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A green approach for the electrochemical synthesis of 4-morpholino-2-(arylsulfonyl)benzenamines

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ABSTRACT

Electrochemical synthesis of 4-morpholino-2-arylsulfonyl-benzamines was carried out by the electrochemical oxidation of 4-morpholinoaniline in the presence of arenesulfinic acids at a carbon electrode, in aqueous solution. Our voltammetric data indicate that electrochemically generated *p*-quinone-diimine participates in Michael type addition reaction with arenesulfinic acids and via an *EC* mechanism converts to the title products. This method provides a green, one-pot procedure for the synthesis of 4-morpholino-2-(arylsulfonyl)benzenamines of potential biological significance.

1. Introduction

Electrochemistry provides a versatile means for the selective reduction and oxidation of organic compounds.[1] Unique selectivity due to in situ formation of an active species at the interface, inversion in polarity by transfer of an electron and variability, in product formation by the control of the electric potential are some of the advantages of electrosynthesis.[2] Organosulfones have been used as drugs due to their strong in vitro and in vivo anti-bacterial and anti-fungicidal activity.[3] Further, diphenylsulfone derivatives were found to possess anti-bacterial activity.[4] The incorporation of a diphenylsulfone moiety into various heterocyclic systems was found to increase their biological activity.[5] For example, diphenylsulfone is used as an intermediate for the synthesis of 4,4′-diaminodiphenylsulfone (dapsone) (Fig. 1) which is an anti-leprotic and anti-inflammatory drug.[6]

We anticipated that the synthesis of new diphenylsulfone derivatives would be useful from the point of view of pharmaceutical properties (Fig. 1). This idea prompted us to investigate the electrochemical oxidation of 4-morpholinoaniline (**1**) in the presence of arenesulfinic acids **2a–c** as nucleophiles. This method represents a facile and one-pot electrochemical process for the synthesis of new diphenylsulfone derivatives in good yields and purities.

Cyclic voltammograms of 1 mM solutions of 4-morpholinoaniline (**1**) in aqueous solutions at various pHs are shown in Figure 2. In acidic media, the cyclic voltammograms show one anodic (A_1) and a corresponding cathodic peak (C_1), which correspond to the transformation of 4-morpholinoaniline (**1**) into *p*-quinone-diimine (**1ox**) and vice versa within a quasi-reversible two-electron process (Fig. 2, pH 2 and 5).[7] Under these conditions, the peak current ratio (I_{pC1}/I_{pA1}) of nearly unity, can be considered a criterion for the stability of *p*-quinone-diimine (**1ox**) produced at the surface of the electrode under the experimental conditions. In other words, the side reactions are too slow to be observed on the cyclic voltammetry time scale. In neutral and basic solutions, the peak current ratio (I_{pC1}/I_{pA1}) is less than unity and decreases with increasing pH (Fig. 2, pH 7 and 10). The electrochemical oxidation of aromatic amines is quite complex, depending on their structure and the electrolysis conditions leading to a variety of products. The products may vary largely by using aqueous or non-aqueous, neutral, acidic, or basic conditions.[8] Therefore, in this study in order to minimize side reactions, a solution containing phosphate buffer (pH 2.0, 0.2 M) was selected as a suitable medium for the electrochemical study and the synthesis of new diphenylsulfone derivatives **4a–c** (Scheme 1).

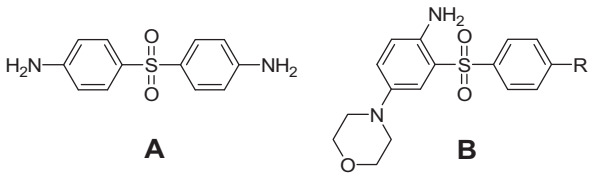

Figure 1. The structure of dapsone (**A**) and compounds reported here (**B**).

