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Electrochemical generation of Michael acceptor: A green method for the synthesis of 4-amino-3-(phenylsulfonyl)diphenylamine derivatives†

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Electrochemical oxidation of 4-aminodiphenylamine in aqueous solution and in the presence of some aryl sulfinic acids as nucleophiles was studied and its reaction mechanism was discussed. Using the voltammetric data, a one-pot and environmentally friendly electrochemical approach for the synthesis of 4-amino-3-(phenyl sulfonyl)diphenylamine derivatives via the Michael type addition reaction of anodically generated N-phenylquinonediimine with aryl sulfinic acids, at a carbon electrode, without toxic reagents and solvents is reported.

Introduction

Arylsulfone compounds are widely used as building blocks for some drugs, such as Laropiprant and Vioxx. They have also been shown to have antibacterial, antifungal and antitumor properties.1,2 On the other hand, diphenylsulfone compounds were found to exhibit anti-bacterial activity.3 The incorporation of a diphenylsulfone moiety into some heterocyclic compounds was found to increase their biological activity.7 For example, diphenylsulfone is used for the synthesis of dapsone (4,4-diaminodiphenylsulfone) (Figure 1) which is a bacteriostatic drug that inhibits dihydrofolic acid synthesis by competition with para-aminobenzoic acid.5 It was also shown that, dapsone has anti-inflammatory and bacteriostatic properties comparable with those of nonsteroidal anti-inflammatory drugs.5,7 In addition, it can inhibit cellular adhesion, chemotaxis, and the expression of prostaglandin, leukotrienes, IL-8, TNFα.8

The most common methods for the synthesis of sulfone derivatives are the sulfonation of amines using aryl sulfonyl halides, the oxidation of sulfides or aryl sulfonic acids in the presence of a strong acid catalyst.9-11 Major disadvantage of these methods is an incompatibility with numerous functional groups.12 Our interest in the design and electrochemical synthesis of new compounds with medicinal activity13-16 prompted us to synthesize new molecules similar to dapsone under mild and ambient condition. Herein we investigated the electrochemical oxidation of 4-aminodiphenylamine (4-APA) in the presence of sulfinic acid sodium salts as nucleophiles and showed that the anodically generated N-phenylquinonediimine as a Michael acceptor reacts with sulfinic acids. In this work, we have discovered an easy and one-pot electrochemical method for the synthesis of new 4-amino-3-(phenylsulfonyl) diphenylamine derivatives in the high yield and purity, using an environmentally friendly method with high atom economy. Atom economy is defined as the percentage of reactants that go into final products. From green chemistry and waste management viewpoints, this method also minimizes metallic catalyst consumption as a great pollutant and on the other hand, catalyst recycling cost decreases particularly.17

Results and discussion

pH studies

Cyclic voltammetry of 4-APA in aqueous perchloric acid solution (pH = 1.0, c = 0.2 M) is shown in Figure 2, curve d. The voltammogram showed one anodic peak (A1) at 0.42 V due to the oxidation of 4-APA to N-phenylquinonediimine (N-PQD) and one cathodic peak (C1) at 0.38 V during the reverse scan due to the reduction of N-PQD to 4-APA (Scheme 1). Under these conditions, the peak current ratio (Ipc1/Ipa1) is independent of scan rate and equal to unity which can be considered as a criterion for the stability of electrogenerated N-PQD under the experimental conditions. In other words, any side reactions, such as hydroxylation,18 dimerization,19,20
oxidative ring cleavage\textsuperscript{21} or hydrolysis\textsuperscript{22,23} on electrochemically generated \textit{N-PQD} are too slow to be observed at the time scale of cyclic voltammetry.

\begin{align*}
E_{1/2} = E_{1/2} - (2.303 \text{ mRT/2F}) \text{ pH}
\end{align*}

where \textit{m} is the number of protons involved 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 \(\{(E_{pA1} + E_{pC1})/2\}\). The values of \(E_{1/2}\) as a function of solution’s pH are plotted in Fig. 3. As can be seen, \(E_{1/2}\) was shifted to negative potentials with the slope of about 50 mV/pH (\(E_{1/2} = -0.050\text{pH} + 0.45\)) which is in agreement with the theoretical slope (2.303\text{mRT/2F}) of 59 mV/pH with \(m\) about 2. This shows that the same numbers of electrons and protons\textsuperscript{21-24} are involved in the redox processes, at pH value between 0-11. On the basis of the reported \(pK_a\) values of primary and secondary amine moieties of \textit{4-APA} (5.15 and \(\approx\) 0.8, respectively) (Scheme 2),\textsuperscript{24} we can conclude Scheme 1 for the electrochemical oxidation of \textit{4-APA} in the pH range 0-11.

