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LETTER

Electrochemical Synthesis of 1-*N*-phenyl-4-(sulfonyl)benzene-1,2-diamine Derivatives. A Mild and Regioselective Protocol†

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Regioselective synthesis of *1-N*-phenyl-4-(sulfonyl)benzene-1,2-diamine derivatives was carried out by anodic oxidation of 2-aminodiphenylamine in water/ethanol mixture in the presence of some sulfinic acids as nucleophiles using both controlled-potential and constant current techniques. Our voltammetric data indicate that the anodic oxidation of 2-aminodiphenylamine produces 1-*N*-phenyl-*o*-benzoquinone diamine. This compound acts as a Michael acceptor providing 1-*N*-phenyl-4-(arylsulfonyl)benzene-1,2-diamines in high yields. In this new methodology, a mixture of water/ethanol was used as the solvent, a carbon rod as the anode and avoids the use of toxic and/or hazardous reagents.

Introduction

Aryl sulfone-containing compounds are important synthetic targets and widely used as synthons for synthetic organic chemists due to their chemical properties[1] and biological activities.[2] These compounds are useful building blocks in medicinal chemistry and found on several drugs, including antimigraine Vioxx®,[3] antibacterial dapsone (Fig. 1)[4] and antiandrogen Casodex®.[5] Furthermore, these compounds have shown promising antitumor,[6] antifungal,[7] antibacterial activities[8] and are used as inhibitors for several enzymes such as cyclooxygenase-2 (COX-2),[9] HIV-1 reverse transcriptase,[10] integrin VLA-4[11] and ATPase.[12] It should be noted that, despite the importance of dapsone, it has some haematological side effects due to its hydroxylamine metabolites.[13] The formation of hydroxylamine is catalyzed either by hepatic enzymes such as cytochrome P450.[14]

On the other hand, 2-aminodiphenylamine (**2ADPA**) and its derivatives are interesting compounds due to their wide application as precursors for the synthesis of biologically active compounds, as fluorescent material, as lubricant antioxidants, in dye formulations and in polymer synthesis.[15] Due to their important applications, numerous synthesis strategies have been reported.[15]

The most common strategies towards diarylsulfone synthesis typically involve the oxidation of corresponding sulfides and sulfoxides,[16] the sulfonylation of arenes in the presence of strong acids[17] and classic Friedel–Crafts type sulfonation reactions.[18] The majority of these processes[19] generally suffer from significant limitations, such as harsh conditions, high temperature, lack of regiospecificity or incompatibility with numerous functional groups.[20] Therefore, more effective and environmentally friendly methods are needed. In contrast to one-pot chemical synthesis where the control on the oxidation of a single component is difficult, controlled-potential electrolysis serves as a powerful method for the synthesis of a desirable product via selective oxidation of a target reagent.[21]

These findings (including the importance of diarylsulfone compounds, significant limitations in their synthesis, efficiency of electrochemical methods in organic synthesis and the synthesis of compounds that may have medicinal properties) motivated us to synthesize some new organic compounds under greener conditions, based on the anodic oxidation of **2ADPA** (Fig. 1). Electrochemical oxidation of **2ADPA** in the absence of nucleophiles has been studied previously by Cotarelo et al.[22] and Losito et al.[23] In both studies, the authors reported the dimerization of **2ADPA**.

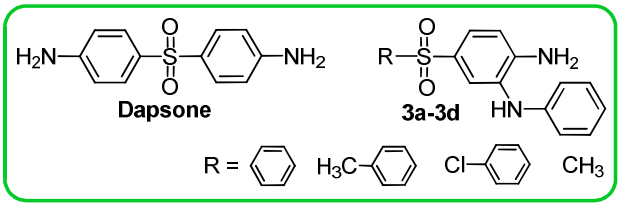

Fig. 1 The structures of dapsone and synthesized compounds (**3a-3d**).