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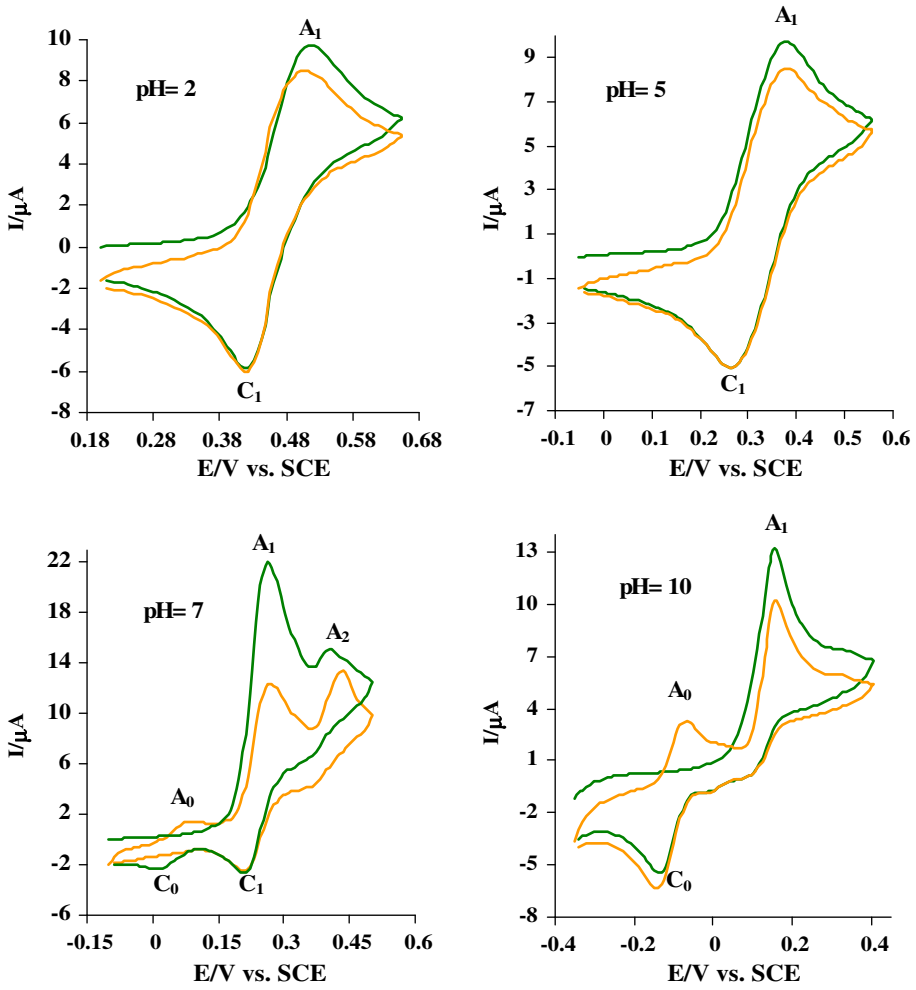


Figure 2. First (green lines) and second (orange lines) cyclic voltammograms of 1 mM 4-morpholinoaniline (**1**) at a glassy carbon electrode, in buffered solutions (various pHs, same ionic strength). Scan rate: 100 mV s^{-1}; t = 25 ± 1 °C.

Cyclic voltammograms of a 1 mM solution of 4-morpholinoaniline (**1**) in an aqueous solution containing 0.2 M phosphate buffer (pH 2), in the presence of 1 mM toluenesulfinic acid (**2a**) are shown in Figure 3 curve b. As can be seen, the cathodic peak (C_1) disappeared completely and a new anodic peak (A_2) appeared at more positive potentials. Also, the potential of peak A_1 (E_{pA1}) shifted toward a less positive potential. The occurrence of a chemical reaction is supported by the decrease in the current of peak C_1 during the reverse scan, which could indicate that *p*-quinone-diimine **1ox** formed at the surface of the electrode is consumed by a chemical reaction with **2a**.[9] The current of peak C_1 strongly depends on the potential scan rate. At lower scan rates, the peak current ratio (I_{pC1}/I_{pA1}) is less than one and increases when the sweep rate increases.[9] A similar situation was observed when the **2a** to 4-morpholinoaniline (**1**) concentration ratio was decreased.