The presence of the same numbers of electrons and protons in the redox processes in pHs less than 5.15 (Scheme 1), shows that the oxidation products are in protonated forms.\textsuperscript{24} In pH values less than 0.8, the high acidity of solution may be responsible for the generation of diprotonated quinoid form (\textit{N-DPQH}) during the oxidation of \textit{4-APA}. Bergamini et al reported that \(pK_a\) of \textit{N-DPQH} is about 5.6 (very close to the \(pK_a\) for \textit{4-APA}).\textsuperscript{24} So, we can assert therefore that the similarity of the basicity of \textit{4-APA} and \textit{N-PQD} can be responsible for the two-electron/two-proton process in 0.8 < pHs < 5.15.

\begin{align*}
\text{Mechanistic studies}
\end{align*}

The electrochemical oxidation of \textit{4-APA} in the presence of 4-toluenesulfonic acid (\textit{1a}) was also studied in the pH range 2-9 (Figure 4, curves b). A comparison of voltammogram of \textit{4-APA} in the absence of \textit{1a} with that in the absence of \textit{1a} at pH 2.0 shows that: (a) a new redox couple (\textit{A3/C3}) appears at more positive potentials; (b) the anodic peak \(A_1\) current (\(I_{pA1}\))
increases slightly and its potential shifts to less positive values and (c) in the reverse scan, the cathodic peak C1 nearly disappears. These observations indicate that a chemical reaction follows the electron transfer process: N-PQD formed at the surface of the electrode by the two-electron oxidation of 4-APA is consumed in a reaction with 1a. In this Fig. curve c, is cyclic voltammogram of 1a.

This is further confirmed by the effect of the scan rate and of the concentration of 1a on the cyclic voltammogram of 4-APA in the presence of 1a. Our data shows that, \( I_{pA1} \) increases with respect of that of peak A2 upon increasing the scan rate as does the current of peak C1 (\( I_{pC1} \)) (Figure 5). Such increase at faster scan rates is related to a decrease of the experimental time scale. A faster scan rate results in a lesser amount of N-PQD reacting with 1a, hence the observe increase of the peak current ratio (\( I_{pC1}/I_{pA1} \)). Figure 5 also shows that \( E_{pA1} \) shifts to positive potentials with increasing potential scan rate. Because of the following reaction, \( E_{pA1} \) is less positive than \( E_{pC1} \) in the absence of 1a (Fig. 4). However, it shifts in a positive direction (toward the unperturbed curve) with increasing \( v \) (Figure 5).

In addition, upon the increasing of the concentration of 1a, \( I_{pA2} \) and \( I_{pC2} \) increase, and \( I_{pC1} \) decreases. Peak A2 is due to the oxidation of adduct formed by the reaction of N-PQD with 1a. The higher the concentration of 1a, the faster is its reaction with N-PQD, the lesser is the amount of N-PQD be reduced (peak C1).

Contrary to pH 2.0, the cyclic voltammograms of 4-APA in the presence of 1a (curves b) in pH values 5.0, 7.0 and 9.0, do not show any sign of reactivity of N-PQD toward 1a in the time scale of our experiments. A plot of peak current ratio (\( I_{pA1}/I_{pC1} \)) in the absence (curves a) and presence of 1a (curves b) in pH values 2-9 is shown in Fig. 4, inset. It was found that the change of pH has only a great influence on the peak current ratio (\( I_{pC1}/I_{pA1} \)) in the presence of 1a in pH 2.0. Since, in cyclic voltammetry, the peak current ratio is a measure of homogeneous reaction rate or reactivity of N-PQD formed at the surface of the electrode with 1a. In this study, a solution with pH 2.0 has been selected as a suitable medium for the electrochemical synthesis.

