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Chemical and electrochemical oxidative coupling of *N,N*-dialkyl-*p*-phenylenediamines and arylsulfinic acids. Synthesis of sulfonamide derivatives

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ABSTRACT

Electrochemical and chemical oxidation of *N,N*-dialkyl-*p*-phenylenediamines have been studied in the presence of arylsulfinic acids as nucleophiles in aqueous solutions for the synthesis of sulfonamide derivatives. The results indicate that the electrochemically or chemically generated quinone-diimines participate in Michael-type addition reactions with arylsulfinic acids and are converted into the corresponding sulfonamide derivatives.

1. Introduction

The development of efficient, simple, and straightforward chemical and electrochemical processes for the synthesis of widely used organic compounds from readily available reagents are major challenges for chemists in organic synthesis. Sulfonamide derivatives are of considerable interest and have been used extensively as antibacterial,[1] anti-carbonic anhydrase,[2] diuretic[3] and hypoglycemic reagents,[4] and as pharmaceutical agents for the treatment of different diseases such as infections,[5] Alzheimer's disease,[6] HIV,[7] and cancer.[8] Besides clinical uses, a number of sulfonamides have been synthesized and employed in various organic transformations, for example as organocatalysts for Michael and aldol reactions[9] and as chelate extraction reagents for divalent metal cations.[10]

A literature survey revealed that only our previous Letter has reported an electrochemical synthesis of sulfonamides,[11] but in the vast number of chemical methods reported for the synthesis of sulfonamides, various catalysts and harsh conditions have been used.[1,12–14] Consequently, there is an opportunity for further development toward mild conditions, increased variation of the substituents in the substrates and improved yields. Based on our own experience in the synthesis of organic compounds via electrochemical routes,[15–18] and our previous study on the synthesis of sulfonamide derivatives,[11] and following the valuable works of Compton et al. on the electrochemical oxidation of *N,N*-dialkyl-*p*-phenylenediamines and subsequent 1,4-Michael addition,[19–25] herein we describe convenient chemical and electrochemical methods for the synthesis of sulfonamides by oxidation of *N,N*-dialkyl-*p*-phenylenediamines in the presence of arylsulfinic acids. This work has led to the development of facile and environmentally friendly electrochemical and chemical methods for the synthesis of sulfonamides.

We performed the electrochemical oxidation of *N,N*-dialkyl-*p*-phenylenediamines **1a,b** in the presence of 4-chlorobenzenesulfinic acid (**3a**) and the chemical oxidation of *N,N*-dialkyl-*p*-phenylenediamines **1a,b** in the presence of arylsulfinic acids **3a–c** in aqueous solution using potassium ferricyanide as the oxidizing agent.

2. Results and discussions

A cyclic voltammogram of a 1.0 mM solution of *N,N*-diethyl-*p*-phenylenediamine (**1a**) in aqueous solution containing 0.2 M phosphate buffer, pH 7.5, is shown in Figure 1, curve a. One anodic peak (A_1) and the corresponding cathodic peak (C_1) were evident, which correspond to the transformation of **1a** into the quinone-diimine **2a** and vice versa within a two-electron process (Scheme 1).[11,16,19–25]

In the presence of 1.0 mM 4-chlorobenzenesulfinic acid (**3a**), the cathodic peak (C_1) decreased and a new anodic peak (A_2) appeared at a more positive potential (Fig. 1, curve b). This indicated the reactivity of the electrochemically generated quinone-diimine

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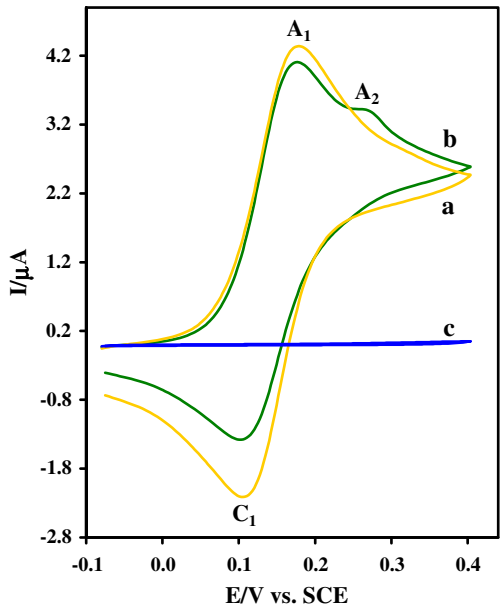


Figure 1. Cyclic voltammograms of 1.0 mM *N,N*-diethyl-*p*-phenylenediamine (**1a**): (a) in the absence, (b) in the presence of 1.0 mM 4-chlorobenzenesulfinic acid (**3a**) and, (c) 1.0 mM **3a** in the absence of **1a**, at a glassy carbon electrode, in aqueous solution containing 0.2 M phosphate buffer (pH 7.5). Scan rate: 10 mV s^{-1}.

