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Electrochemical oxidation of aminophenols in the presence of benzenesulfinate

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ABSTRACT

The anodic oxidation of aminophenols and their amino-protected derivatives was investigated by using cyclic voltammetry and preparative electrolysis methods. The results showed that like the catechols the amino-protected aminophenol could also undergo Michael addition, and that the benzenesulfonate group was regioselectively introduced at the *meta*-position of the amino group. In contrast, the expected products were not formed from the oxidation of unprotected aminophenols. Finally, a reaction mechanism is proposed.

1. Introduction

Oxidative dearomatization of *ortho*- and *para*-substituted phenols produces cyclohexadienones, substances that have been widely used in the synthesis of natural products and other materials.[1] Frequently, various oxidizing systems based on heavy metals[2] and organic oxidants[3] have been utilized in their construction. Chemo- and regioselective oxidative dearomatization using less toxic organic oxidants, such as hypervalent iodine reagents (including $PhI(OAc)_2$ and $PhI(OTf)_2$) have received attention recently; these processes occur under mild conditions.[4] For example, *para*-substituted phenols are oxidatively dearomatized using $PhI(OAc)_2$ as the oxidant, combining an amine-catalyzed enantioselective desymmetrizing Michael addition, to form highly functionalized polycyclic molecules.[4d] In addition, *ortho*-substituted phenols were oxidatively dearomatized to produce chiral *o*-benquinol, which was further used in the synthesis of the natural product called biscarvacrol.[4e] The underlying mechanisms for each of these examples involve the in situ formation of cyclohexadienones and a sequent Michael reaction.

Electrochemical oxidation, using the electron as a reagent, provides an alternative approach for the oxidative dearomatization of electron-rich catechols, that frequently follows environmentally benign practices. Tabakovic[5] first reported the electrochemical synthesis of coumestan using an anodic oxidation of catechols. Later, Nematollahi[6] studied the mechanism by cyclic voltammetry and synthesized a variety of polyhydroxylated aromatics. In recent years, our interest in the potential HIV integrase inhibitory activity of polyhydroxylated aromatics has led us to investigate the anodic oxidation of catechols in the presence of *S*-,[7] *C*-mononucleophiles[8] and *C*,*N*-dinucleophiles,[9] leading to the electrochemical synthesis of substituted catechols and fused indole derivatives containing free hydroxyl groups.

Considering that electron rich benzene derivatives, including the *o*-aminophenols and *p*-aminophenols, could possibly form iminocyclohexadienone structures (i.e., analogues of cyclohexadienone)[10] upon oxidative dearomatization, we reasoned that they may undergo Michael addition in a manner analogous to the chemistry observed for catechols. To explore such a hypothesis, we report herein the in situ anodic oxidation of amino-(un)protected aminophenol (**1a**–**d** and **2a**,**b**) in the presence of benzenesulfinate as nucleophiles (Fig. 1). The results indicate that similar reactions do occur for the amino-protected aminophenols.

2. Results and discussion

2.1. Cyclic voltammetric studies

The electrochemical behaviour of aminophenols (**1a**,**b** and **2a**) and their corresponding amino-protected derivatives (**1c**,**d** and **2b**)

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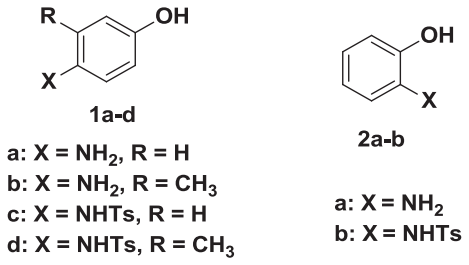


Fig. 1. Structures of starting aminophenols **1a**–**d** and **2a**,**b**.

in the absence and presence of benzenesulfinate was firstly examined by cyclic voltammetry (CV) carried out at room temperature in a mixed solution of acetonitrile and water containing 0.2 M acetate buffer (pH 7.0) as the supporting electrolyte. For comparison, catechol was also investigated. The CV results are summarized in Table 1 and typical CVs are shown in Fig. 2.