Following our experience in electrochemical synthesis of new compounds with medicinal activity based on the in-situ generation of Michael acceptor,[24] in the present study, we aimed to synthesize some new compounds with both structures of diarylsulfone and **2ADPA** (Fig. 1) by electrochemical oxidation of **2ADPA** in the presence of sulfinic acids (**1a**-**1d**) as nucleophiles under greener

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† Electronic Supplementary Information (ESI) available: Electrolysis cell, ^{1}H NMR, 2D NMR, ^{13}C NMR, FT-IR, MS, elemental analysis of all compounds and details of X-ray crystallography. See DOI: 10.1039/x0xx00000x

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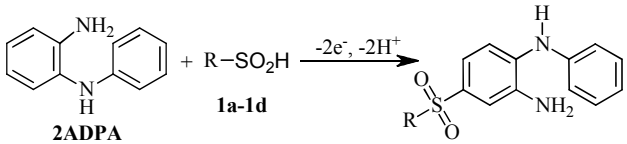
conditions (Scheme 1). The method allows a one-pot regioselective synthesis of 1-*N*-phenyl-4-(sulfonyl)benzene-1,2-diamines. In this paper, we also discussed the reaction mechanism of the synthesis of 1-*N*-phenyl-4-(sulfonyl)benzene-1,2-diamine derivatives.



	R	Isolated yield	mp (°C)
a		80	160-162
b	Me	85	136-138
c	Cl	78	145-147
d	Me	90	137-139

Scheme 1 The overall reaction of electrooxidation of **2ADPA** in the presence of **1a-1d**.

Results and discussion

Cyclic voltammogram of **2ADPA** in water (phosphate buffer, *c*=0.2 M, pH = 2.0)/ethanol (70/30, v/v) mixture is shown in Fig. 2 curve a. As can be observed, one anodic A_1 and its corresponding cathodic peak (C_1) was obtained, which correspond to the transformation of **2ADPA** to 1-*N*-phenyl-*o*-benzoquinone diimine (**NPBQD**) and vice versa within a quasi-reversible two-electron process. Fig. 2 curve b, shows the recorded cyclic voltammogram for a solution containing both **2ADPA** and benzenesulfinic acid (**1a**). Comparing the voltammograms in Fig. 2, it can be observed that the cathodic peak current (I_{pC1}) disappears. Under these conditions, the peak current ratio (I_{pC1}/I_{pA1}) depends on the potential scan rate and **1a** concentration. It increases with increasing potential scan rate and decreasing **1a** concentration.

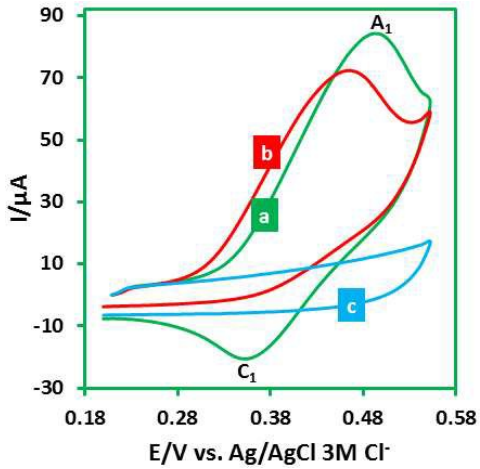
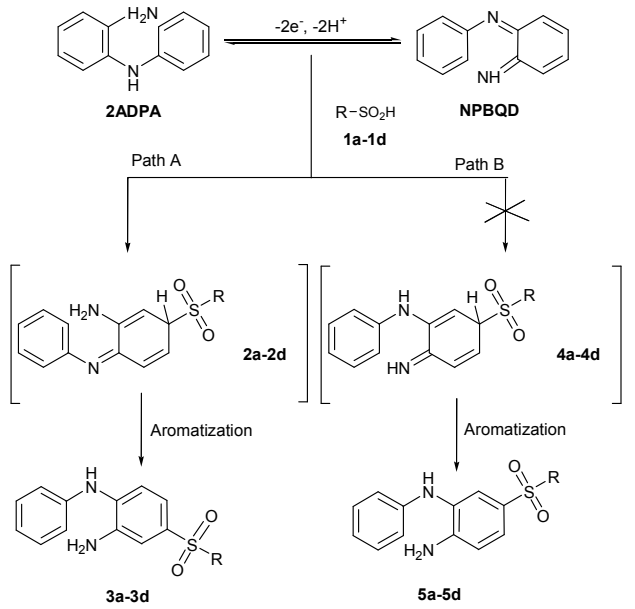