Controlled-potential coulometry was performed in an aqueous phosphate buffer (pH = 2.0, \( c = 0.2 \) M) solution containing 4-APA (0.25 mmol) and 1a (0.25 mmol) at 0.30 V vs. Ag/AgCl. The electrolysis progress was monitored using cyclic voltammetry (Figure 6). As shown, the following changes: a) decrease in the anodic peak current A1, b) increase in the anodic peak current A2 and c) disappearance of peak A1 after consumption of about 2e\(^{-} \) per molecule of 4-APA, are observed in cyclic voltammograms during the advancement of coulometry.

Figure 5. Cyclic voltammograms of 4-APA (1.0 mM) in the presence of 4-toluenesulfinic acid (1a) (1.0 mM) at various scan rates. Scan rates from a) to g) are: 50, 100, 150, 250, 1000, 2500 and 5000 mV s\(^{-1}\), respectively, at glassy carbon electrode in aqueous phosphate buffer (pH = 2.0, \( c = 0.2 \) M). Temperature = 25 ± 1 °C.
The coulometry and voltammetry results, the (1H, 13C) NMR and FTIR data and the molecular mass of 338 of the isolated electrolysis product all point out to N1-phenyl-3-tosylbenzene-1,4-diamine (3a) which would have been formed according to the pathway shown in Scheme 3 (E,Ci mechanism). In proposed mechanism, for simplification the protonation of species are omitted. The first step (E1) is the generation of N-PQD. In the next step, N-PQD would serve as a Michael acceptor in a reaction with 1a to form the final product 3a (C1 step). The oxidation of 3a is more difficult than the oxidation of 4-APA due to the presence of the electron-withdrawing tolylsulfonyl group. Therefore, the oxidation of 3a did not occur during the electrochemical oxidation at the potential of 0.30 V. According to the proposed mechanism, the anodic peak A2 should correspond to the oxidation of 3a to the quinonedimine 3a\textsubscript{ox}. Obviously, the cathodic peak C2 corresponds to the reduction of 3a\textsubscript{ox} to 3a.

The calculated atom economy for the synthesis 3a-3c are 99.41, 99.39 and 99.45%, respectively. The high atom economy indicates that all atoms (except two hydrogen atoms) from the two starting materials are incorporated into the product.

According to Scheme 3, the overall reaction mechanism for electrochemical synthesis of 3a-3c is shown in Scheme 4:

![Scheme 4](image)

The calculated atom economy for the synthesis 3a-3c are 99.41, 99.39 and 99.45%, respectively. The high atom economy indicates that all atoms (except two hydrogen atoms) from the two starting materials are incorporated into the product.

**Figure 6.** Cyclic voltammograms of 4-APA (0.25 mmol) in the presence of 4-toluene sulfonic acid (1a) (0.25 mmol) during controlled potential coulometry at 0.30 V vs. Ag/AgCl (3 M) in aqueous phosphate buffer (pH = 2.0, c = 0.2 M). Scan rate: 100 mV s\textsuperscript{-1}. Temperature \(25 \pm 1^\circ\text{C}\).

% Atom Economy = \(\frac{\text{Mass of atoms in desired product}}{\text{Mass of atoms in reactants}} \times 100\)

Eq. 1

According to Scheme 3, the overall reaction mechanism for electrochemical synthesis of 3a-3c is shown in Scheme 4:

![Scheme 4](image)

The calculated atom economy for the synthesis 3a-3c are 99.41, 99.39 and 99.45\%, respectively. The high atom economy indicates that all atoms (except two hydrogen atoms) from the two starting materials are incorporated into the product.

**Figure 7.** Variation of anodic peak current (\(I_{pa1}\)) versus consumed charge. All data obtained from Fig. 6.

![Figure 7](image)

The calculated atom economy for the synthesis 3a-3c are 99.41, 99.39 and 99.45\%, respectively. The high atom economy indicates that all atoms (except two hydrogen atoms) from the two starting materials are incorporated into the product.

4-APA can be attacked by 1c from sites A or B to yield two types of compounds (3c and 4c) (Scheme 5). However, single-crystal X-ray diffraction analysis of synthesized compound confirms the structure of 3c (Figure 8).

This regioselectivity may presumably be due to the large steric hindrance in the molecule 4c in comparison with 3c. The steric energies have been calculated for 3c and 4c, using MM2 program after minimization of structures (Fig. 9). Results indicate that structure 3c is energetically more stable than the 4c with about 11 kcal/mol lower energy.