Table 1
Oxidation and reduction potentials of aminophenols and catechol[a]

Entry	Compounds	E_p (ox)	E_p (red)
1	**1a**	0.25	0.02
2	**1b**	0.22	−0.01
3	**1c**	0.57	0.13
4	**1d**	0.56	0.11
5	**2a**	0.36, 0.99	—
6	**2b**	0.55	—
7	Catechol	0.48	0.04

[a] Concentration of substrates: 1 mM; electrolyte: 0.2 M acetate buffer solution/acetonitrile (3:1 (v/v), pH 7); working electrode: glassy carbon; reference electrode: Ag/AgCl (3 M); scan rate: 100 mV/s.

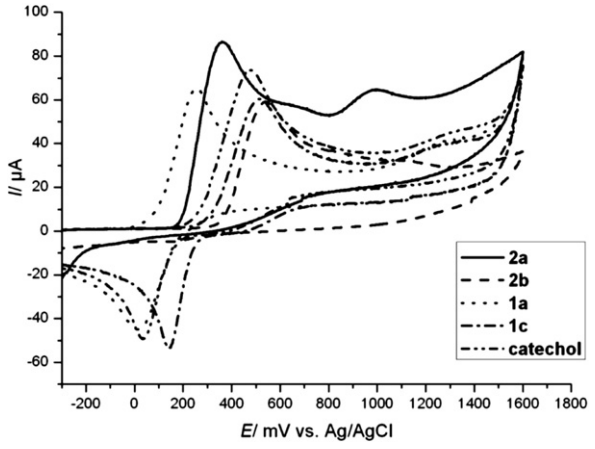


Fig. 2. Cyclic voltammograms of 2 mM of *o*-aminophenol (**2a**), *N*-(2-hydroxyphenyl)-4-methylbenzenesulfonamide (**2b**), *p*-aminophenol (**1a**), *N*-(4-hydroxyphenyl)-4-methylbenzenesulfonamide (**1c**) and catechol at a glassy carbon working electrode, platinum wire counter and Ag/AgCl reference electrodes, in a mixed solution of acetate buffer (0.2 M, pH 7) and acetonitrile (v/v=3:1), scan rate: 100 mV/s.

As shown in Fig. 2, the CV of **1a** exhibits a reversible oxidation wave at 0.25 V versus Ag/AgCl (KCl 3 M) when scanning anodically, and a reduction peak at 0.02 V during the reverse scan. In the case of **1b**, a similar reversible CV was observed; the oxidation and reduction peaks were located at 0.22 V and −0.01 V versus Ag/AgCl. Moreover, the ratio of the current amplitudes for the oxidation and reduction processes, I_p^{ox}/I_p^{red}, was equal to unity indicating that the in situ formed iminocyclohexadienone intermediates are stable under pH 7 acetate buffer, and that the side-reactions, such as hydroxylation or dimerization reactions are too slow to be observed on the time scale of the cyclic voltammetry experiment.[5–9] The amino-protected aminophenols **1c** and **1d** also exhibited reversible electrochemical behaviour. Compared with *p*-aminophenols **1a** and **1b**, the potentials of amino-protected *p*-aminophenols **1c** and **1d** shift positively, with the oxidation peak potential and reduction peak potential at 0.57 V and 0.13 V for **1c** and at 0.56 V and 0.11 V for **1d**, respectively, due to the inductive effect of the tosyl group.

Next, *o*-aminophenols **2a** and **2b** were investigated in the absence of benzenesulfinate; the results indicate that CVs of all *o*-aminophenol derivatives, including *o*-aminophenol (**2a**) and amino-protected *o*-aminophenols **2b** exhibit an irreversible redox couple, a behaviour that is quite different from that of the *p*-aminophenols. As shown in Fig. 2 and Table 1, upon scanning anodically, **2a** exhibits two irreversible oxidation waves at +0.36 V and +0.99 V versus Ag/AgCl (KCl 3 M). Similarly, the irreversible oxidation wave of **2b** is 'centered' at about 0.55 versus Ag/AgCl (KCl 3 M). These results clearly demonstrate that, the in situ generated intermediate from *o*-aminophenols **2a** or **2b** are not stable under the reaction conditions and undergo chemical reaction(s) even on the time scale of CV, regardless of whether the amino group is protected or not.