Fig. 2 Cyclic voltammograms of **2ADPA** (0.25 mM) (a) in the absence of benzenesulfinic acid (b) and in the presence of benzenesulfinic acid (0.25mM). (c) Benzenesulfinic acid (0.25 mM) in the absence of **2ADPA.** These voltammograms were performed at a glassy carbon electrode in water (phosphate buffer, *c*= 0.2 M, pH = 2.0)/ethanol (70/30, v/v) mixture. Scan rate 3 V s^{-1}. Temperature = 25 °C.

These observations indicate that electrochemically generated **NPBQD** is consumed by a chemical reaction with **1a**. Controlled potential coulometry (CPC) was used to investigate the number of electrons being transferred during oxidation of **2ADPA** in the presence of **1a.** It was carried out at potential beyond the oxidation peak for **2ADPA** (0.53 V versus Ag/AgCl 3M Cl^-). CPC establishes the occurrence of an overall two-electron process. From the diagnostic criteria of the cyclic voltammetry and controlled potential coulometry, the electrochemical behavior of **2ADPA** in the presence of **1a** is characteristic of an *EC* mechanism (Scheme 2).



Scheme 2 Proposed mechanism for the electrochemical oxidation of **2ADPA** in the presence of sulfinic acids.

According to the Scheme 2, the generation of **NPBQD** (E_r step) is followed by addition of **1a**-**1d** to quinonediimine ring (C_i step), giving rise to a **3a-3d** as the final products. The oxidation of **3a-3d** is more difficult than the oxidation of the starting molecule (**2ADPA**) because of the presence of the electron-withdrawing sulfonyl group as well as by the insolubility of the final products **3a-3d** in H_2O/EtOH (70/30, v/v) mixture. Consequently, the oxidation of **3a-3d** did not occur during the electrochemical oxidation at the potential of 0.53 V versus Ag/AgCl 3M Cl^-. The experimental details and characterization data for **3a-3d** are given in Electronic Supplementary Information (ESI†). In the proposed mechanism, the generated **NPBQD** can be attacked by **1a-1d** through the paths A or B to form the final products **3a-3d** or **5a-5d** respectively. However, single-crystal X-ray diffraction analysis of product confirms selective formation of **3a-3d** (Fig. 3).

This phenomenon can be explained by the fact that the regioisomers **2a-2c** are more stable than the regioisomers **4a-4c** due to the conjugation of a phenyl (aryl) ring with the 2,5-cyclohexadien-1-imine **2a-2c**. Hyperconjugation with the methyl group in **2d** appears to be sufficiently stabilizing to ensure a high regioselectivity of the addition of RSO_2H to **NPBQD** as well. These

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results show that, for the addition of a soft nucleophile such as RSO_2H to **NPBQD**, the transition state is late.