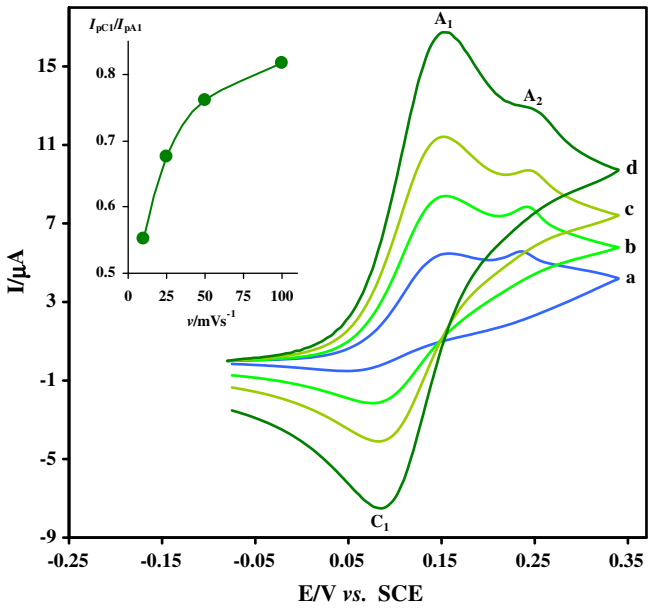
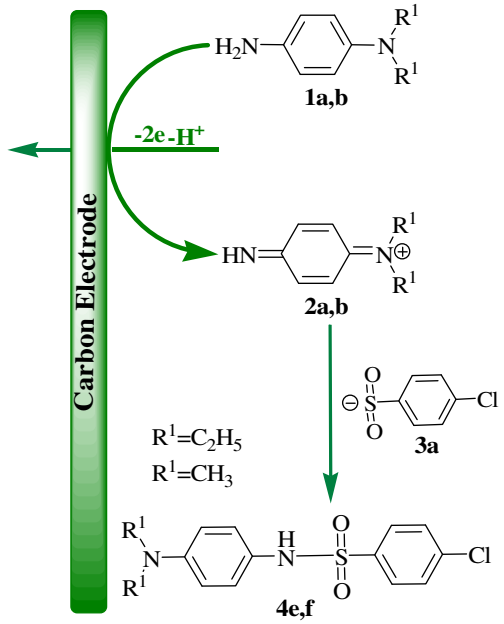


Figure 2. Typical cyclic voltammograms of 1.0 mM *N,N*-diethyl-*p*-phenylenediamine (**1a**) in the presence of 3.0 mM 4-chlorobenzenesulfinic acid at a glassy carbon electrode, in aqueous solution containing 0.2 M phosphate buffer (pH 7.5). Scan rates from (a) to (d) are 10, 25, 50, and 100 mV s^{-1}, respectively. Inset: variation of peak current ratio (I_{pC1}/I_{pA1}) versus scan rate.



Scheme 1. Electrochemical oxidation of **1a** and **1b** in the presence of 4-chlorobenzenesulfinic acid (**3a**).

2a toward **3a**. Additional voltammetric studies were performed by varying the potential scan rate. Figure 2 shows the cyclic voltammograms of *N,N*-diethyl-*p*-phenylenediamine (**1a**) in the presence of **3a** at various scan rates. The voltammograms show that proportional to the augmentation of the potential sweep rate, the peak current ratio (I_{pC1}/I_{pA1}) increases and the current of peak A_2 decreased. Furthermore, the current function for peak A_1, ($I_{pA1}/v^{1/2}$) changes only slightly with increasing scan rate.

Controlled-potential coulometry was performed in aqueous solution containing 0.1 mmol of **1a** and 0.1 mmol of **3a** at 0.20 V versus the SCE. The electrolysis progress was monitored using cyclic voltammetry (Fig. 3). It was shown that, in proportion to the progress of the coulometry, the anodic peaks (A_1 and A_2) decrease. All the anodic and cathodic peaks disappeared when the charge consumption became about $2e^-$ per molecule of **1a**.