In addition, for comparison, the CV of catechol was also investigated. Similar to previous reports,[5–7] it gives a reversible oxidation peak at 0.48 V versus Ag/AgCl and a reduction peak at 0.04 V versus Ag/AgCl.

Finally, the electrochemical oxidation of amino-protected aminophenol in the presence of benzenesulfinate was investigated. As shown in Fig. 3 using **1c** as an example, when 1 equiv amount of benzenesulfinate **3a** was added to the solution of **1c**, the voltammogram of the mixture exhibits two anodic peaks A_1 (+0.55 V vs Ag/AgCl) and A_2 (+1.02 V vs Ag/AgCl), whereas the cathodic peak shift to 0.10 V versus Ag/AgCl and its cathodic current decreases dramatically (curve c, Fig. 3). Curve b in Fig. 3 is the CV of benzenesulfinate **3a**, where one irreversible anodic wave at 0.84 V is observed. The behaviour that the cathodic current decreases indicates a chemical reaction occurs between the electrochemically generated iminocyclohexadienone intermediate and benzenesulfinate, and therefore Michael addition products may be formed upon anodic oxidation of a mixture of amino-protected aminophenol and benzenesulfinate when the electrolyzed potential was controlled at the anodic potential of amino-protected aminophenol

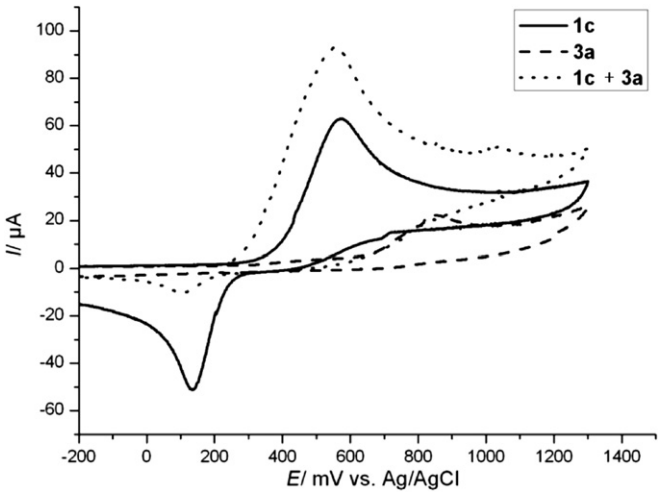


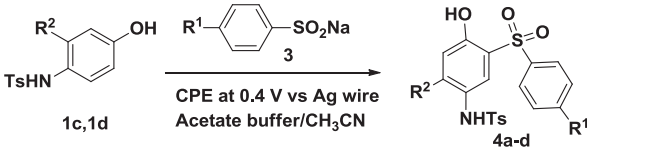
Fig. 3. Cyclic voltammograms of *N*-(4-hydroxyphenyl)-4-methylbenzenesulfonamide (**1c**), 2 mM of sodium benzenesulfinate (**3a**) and a mixture of 2 mM of **1c** and 2 mM of **3a**, at a glassy carbon working electrode, platinum wire counter and Ag/AgCl (3.0 M) reference electrodes, in a mixed solution of acetate buffer (0.2 M, pH 7) and acetonitrile (v/v=3:1), scan rate: 100 mV/s.

(0.55 V vs Ag/AgCl for **1c**), where, undesired oxidation of benzenesulfinate will not take place due to their significantly higher anodic potentials (0.84 V vs 0.55 V).

In a word, the electrochemical behaviour of the *p*-aminophenols, including their derivatives where the amino group is protected, display a reactivity pattern that is similar to catechol, whereas, *o*-aminophenols are quite different and their in situ generated intermediate(s) are less stable than those derived from catechol.

