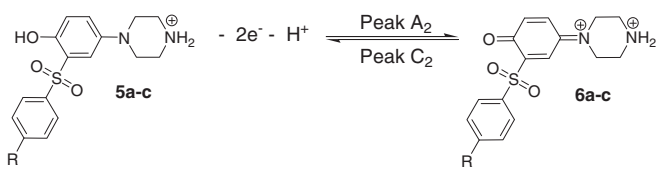
The overall reaction:



Scheme 3.

the decrease in the height of peak A_1, the current of anodic and cathodic peaks A_2 and C_2 increases. The anodic peak A_1 disappears when the charge consumption becomes about $2e^-$ per molecule of **1**. These coulometry and voltammetry results accompanied by the NMR (^1H and ^{13}C) data and molecular mass of 318 of final product allows us to propose an *EC* mechanism for the electrochemical oxidation of **1** in the presence of benzenesulfinic acid (**3a**) (Scheme 3).

The generation of *p*-quinone-imine **2** is followed by a Michael type addition reaction of **3a** on *p*-quinone-imine **2**, producing the diphenylsulfone **5a** as the final product. The oxidation of **5a** is more difficult than the oxidation of the starting molecule **1** by virtue of the presence of the electron-withdrawing sulfonyl group on **5a**. Therefore, over-oxidation of **5a** was circumvented during the electrolysis. According to our results, the anodic peaks A_1 and A_2 pertain to the oxidation of 4-(piperazin-1-yl)phenol (**1**) and diphenylsulfone **5a**, to *p*-quinone-imine **2** and **6a** (Scheme 4), respectively. Obviously, the cathodic peaks C_1 and C_2 are related to the reduction of *p*-quinone-imine **2** and **6a** into **1** and **5a**.



Scheme 4.

Conclusions

The results show that 4-(piperazin-1-yl)phenol (1) is oxidized to the corresponding *p*-quinone-imine which is then attacked by an aryl sulfinic acid in a Michael-like reaction. The product, a derivative of 2-(phenylsulfonyl)-4-(piperazin-1-yl)phenol, is obtained via an *EC* mechanism, after the consumption of $2e^-$ per molecule of **1**. The products are obtained in good yield and high purity. Our research has led to the development of a facile, environmentally friendly method that occurs under mild reaction conditions.

Acknowledgments

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28. See supplementary material at http://dx.doi.org/10.1149/2.033204jes for FT-IR, ^{1}H NMR, ^{13}C NMR and MS spectra of compounds 5a-5c.