These observations allow us to propose the pathway outlined in Scheme 1 for the electrooxidation of **1a** in the presence of **3a**. Generation of quinone-diimine **2a** is followed by a Michael-type addition reaction of **3a** to quinone-diimine **2a**, producing sulfonamide

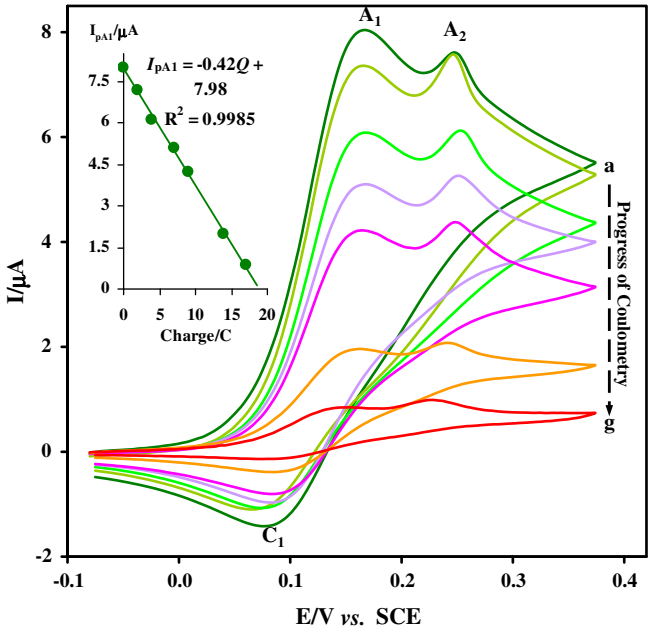


Figure 3. Cyclic voltammograms of 0.1 mmol *N,N*-diethyl-*p*-phenylenediamine (**1a**) in the presence of 0.1 mmol 4-chlorobenzenesulfinic acid (**3a**) during controlled potential coulometry at 0.20 V versus the SCE after consumption of (a) 0, (b) 2, (c) 4, (d) 7, (e) 9, (f) 14, and (g) 17 C. Inset: variation of anodic peak current (I_{pA1}) versus charge consumed. Scan rate: 20 mV s^{-1}.

4e as the final product. Oxidation of **4e** is more difficult than oxidation of the parent starting molecule **1a** by virtue of the presence of the electron-withdrawing *p*-tolylsulfonyl group as well as by the insolubility of **4e** in the phosphate buffer (pH 7.5) solution.

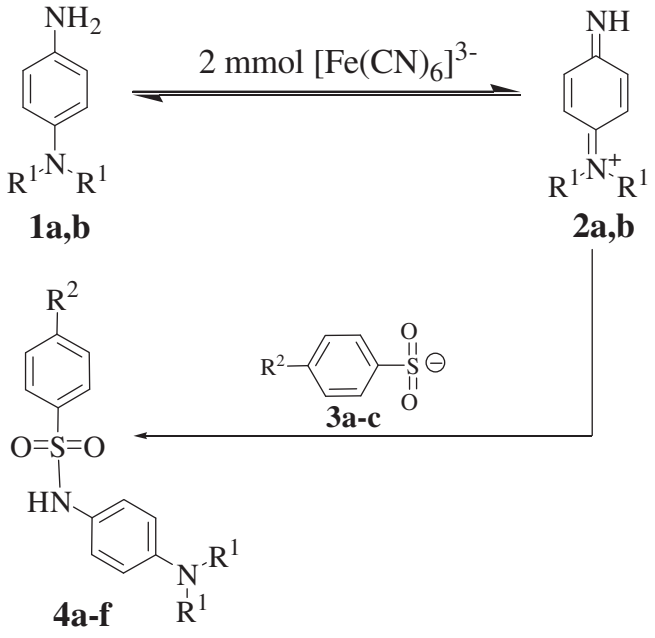
According to our results, the anodic peaks of the voltammograms presented in Figure 1 (A_1 and A_2) pertain to the oxidation of *N,N*-diethyl-*p*-phenylenediamine (**1a**) and sulfonamide **4e**, respectively. Obviously, the cathodic peak C_1 corresponds to the reduction of quinone-diimine **2a**. Similar results were obtained for the electrochemical oxidation of *N,N*-dimethyl-*p*-phenylenediamine (**1b**) in the presence of **3a**.

In chemical oxidation, a suitable oxidizing agent is one that only oxidizes *N,N*-dialkyl-*p*-phenylenediamines **1a,b** to the quinone-diimines without any side effects on the arylsulfinic acids **3a–c**. Potassium ferricyanide is a stable, easily handled and commercially available oxidizing agent. Recently, we demonstrated the suitability of potassium ferricyanide with an oxidation potential of 0.24 V versus a SCE, for the oxidation of catechols.[26,27] Several aqueous media with different pHs were investigated during the course of this study. The best results were achieved using an aqueous phosphate buffer (pH 7.5). When *N,N*-dialkyl-*p*-phenylenediamines (**1a,b**) were treated with potassium ferricyanide in the presence of arylsulfinic acids **3a–c** in an aqueous solution containing 0.2 M phosphate buffer (pH 7.5), sulfonamides **4a–f** were obtained in good yields (Scheme 2, Table 1).

As shown in Table 1, treatment of *N,N*-dialkyl-*p*-phenylenediamines **1a,b** and arylsulfinic acids **3a–c** in the presence of potassium ferricyanide afforded the corresponding sulfonamide derivatives in good yields.