2.2. Electrochemical oxidation of the aminophenols in the presence of sodium benzenesulfonate

After carrying out CV analysis of aminophenols, we then turned our attention to the preparative electrolysis. The amino-protected *p*-aminophenols were firstly subjected to anodic oxidation in the presence of nucleophiles; thus, a solution of an equivalent of *N*-(4-hydroxyphenyl)-4-methylbenzenesulfonamide (**1c**) and sodium benzenesulfinate (**3a**) was electrolyzed at a controlled potential of 0.4 V versus Ag wire (~0.6 V vs Ag/AgCl) (Scheme 1). Due to the



1c: $R^2 = H$
1d: $R^2 = CH_3$

4a: $R^1 = H$, $R^2 = H$ (55%)
4b: $R^1 = CH_3$, $R^2 = H$ (53%)
4c: $R^1 = H$, $R^2 = CH_3$ (66%)
4d: $R^1 = CH_3$, $R^2 = CH_3$ (72%)

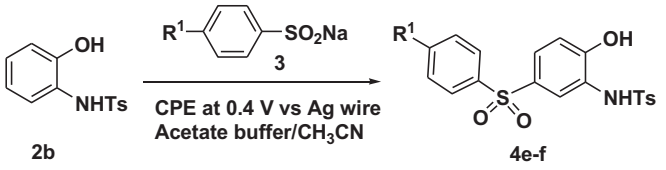
Scheme 1. Anodic oxidation of **1c** and **1d** in the presence of sodium benzenesulfonate **3**.

low solubility of **1c**, acetonitrile was added as a co-solvent. Accordingly, a mixed solvent of acetate buffer solution and acetonitrile (3:1 ratio of acetate buffer to acetonitrile, pH 7) was used as supporting electrolyte. As the electrolysis proceeded, the colour of the anolyte became darker and eventually changed to brown. Precipitation occurred. Meanwhile the current decreased from an initial value of 30 mA to less than 2 mA. After filtration, a white powder was obtained in a 55% yield and was identified to be *N*-[4-hydroxy-5-(phenylsulfonyl)phenyl]benzenesulfonamide (**4a**). The reaction was also carried out using constant current technique; however, a complex mixture was generated when the electrolysis was performed at 10 mA or 20 mA of current. Therefore, the controlled potential technique is preferable for the present case.

Next, the controlled potential electrolysis of **1c** was performed in the presence of **3b**, leading to the formation of adduct **4b** in a 53% yield (Scheme 1). Similarly, a reaction also took place for alkyl-substituted *p*-aminophenol and better yields were obtained in the case of *N*-(4-hydroxy-2-methylphenyl)-4-methylbenzenesulfonamide (**1d**). For example, 66% of **4c** and 72% of **4d** were generated when **3a** and **3b** (respectively) were used as a nucleophile to trap the in situ formed iminocyclohexadienone from **1d**.

To determine the limitation and scope of the anodic oxidation of aminophenols in the presence of sodium benzenesulfonate, we then investigated the anodic oxidation of amino-protected *o*-aminophenol. As shown in Scheme 2, the anodic oxidation of **2b** in the presence of **3** gave **4e** and **4f** in 51% and 56% yields, respectively.

The above results indicate that the iminocyclohexadienones, generated in situ from the oxidative dearomatization of aminophenols **1c**, **1d** and **2b**, systems whose amino groups are protected by a benzenesulfonyl group, do undergo Michael addition with the benzenesulfonate. Based upon these observations, we were interested in determining how the reaction between iminocyclo-



4e: $R^1 = H$ (51%)
4f: $R^1 = CH_3$ (56%)

Scheme 2. Anodic oxidation of **2b** in the presence of sodium benzenesulfonate **3**.