Controlled-potential coulometry was performed in an aqueous solution containing 0.25 mmol of **1** and 0.25 mmol of **2a** at 0.4 V versus saturated calomel electrode (SCE). The electrolysis progress was monitored using cyclic voltammetry (Fig. 4). It was found that, proportional to the advancement of coulometry, the anodic peaks (A_1 and A_2) decreased. All the anodic and cathodic peaks disappeared when the charge consumption was about 2e^- per molecule of **1**. These observations allow us to propose the pathway shown in Scheme 1 for the electrooxidation of **1** in the presence of **2a**.

The generation of *p*-quinone-diimine (**1ox**) is followed by a Michael type addition reaction of **2a** on *p*-quinone-diimine (**1ox**),

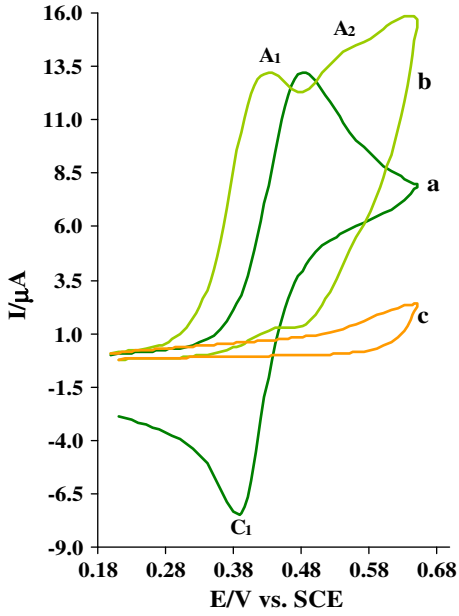


Figure 3. Cyclic voltammograms of 1 mM 4-morpholinoaniline (**1**): (a) in the absence and (b) in the presence of 1 mM toluenesulfinic acid (**2a**) and, (c) 1 mM **2a** in the absence of **1**, at a glassy carbon electrode, in aqueous solution containing 0.2 M phosphate buffer (pH 2). Scan rate: 100 mV s^{-1}; t = 25 ± 1 °C.

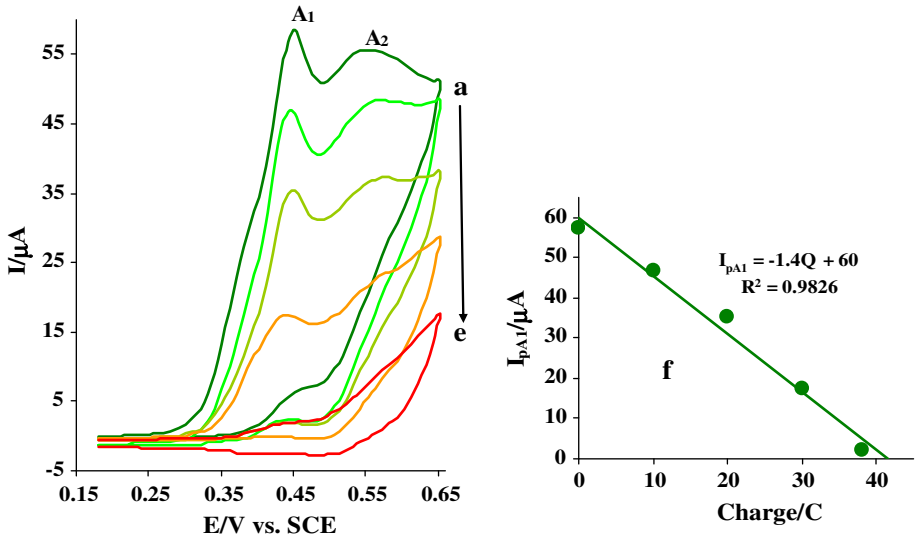
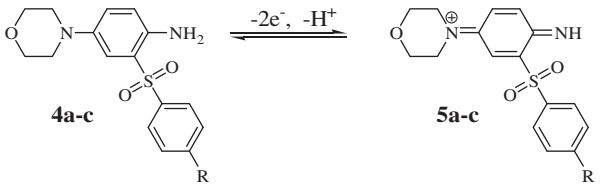