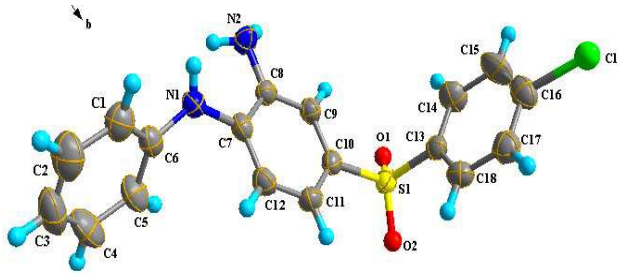


Fig. 3 ORTEP view of X-ray crystal structure of **3c**

On the other hand the pKa values for **2ADPAH**$^+$ and **2ADPAH$_2$**$^{2+}$ are 3.90 and -3.59, respectively.[25] It shows that **2ADPA** is highly resistant to the formation of **2ADPAH$_2$**$^{2+}$. This also means that at our experimental conditions (pH = 2.0), only the terminal imino group is in the protonated form and for this reason nucleophilic attack to **NPBQD** is highly regioselective, occurring at the *meta* position of the C=NH_2^+.

In order to investigate the electrochemical properties of **3a**, cyclic voltammogram of it was recorded (Fig. 4, curve b).The cyclic voltammogram shows one anodic (A_2) and a corresponding cathodic peak (C_2), which correspond to the transformation of **3a** into *o*-quinone-diimine **3a$_{ox}$** and vice versa within a two-electron process (Scheme 3). In comparison with **2ADPA** (curve b), the half wave potential ($E_{1/2}$) of **3a** is more positive than $E_{1/2}$ of **2ADPA**. The result was predictable: the attachment of an electron-withdrawing group to the phenyl ring increases the oxidation potential.

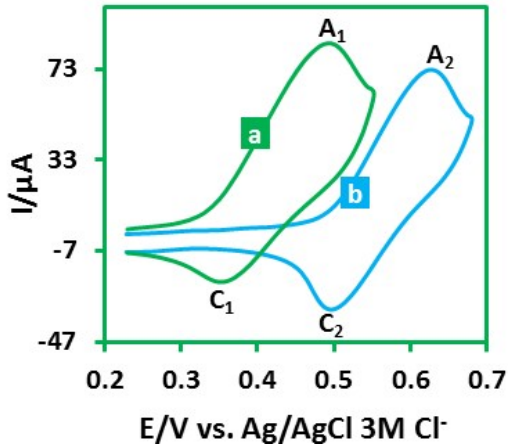
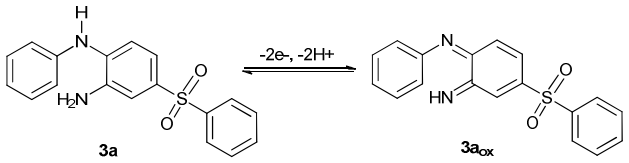


Fig. 4 Cyclic voltammogram of (a) **2ADPA** (1.0mM), (b) **3a** (1.0 mM). Other conditions are as same as **Fig. 2**



Scheme 3 Electrochemical oxidation of **3a.**

According to the second principle of green chemistry (atom economy), which was developed by Trost,[26] "*synthetic methods should be designed to maximize incorporation of all materials used in the process into the final product*".[27] The atom economy was calculated according to the equation: % atom economy = (FW of atoms utilized/FW of all reactants) × 100. According to Scheme 1, the % atom economy in the synthesis **3a-3d** are 99.38, 99.41, 99.44, and 99.24%, respectively. The high atom economy confirms that all atoms (except two hydrogen atoms) from the starting materials are incorporated into the product.

Constant-current synthesis was also performed to improve the synthetic procedure of **3a-3d**. To achieve high yield of product (**3a-3d**), the effect of current density was investigated in the range of 0.05 to 1.5 mA cm^{-2}, while the other parameters (temperature = 298 K, charge = 50 C, electrode surface = 31 cm^2, **2ADPA** = 0.25 mmol, and **1a**-**1d** = 0.25 mmol) are kept constant. The results showed that, the highest products yields (75-85%) were obtained at low current densities (0.35-0.50 mA cm^{-2}) (Table 1). The lower current densities result in longer reaction time and the higher current densities result in occurrence of some side reactions such as oxidation of water, nucleophile and product, and consequently, a decrease in the product yield and energy efficiency. In addition, the current efficiency at optimum current density is shown in Table 1. Our results also indicate that, with increasing the current density, the current efficiency decreases. The lower current efficiency in higher current densities is attributed to the large contribution of side reactions (oxidation of water, nucleophile and product).

entry	current density (mA cm^{-2})	current efficiency (%)	product yield (%)
3a	0.40	91	80
3b	0.40	90	80
3c	0.50	85	75
3d	0.35	95	85

Table 1 The effect of current density on the current efficiency and product yield of **3a-3d**.