![Figure 8](image)

The calculated atom economy for the synthesis 3a-3c are 99.41, 99.39 and 99.45\%, respectively. The high atom economy indicates that all atoms (except two hydrogen atoms) from the two starting materials are incorporated into the product.

**Figure 8.** Single crystal X-ray diffraction analysis of synthesized compound confirms the structure of 3c (Figure 8).

The calculated atom economy for the synthesis 3a-3c are 99.41, 99.39 and 99.45\%, respectively. The high atom economy indicates that all atoms (except two hydrogen atoms) from the two starting materials are incorporated into the product.

**Figure 9.** Single crystal X-ray diffraction analysis of synthesized compound confirms the structure of 3c (Figure 8).
Scheme 5. The structures of possible compounds.

Figure 8. ORTEP view of X-ray crystal structure of 3c.

Figure 9. The results of MM2 calculation for 3c (above) and 4c (below).

In order to investigate the electrochemical properties of the isolated product (3c), its voltammetric behavior was examined. The cyclic voltammogram of saturated solution of 3c in aqueous phosphate buffer (pH = 2.0, c = 0.2 M)/ethanol (90/10 v/v) is shown in Fig. 10. Contrary to 4-APA, in potential scan rate 100 mV s\(^{-1}\), it shows an irreversible feature with one anodic peak (A\(_2\)) at 0.44 V vs. SCE which corresponds to the transformation of 3c to 3c\(_{\text{ox}}\) (Scheme 3). In addition, in comparison with 4-APA, \(E_{pA2}\) is more positive than \(E_{pA1}\). The results were predictable. In general, the attachment of an electron-withdrawing group (EWG) to a molecule, unstable the oxidized form of molecule and arrives it in the fast following chemical reaction(s).\(^{13,27}\) In this case, the presence of arylsulfonyl group with electron withdrawing character in the structure of 3c unstable the electro-generated quinonediimine 3c\(_{\text{ox}}\) and arrives it in the fast following chemical reactions such as hydroxylation,\(^{18}\) dimerization,\(^{19,20}\) oxidative ring cleavage\(^{21}\) and/or hydrolysis.\(^{22,23}\)

The effect of the potential scan rate on the cyclic voltammogram of 3c was also studied (Fig. 11). The obtained data show that with increasing scan rate, the peak current ratio \((I_{pC2}/I_{pA2})\) increase. The time scale of a cyclic voltammetry experiment is determined by the potential scan rate, as increasing the scan rate decreases the experimental time scale and removes the effects of the following chemical reaction(s) appearing as an increase in \(I_{pC2}/I_{pA2}\).

Conclusions

The present method for the synthesis of 4-amino-3-(phenylsulfonyl)diphenylamine derivatives has several advantages over conventional methods. This process is practically convenient to carry out and can be performed at atmospheric pressure and room temperature. Neither catalyst nor organic/inorganic oxidizing agents are necessary and the
reaction can be performed under green and mild condition with high atom economy (>99%). The in situ formation of N-phenylquinodimine is achieved and there is no need to prepare N-phenylquinodimine in advance.

Experimental section

Apparatus and reagents

The working electrode used in macro-scale electrolysis and controlled-potential coulometry was an assembly of four ordinary soft carbon rods (6 mm diameter and 4 cm length), placed as single rods in the edges of a square with a distance of 3 cm, and a large stainless steel cylinder (25 cm² area) constituted the counter electrode. The working electrode used in the cyclic voltammetry experiments was a glassy carbon disc (1.8 mm diameter) and a glass carbon rod was used as the counter electrode. The electrochemistry were performed under controlled-potential condition in a two compartments cell, separated by an ordinary porous glassy diaphragm (a tube with 1.5 cm diameter) and equipped with a magnetic stirrer. 4-APA, aryl sulfonic acids, 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.). More details are described in the previous paper.

Electroorganic synthesis of 3a-3c.

A solution of phosphate buffer (c = 0.2 M, pH = 2.0)/ethanol (50/50 v/v) mixture, containing 4-APA (0.25 mmol) and 1a (1b or 1c) (0.25 mmol), was electrolyzed in a divided cell at 0.30 V vs. Ag/AgCl (3M). The electrolysis was terminated when the decay of 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 and recrystallized from acetone/n-hexane mixture (30/70 v/v).