3. Electrochemical syntheses of 4e and 4f[18]

An aqueous solution of phosphate buffer (70 ml) (pH 7.5, c = 0.2 M) containing 1.0 mmol of *N,N*-diethyl-*p*-phenylenediamine (**1a**) [or *N,N*-dimethyl-*p*-phenylenediamine (**1b**)] and 1.0 mmol of 4-chlorobenzenesulfinic acid (**3a**) was electrolyzed at 0.20 V versus the SCE, in an undivided cell equipped with a carbon rod as the anode and a stainless steel cathode. The electrolysis was terminated when the current decay became greater than 95%. The oxidation was interrupted during electrolysis and the carbon anode was washed in acetone in order to reactivate it. On completion of electrolysis, the cell was placed in a refrigerator overnight. The solid which precipitated was collected by filtration and was washed with H_2O. The products were purified by column chromatography [silica gel, EtOAc/*n*-hexane (40/60) for **4e** and (75/25) for **4f**]. The isolated yields of products **4e** and **4f** were 75% and 78%, respectively. All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS.



Scheme 2. Chemical oxidation of **1a,b** in the presence of **3a–c**.

Table 1
Synthesis of sulfonamide derivatives **4a–f** via chemical oxidation

Entry	Product	R^1	R^2	Time (min)	Mp (°C)	Isolated yield (%)
1	**4a**	C_2H_5	CH_3	15	154–156	92
2	**4b**	C_2H_5	H	15	122–124	88
3	**4c**	CH_3	CH_3	35	147–149	75
4	**4d**	CH_3	H	30	136–137	78
5	**4e**	C_2H_5	Cl	25	148–150	85
6	**4f**	CH_3	Cl	35	112–114	80

4. Chemical synthesis of 4a–f

To a vigorously stirred solution of a phosphate buffer (pH 7.5, c 0.2 M) was added a solution of *N,N*-dialkyl-*p*-phenylenediamines **1a,b** (1.0 mmol) and arylsulfinic acid **3a–c** (1.0 mmol). A solution of potassium ferricyanide (2.0 mmol) (40 ml) was added dropwise over a period of 15–35 min. The reaction mixture became dark in color and precipitates were formed. At the end of the reaction, the mixture was placed in a refrigerator overnight. The solid materials were collected by filtration. Products **4a** and **4b** were washed with H_2O and recrystallized from acetone/*n*-hexane. The other products were purified by column chromatography [silica gel, EtOAc/*n*-hexane (40/60) for **4e**, (75/25) for **4f** and (35/65) for **4c** and **4d**]. The products were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS.

5. Characterization data[11]

5.1. 4-Chloro-*N*-[4(diethylamino)phenyl]benzenesulfonamide ($C_{16}H_{19}ClN_2O_2S$) (4e)

Mp 148–150 °C. IR (KBr): 3236, 2974, 1611, 1517, 1399, 1334, 1267, 1157 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.2 (t, 6H, J = 7), 3.3 (q, 4H, J = 7), 6.5 (d, 2H, J = 8), 6.7 (d, 2H, J = 9), 7.4 (d, 2H, J = 8), 7.7 (d, 2H, J = 9). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 12.4, 44.3, 112.0, 123.5, 126.5, 128.9, 138.1, 138.7, 146.7. MS (EI): *m/z* (relative intensity); 338 ($M^{+\cdot}$) (5), 175 (22), 163 (100), 133 (55), 119 (90), 111 (87), 91 (55), 75 (85), 50 (42), 29 (53), 27 (50).

5.2. 4-Chloro-*N*-[4(dimethylamino)phenyl]benzenesulfonamide ($C_{14}H_{15}ClN_2O_2S$) (4f)

Mp 112–114 °C. IR (KBr): 3258, 2796, 1611, 1519, 1476, 1397, 1335, 1227, 1161, 1092 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.9 (s, 6H), 6.6 (d, 2H, J = 8), 6.8 (d, 2H, J = 7), 7.4 (d, 2H, J = 8), 7.6 (d, 2H, J = 7). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 40.4, 112.8, 124.6, 125.9, 128.9, 138.1, 138.9, 149.4 ppm. MS (EI): *m/z* (relative intensity); 310 ($M^{+\cdot}$) (2), 163 (18), 135 (100), 119 (52), 111 (47), 75 (38), 65 (32), 50 (32), 42 (28), 41 (23), 18 (17).

In conclusion, we have described facile, convenient and versatile protocols for the electrochemical and chemical syntheses of sulfonamides using commercially available starting materials in aqueous solution. Mild reaction conditions, short reaction times and good to excellent yields are attractive features of the procedures. We believe that the experimental simplicity and use of

water as an environmentally friendly solvent give these procedures great potential.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.014.

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