Conclusions

In this work, the synthesis of compounds **3a-3d** was carried out successfully by the electrochemical oxidation of **2ADPA** in the presence of sulfinic acid derivatives, using both constant current and controlled-potential techniques. The presented constant current method has two series of advantages over conventional methods. Firstly, it is practically convenient to carry out. It uses mild and one-pot conditions with high atom economy (> 99%) and high current efficiency (> 90%). It proceeds at room temperature and in H_2O/EtOH mixture solution, without any catalysis, strong acids or bases. Secondly, in this method, the products were obtained regioselectively in high yields (> 75%).

Experimental section

Apparatus and reagents

Cyclic voltammetry, controlled-potential coulometry and preparative electrolysis were performed using an Autolab model PGSTAT 20 potentiostat/galvanostat. The working

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electrode used in the voltammetry experiments was a glassy carbon disc (1.8 mm^2 area) and platinum wire was used as counter electrode. The working electrode used in controlled-potential coulometry and preparative electrolysis was an assembly of four carbon rods (31 cm^2 from KIGCO, Mashhad, Iran) and large platinum gauze (35 cm^2 area) constitute the counter electrode placed as single rods in the edges of a square with a distance of 3 cm. The electrochemical oxidations were performed under controlled-potential and constant current conditions in one compartments cell equipped with a magnetic stirrer (see Supporting Information). The working electrode potentials were measured versus Ag/AgCl 3M Cl^- (all electrodes from AZAR electrode). All experiment was carried out at a temperature of 25 ± 1 °C. 2-Aminodiphenylamine (**2ADPA**), sulfinic acids (**1a**-**1d**), phosphate salts and ethanol were obtained from commercial sources. These chemicals were used without further purification. The glassy carbon electrode was polished using alumina slurry (from Iran Alumina Co.). Melting points were measured with an Electrothermal 9100 apparatus (Rochford, UK). IR spectra (KBr) were recorded on Perkin–Elmer GX FT-IR spectrometer. NMR spectra were recorded with a Bruker DRX-500, 400 AVANCE (Rheinstetten, Germany) instruments (500, 400 MHz for ^1H and 125, 100 MHz for ^{13}C). Chemical shifts are given in ppm (δ) relative to internal TMS, and coupling constants, *J,* are reported in Hz. Mass spectra were recorded with an Agilent-5975C inert XL MSD mass spectrometer (USA) operating at an ionization potential of 70 eV. X-ray data for **3c** (CCDC 1407863) was collected on a STOE IPDS-II diffractometer with graphite monochromated Mo-Kα radiation. For **3c**, a blue crystal was chosen using a polarizing microscope and mounted on a glass fibre which is used for data collection. Data was collected at a temperature of 298(2) K in a series of ω scans in 1° oscillations and integrated using the Stöe X-AREA[28] software package. The numerical absorption correction was applied using the X-RED[29] and X-SHAPE[30] software packages. The data was corrected for Lorentz and Polarizing effects. The structures were solved by direct methods using SIR2004.[31] The non-hydrogen atoms were refined anisotropically by the full-matrix least-squares method on F^2 using SHELXL.[32] The hydrogen atoms of the –NH and NH_2 groups were found in difference Fourier maps and refined isotropically. Other hydrogen atoms were added at ideal positions and constrained to ride on their parent atoms. The Flack parameter 0.35(4) means that the absolute structure could not be confirmed. For more information about structure of **3c** please see Supporting Information.