Figure 4. Cyclic voltammograms of 0.25 mmol 4-morpholinoaniline (**1**) in the presence of 0.25 mmol toluenesulfinic acid (**2a**) during controlled potential coulometry at 0.4 V versus SCE. After consumption of: (a) 0, (b) 10, (c) 20, (d) 30 and, (e) 38 coulombs. Curve f: variation of peak current (I_{pA1}) versus charge consumed. Scan rate: 100 mV s^{-1}; t = 25 ± 1 °C.

producing the diphenylsulfone **4a** as the final product. The oxidation of **4a** is more difficult than the oxidation of the starting molecule **1** by virtue of the presence of the electron-withdrawing tolylsulfonyl group on **4a**. Therefore, over-oxidation of **4a** was circumvented during the reaction because of the presence of the electron-withdrawing group as well as by the insolubility of the final product **4a** in the phosphate buffer (pH 2) solution.

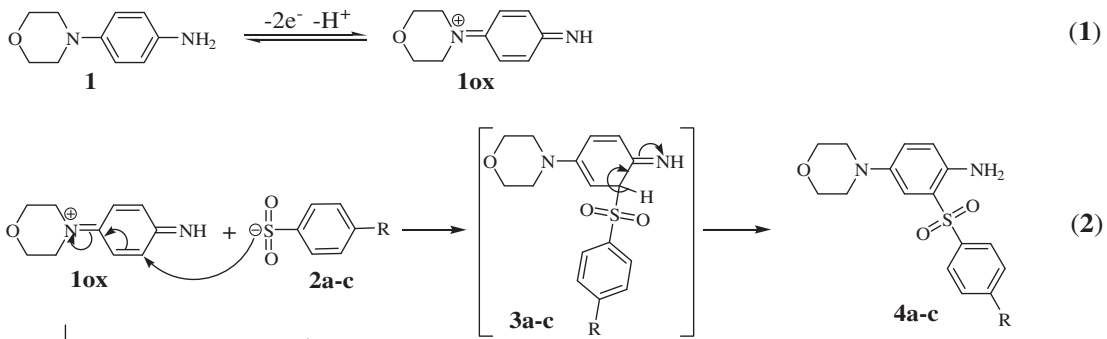
According to our results, the anodic peaks of the voltammograms presented in Figure 3 (A_1 and A_2) pertain to the oxidation of 4-morpholinoaniline (**1**) and diphenylsulfone **4a**, to *p*-quinone-diimines **1ox** and **5a**, respectively (Schemes 1 and 2). Obviously, the cathodic peak C_1 corresponds to the reduction of *p*-quinone-diimine **1ox** into **1**.

In contrast to 4-morpholinoaniline (**1**), the presence of a toluenesulfinic group with electron-withdrawing character results in an increase in the reactivity of *p*-quinone-diimine **5a** toward fast side reactions. Therefore, on the time scale of our experiments, the cathodic counterpart of oxidation of **5a** was not observed.



Scheme 2.