N1-Phenyl-3-tosylbenzene-1,4-diamine (C15H18N2O2S) (3a)

Isolated yield: 72%. IR (KBr, cm⁻¹): 3429, 3347, 1599, 1514, 1284, 1142, 751, 586. ¹H NMR (400 MHz DMSO-d6): δ 2.36 (s, 3H, methyl), 5.83 (s, 2H, NH₂, disappeared by the addition of D₂O), 6.71 (t, 1H), 6.76 (d, 2H, J = 8.8 Hz), 6.83 (d, 2H, J = 7.6 Hz), 7.12-7.18 (m, 3H), 7.40 (d, 2H, J = 8.4 Hz), 7.44 (d, 1H, J = 2.4 Hz), 7.81 (d, 2H, J = 8.4 Hz), 7.86 (s, 1H, NH, disappeared by the addition of D₂O). ¹³C NMR (100 MHz DMSO-d6): δ 21.5, 115.0, 118.8, 119.0, 119.1, 120.8, 127.2, 128.6, 129.7, 130.3, 132.7, 133.8, 142.3, 144.4, 145.5. MS (EI) m/z (relative intensity): 338 (100), 263 (41), 236 (38), 183 (41), 154 (29), 69 (38).

3-((4-Chlorophenylsulfonyl)-N1-phenylbenzene-1,4-diamine (C18H15ClN2O2S) (3b)

Isolated yield: 70%. IR (KBr, cm⁻¹): 3428, 3353, 2923, 2853, 1631, 1598, 1516, 1486, 1397, 1314, 1146, 1088, 758, 587, 480. ¹H NMR (400 MHz DMSO-d6): δ 5.86 (s, 2H, NH₂, disappeared by the addition of D₂O), 6.72 (t, 1H), 6.79 (d, 2H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.0 Hz), 7.17 (m, 3H), 7.44 (d, 1H, J = 2.4 Hz), 7.68 (dd, 2H, J = 8.8, 2.0 Hz) 7.89 (s, 1H, NH, disappeared by the addition of D₂O), 7.94 (dd, 2H, J = 8.8, 2.0 Hz). ¹³C NMR (100 MHz DMSO-d6): δ 115.1, 118.7, 118.9, 119.3, 119.9, 129.8, 129.1, 129.7, 130.0, 132.9, 138.9, 140.4, 142.5, 145.4. MS (EI) m/z (relative intensity): 358 (21), 324 (14), 252 (100), 195 (43), 171 (64), 135 (75), 85 (86).

N1-phenyl-3-(phenylsulfonyl)benzene-1,4-diamine (C18H16N2O2S) (3c)

Isolated yield: 72%. IR (KBr, cm⁻¹): 3451, 3404, 3366, 1634, 1598, 1505, 1312, 1292, 1142, 1095, 751, 588, 537. ¹H NMR (400 MHz DMSO-d6): δ 5.86 (s, 2H, NH₂, disappeared by the addition of D₂O), 6.72 (t, 1H), 6.78 (d, 1H, J = 8.8 Hz), 6.83 (d, 2H, J = 7.6 Hz), 7.15 (m, 3H), 7.45 (d, 1H, J = 2.4 Hz), 7.61 (t, 2H), 7.69 (t, 1H), 7.88 (s, 1H, NH, disappeared by the addition of D₂O), 7.93 (dd, 2H, J = 8.4, 1.6 Hz). ¹³C NMR (100 MHz DMSO-d6): δ 115.0, 118.8, 119.0, 119.1, 120.4, 127.1, 128.7, 129.7, 132.8, 133.9, 141.7, 142.5, 145.5. MS (EI) m/z (relative intensity): 324 (39), 252 (55), 223 (17), 195 (38), 149 (28), 115 (61), 55(100).

Acknowledgements

We acknowledge the Bu-Ali Sina University Research Council and the Center of Excellence in Development of Environmentally Friendly Methods for Chemical Synthesis (CEDEFMCS) for their support of this work.

Notes and references

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† Electronic Supplementary Information (ESI) available: FT-IR, ¹H NMR and ¹³C NMR spectra of 3a-3c and crystallographic Information data of 3c (CIF). See DOI: 10.1039/c000000x/