General electrochemical procedure

In a typical procedure, a water (phosphate buffer, *c* = 0.2 M, pH = 2.0)/ethanol (70/30, v/v) mixture (*ca*. 100 ml), containing **2ADPA** (0.25 mmol) and **1** (0.25 mmol), was electrolyzed in an undivided cell at 0.53 V vs Ag/AgCl 3M Cl^-, equipped with a carbon anode and a large platinum gauze cathode at 25 °C (see Supporting Information). The electrolysis was terminated when the decay of the current became more than 95%. At the end of electrolysis, the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration, washed copiously with distilled water, recrystallized from diethyl ether. It should be noted that, the supporting electrolyte can be recycled and reused.[33] For this purpose after separation of precipitate, duo to removing the trace organic materials including substrates and by-products, the extraction method was used with ethylacetate. The aqueous phase can be reused in subsequent reactions. The products were characterized by their physical, crystallographic and spectroscopic data.

1-N-phenyl-4-(phenylsulfonyl)benzene-1,2-diamine ($C_{18}H_{16}N_2O_2S$) (**3a**). Isolated yield: 80%. mp 160-162 °C; FT-IR (KBr) (cm^{-1}): 3440, 3390 and 3351 (medium, stretching NH_2 and NH), 1590, 1508 (medium, stretching C=C), 1294 (strong, stretching aromatic C–N and S=O), 1151 (strong, stretching S=O); ^1H NMR, δ ppm (500 MHz, $CDCl_3$): 3.73 (s, 2H, NH_2, disappeared by addition of D_2O), 5.61 (s, 1H, NH, disappeared by addition of D_2O), 6.94 (d, 2H, *J* = 7.5 Hz, Ar-H), 6.99 (t, 1H, *J* = 8.5 Hz, Ar-H), 7.17 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.27-7.33 (m, 4H, Ar-H), 7.46-7.54 (m, 3H, Ar-H), 7.91 (s, 2H, Ar-H); ^{13}C NMR, δ ppm (125 MHz, $CDCl_3$): 115.9, 118.1, 119.3, 120.3, 122.5, 127.7, 129.6, 129.9, 133.2, 134.2, 136.9, 138.3, 142.3, 142.9; Anal. Calcd for $C_{18}H_{16}N_2O_2S$ (324.09): C, 66.64; H, 4.97; N, 8.64; O, 9.86; S, 9.88. Found: C, 66.69; H, 4.99; N, 8.69; O, 9.90; S, 9.93. MS (EI) *m/z* (%): 324 (100).

1-N-Phenyl-4-tosylbenzene-1,2-diamine ($C_{19}H_{18}N_2O_2S$) (**3b**). Isolated yield: 85%. mp 136-138 °C; FT-IR (KBr) (cm^{-1}): 3444, 3392 and 3353 (medium, stretching NH_2 and NH), 1589 and 1508 (medium, stretching C=C), 1297 (strong, stretching aromatic C–N and S=O), 1149 (strong, stretching S=O); ^1H NMR, δ ppm (500 MHz, $CDCl_3$): 2.37 (s, 3H, CH_3), 3.77 (s, 2H, NH_2, disappeared by addition of D_2O), 5.61 (s, 1H, NH, disappeared by addition of D_2O), 6.94 (d, 2H, *J* = 7.5 Hz, Ar-H), 6.98 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.16 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.27-7.31 (m, 6H, Ar-H), 7.78 (d, 2H, *J* = 8.0 Hz, Ar-H); ^{13}C NMR, δ ppm (125 MHz, $CDCl_3$): 21.9 (CH_3), 115.7, 118.3, 119.1, 120.1, 122.4, 127.8, 129.9, 130.2, 134.8, 136.6, 138.5, 139.9, 142.4, 144.1; Anal. Calcd for $C_{19}H_{18}N_2O_2S$ (338.11): C, 67.43; H, 5.36; N, 8.28; O, 9.46; S, 9.47. Found: C, 67.49; H, 5.41; N, 8.30; O, 9.49; S, 9.51; MS (EI) *m/z* (%): 338 (100).