The results of this work show that 4-morpholinoaniline (**1**) is oxidized to *p*-quinone-diimine **1ox** which is then attacked by arenesulfinic acid **2a–c**. The final products are obtained via an *EC* mechanism, after consumption of $2e^-$ per molecule of **1**. According to our results, the Michael type reaction of these nucleophiles with the *p*-quinone-diimine leads to the formation of new diphenylsulfone derivatives in good yields and high purities. The presented work represents a facile, reagent-less, and environmentally



	R	Yield (%)	mp (°C)
4a	Cl	90	155-157
4b	H	80	141-142
4c	CH_3	85	165-166

Scheme 1.

friendly method with high atom economy, for the synthesis using a carbon electrode.

The reaction equipment was used as described in earlier papers.[10]

2. General procedure for the synthesis of 4a–c

Phosphate buffer solution (50 ml, 0.2 M, pH 2) containing 0.25 mmol of 4-morpholinoaniline (**1**) and 0.25 mmol of toluenesulfinic acid (benzensulfinic acid or 4-chlorobenzenesulfinic acid) was subjected to electrolysis at 0.4 V versus SCE, in an undivided cell. The electrolysis was terminated when the current decayed to 5% of its original value. The precipitated solid was collected by filtration and was washed several times with water. After drying, the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS. The average current yield is more than 89%. In this method the electrochemical process involved in cathode is the reduction of protons.

2.1. 4-Morpholino-2-(4-methylphenylsulfonyl)benzenamine (4a, $C_{17}H_{20}N_2O_3S$)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 3.10 (s, 4H), 3.91 (s, 4H), 4.90 (br s, ≈2H), 6.65 (1H, d, J = 8.7 Hz), 7.10 (1H, s), 7.29 (2H, d, J = 8.9 Hz), 7.47 (1H, s), 7.83 (2H, d, J = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 51.2, 66.5, 116.7, 119.1, 122.8, 125.4, 127.0, 129.7, 138.5, 144.1, 145.9. IR (KBr): 3418, 3345, 2975, 2920, 2860, 2816, 1626, 1500, 1450, 1284, 1232, 1144, 1117, 951, 814, 661, 586 cm^{-1}. MS (EI): *m/z* (relative intensity); 332 (100), 274 (53), 209 (44), 91 (59), 65 (20).

2.2. 4-Morpholino-2-(phenylsulfonyl)benzenamine (4b, $C_{16}H_{18}N_2O_3S$)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.04 (4H, d, J = 12.4 Hz), 3.85 (4H, d, J = 12.3 Hz), 4.88 (br s, ≈2H), 6.64 (1H, m), 7.05 (1H, d, J = 8.6 Hz), 7.49 (4H, m), 7.93 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.8, 66.7, 116.5, 119.1, 122.2, 125.3, 126.9, 129.0, 133.1, 140.6, 141.5, 143.0. IR (KBr): 3458, 3362, 2962, 2854, 2818, 1634, 1616, 1500, 1446, 1315, 1290, 1230, 1146, 1117, 1095, 947, 866, 818, 754, 723, 690, 590, 550 cm^{-1}. MS (EI): *m/z* (relative intensity); 318 (100), 260 (69), 195 (36), 167 (35), 91 (41), 77 (40).

2.3. 2-(4-Chlorophenylsulfonyl)-4-morpholinobenzenamine (4c, $C_{16}H_{17}N_2O_3SCl$)

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.95 (4H, s), 3.71 (4H, d, J = 3.8 Hz), 5.7 (br s, ≈2H), 6.76 (1H, d, J = 9.6 Hz), 7.14 (2H, d, J = 6.3 Hz), 7.66 (2H, d, J = 8.3 Hz), 7.96 (2H, d, J = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.3, 66.6, 114.3, 119.3, 126.4, 129.2, 129.9, 132.0, 138.8, 140.5, 141.8, 142.6. IR (KBr): 3426, 3350, 2964, 2866, 2814, 1628, 1502, 1450, 1311, 1298, 1277, 1232, 1150, 1117, 1088, 820, 770, 584 cm^{-1}. MS (EI): *m/z* (relative intensity); 352 (100), 294 (64), 229 (23), 111 (26), 91 (48), 65 (24).

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