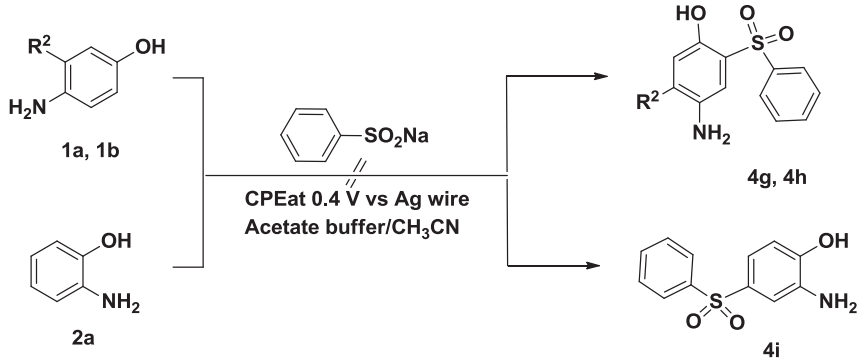
hexadienones and nucleophiles would proceed when the iminocyclohexadienone was generated from *p*-aminophenols (**1a** and **1b**) and *o*-aminophenol (**2a**) wherein the amino group is not protected. Therefore, **1a**, **1b** and **2a** were subjected to oxidation under the conditions used for the oxidation of **1c**; it was observed that the initial current, which was more than 50 mA, soon decreased to less than 5 mA. With the passing of current, polymer formed on the anode surface. After the consumption of starting aminophenols, none of the expected products, **4g**–**i**, were detected by TLC (Scheme 3).

It is noteworthy that structurally, compounds **4** are 1,4-Michael addition products. Note that the benzenesulfinate group is positioned at *meta* to the amino group. In principle, two possible products may be formed from the Michael addition of iminocyclohexadienone due to its asymmetrical structure. Take the reaction of **2b** and **3b** as an example, the in situ formed iminocyclohexadienone may undergo Michael addition to form **4f** and **4f′**. However, the result indicates the exclusive formation of **4f** (Scheme 4). This was demonstrated from the ^{1}H NMR spectrum of reaction product. As shown in Fig. 4, the doublet at 6.88 ppm with coupling constant of 8.4 Hz and the double doublet at 7.47 ppm with coupling constant of 8.4 Hz and 2.4 Hz, comprises an AB system, and the doublet at 6.88 ppm is assigned to the proton signal next to the phenolic hydroxy group of aminophenol unit due to its high field shift. The doublet at 7.64 ppm with coupling constant of 2.4 Hz, is ascribed to be the signal of aromatic proton next to amino group of aminophenol unit; it is spin coupled by the proton at 7.47 ppm (^4J). Therefore, the structure of the product is assigned as **4f**. In contrast, if the structure of the product was **4f′**, the signal of the proton next to the phenolic hydroxy should be doublet situated at high field with a small coupling constant, about 2.4 Hz. The regioselective Michael addition is consistent with a previous literature report.[11]

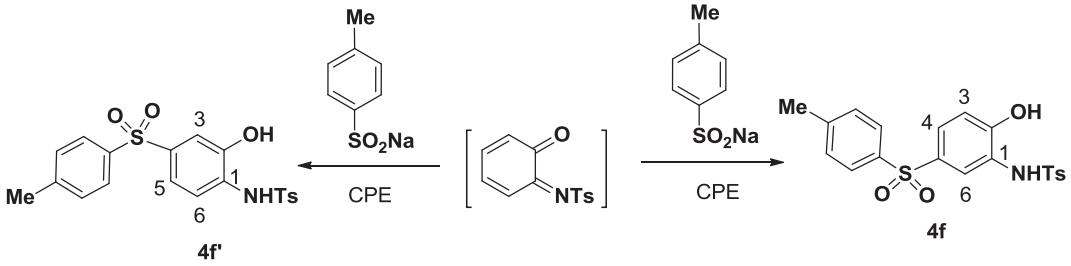
From the mechanistic viewpoint, the formation of compounds **4** can be proposed to arise via an EC mechanism on the basis of the above CV analysis and preparative electrolysis results, as well as related reported results.[6–9] As shown in Scheme 5, the anodic oxidation of aminophenols **1** and **2** in aqueous medium leads to the formation of the corresponding iminocyclohexadienone **5** or **6**.[10] The active intermediate diffuses to the bulk solution and reacts as Michael acceptor with benzenesulfinate to convert to products after aromatization. Since the products have a higher oxidation potential than the starting materials and display low solubility in the supporting electrolyte solution, products **4** precipitate and are formed exclusively.

3. Conclusion

In summary, in order to determine whether the aminophenols undergo reactions similar to catechols, the electrochemical oxidation of aminophenols was studied. It was found that the CVs of *p*-aminophenols **1a** and **1b**, and their amino-protected derivatives (**1c** and **1d**) exhibited similar CVs and gave reversible electrochemical oxidation and reduction waves in the absence of benzenesulfinate, whereas that of *o*-aminophenols (**2a**) and its



Scheme 3. Anodic oxidation of **1a**, **1b** or **2a** in the presence of sodium benzenesulfonate.