4-((4-Chlorophenyl)sulfonyl)-1-N-phenylbenzene-1,2-diamine ($C_{18}H_{15}ClN_2O_2S$) (**3c**). Isolated yield: 78%. mp 135-136 °C; FT-IR (KBr) (cm^{-1}): 3428 and 3353 (medium, N–H), 1590 and 1496 (medium, C=C), 1315 (strong, stretching aromatic C–N), 1301 and 1149 (strong, stretching S=O), 758 (strong, stretching C-Cl); ^1H NMR, δ ppm (400 MHz, DMSO-d_6): 5.38 (s, 2H, NH_2, disappeared by addition of D_2O), 6.92 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.05 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.08 (dd, 1H, *J* = 8.5 Hz, J_{meta} = 2.0 Hz, Ar-H), 7.14 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.22 (d, 1H, J_{meta} = 2.0 Hz, Ar-H), 7.27 (t, 2H, *J* = 7.6 Hz, Ar-H), 7.59 (s, 1H, NH, disappeared by the addition of D_2O), 7.69 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.86 (d, 2H, *J* = 8.8 Hz, Ar-H); ^{13}C NMR, δ ppm (100 MHz, DMSO-d_6): 113.1, 115.8, 117.1, 119.1, 121.5, 129.1, 129.7, 130.1, 131.4, 135.3, 138.4, 139.6, 142.0, 142.8; Anal. Calcd for $C_{18}H_{15}ClN_2O_2S$ (358.05): C, 60.25; H, 4.21; N, 7.81; O, 8.92; S, 8.94. Found: C, 60.31; H, 4.27; N, 7.86; O, 8.96; S, 8.98; MS (EI) *m/z* (%): 358 (100, M^+), 360 [33, (M^+ + 2)].

1-N-phenyl-4-(methylsulfonyl)benzene-1,2-diamine (*C*$_{13}H_{14}N_2O_2S$) (**3d**). Isolated yield: 80%. mp 137-139 °C; FT-IR (KBr) (cm^{-1}): 3337, and 3357 (medium, stretching NH_2 and NH), 2925 (medium, stretching C-H aliphatic) 1591, 1511 (medium, stretching

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C=C), 1295 (stretching aromatic C–N and S=O) 1137 (strong, stretching S=O); ^{1}H NMR, δ ppm (500 MHz, $CDCl_3$): 3.05 (s, 3H, CH_3), 3.53 (s, 2H, NH_2, disappeared by addition of D_2O), 5.66 (s, 1H, NH, disappeared by addition of D_2O), 7.01-7.05 (m, 3H, Ar-H), 7.24-7.35 (m, 5H, Ar-H); ^{13}C NMR, δ ppm (125 MHz, $CDCl_3$): 44.8 (CH_3), 115.2, 115.8, 117.9, 118.8, 119.4, 122.2, 129.6, 136.7, 137.9, 141.9; Anal. Calcd for $C_{13}H_{14}N_2O_2S$ (262.08): C, 59.52; H, 5.38; N, 10.68; O, 12.20; S, 12.22. Found: C, 59.58; H, 5.42; N, 10.63; O, 12.17; S, 12.25. MS (EI) *m/z* (%): 262 (100).

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Electrochemical Synthesis of *N*-phenyl-4-(arylsulfonyl)benzene-1,2-diamine Derivatives. A Mild and Regioselective Protocol

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Graphical Abstract

Regioselective synthesis of *1*-*N*-phenyl-4-(arylsulfonyl)benzene-1,2-diamine derivatives was carried out by electrochemical oxidation of 2-aminodiphenylamine in aqueous solution in the presence of some sulfinic acids as nucleophiles.