Scheme 4. The two possible reaction pathways.

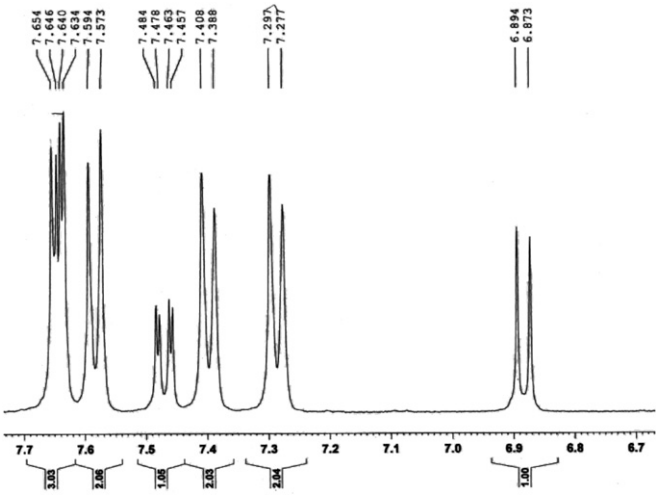


Fig. 4. Partial ^{1}H NMR spectrum of compound **4b**.

amino-protected derivatives shown only an irreversible oxidation wave. These results indicate that under the reaction conditions, the iminocyclohexadienone intermediates from *p*-aminophenols are more stable than those obtained from *o*-aminophenols. Upon preparative scale of electrolysis, polymerization was observed in the cases of the aminophenols themselves. In contrast, Michael addition products were isolated in moderate yields from amino-protected aminophenol derivatives. Based on these results, an EC mechanism was proposed for the formation of compounds **4**.

4. Experimental section

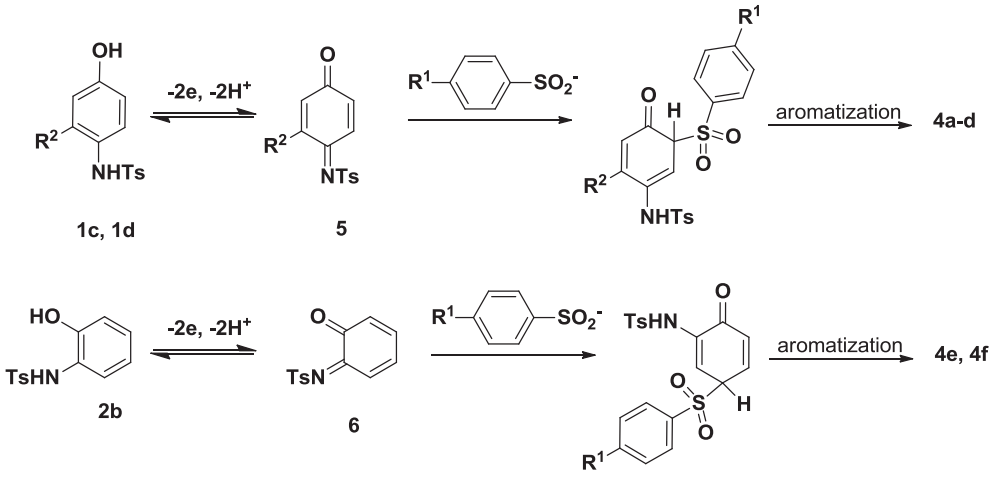
4.1. Instruments and reagents

Cyclic voltammograms were measured by using a 273A Potentiostat/Galvanostat equipped with electrochemical analysis software, using a conventional three-electrode cell. The working electrode was a glassy carbon disk electrode (ca. ϕ=3 mm). The auxiliary and reference electrodes in these studies were Pt and saturated Ag/AgCl, respectively. Glassy carbon was polished with a polishing cloth before each measurement. All electrodes for CV experiments were from CH Instruments, Inc. USA. Acetate buffer was prepared from NaOAc and HOAc, and the pH was monitored using a digital pH meter. The scan rate was 50 mV/s. The concentration of **1**, **2** and **3** was 2 mmol L^{-1}, while that of the supporting electrolyte was 0.2 mol L^{-1}.

For controlled potential coulometry (CPC), an 'H'-type cell, capacity 100 mL, was equipped with a medium glass frit as a membrane. The anode compartment contained an assembly of six graphite rods as the anode, whose upper rims were wrapped by a copper wire, and a polished silver wire as the quasi-reference electrode, immersed in electrolyte solution in a glass cylinder with a fine glass frit at its end. A platinum plate (2 cm^2) served as the counter electrode is immersed in the cathode compartment. The applied potential throughout CPC was 0.6 V versus Ag wire and controlled by the 273A Potentiostat/Galvanostat. During electrolysis, a magnetic stirrer stirred the mixture.

All melting points were measured with a XT4A Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded with a AV 400M Bruker spectrometer (400 MHz ^{1}H frequency, 100 MHz ^{13}C frequency). Chemical shifts are given as δ values (internal standard: TMS). The MS spectra (ESI) were recorded on a Bruker esquire 6000 mass spectrometer. HR-MS (TOF-EI) were recorded on a GCT CA 127 Micronass UK mass spectrometer.

4-Amino-3-methylphenol **1b** and sodium 4-methylbenzenesulfinate **3b** were reagent-grade from Alfa Aesar China (Tianjin Co., Ltd.), whereas *N*-(hydroxyphenyl)benzenesulfonamide **1c**, **1d** and **2b** were prepared according to known procedure.[12] Other chemicals and solvents were from Beijing Chemicals Co. and used without further purification. Doubly distilled de-ionized water was used for preparation of aqueous acetate buffer. All experiments were performed at room temperature and ambient pressure.



Scheme 5. Proposed mechanism for the conversion of amino-protected aminophenols **1c**, **1d** and **2b** to **4a**–**f**.

4.2. General procedure for the synthesis of compounds 4a–f

To the anode compartment, which is kept in water at room temperature, was added 60 mL of 0.2 M sodium acetate buffer (pH=7) and 30 mL of acetonitrile. Meanwhile, 20 mL of a mixed solution of sodium acetate buffer and acetonitrile (v/v=3:1) was added to the cathode compartment. The electrolyte was pre-electrolyzed at 0.6 V versus Ag wire to remove impurity till the current decreased to less than 2 mA. Subsequently, 2 mmol of *N*-(hydroxyphenyl)benzenesulfonamide **1c**, **1d** or **2b** and 2 mmol of sodium benzenesulfinate **3** were added to the cell and electrolysis was continued. The electrolysis was terminated when the starting *N*-(hydroxyphenyl)benzenesulfonamide was consumed as determined by TLC. After electrolysis, the anolyte was neutralized using acetic acid. The formed precipitate was filtered, washed by water several times and dried under vacuum to give the desired compounds **4a**–**f** in white powder.

*4.2.1. N-[4-Hydroxy-3-(phenylsulfonyl)phenyl]-4-methylbenzenesulfonamide (**4a**).* Yield 55%; mp: 184–185 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 6.78 (d, 1H, J=8.8 Hz, Ar–H), 7.20 (dd, 1H, J=8.8, 2.4 Hz, Ar–H), 7.36 (d, 2H, J=8.0 Hz, Ar–H), 7.55–7.59 (m, 5H, Ar–H), 7.66 (t, 1H, J=7.6 Hz, Ar–H), 7.72 (d, 2H, J=7.2 Hz, Ar–H), 10.01 (br, 1H, NH), 10.70 (br, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.4, 118.7, 122.8, 126.6, 127.3, 128.3, 129.3, 130.0, 130.1, 130.5, 133.8, 136.5, 141.4, 144.3, 153.5; FT-IR (KBr): ν 3390, 3254, 1596, 1504, 1466, 1163 cm^{-1}; ESI-MS: m/z 403.9 $[M+H]^+$, 806.8 $[2M+H]^+$; HREI-MS: m/z calcd for $C_{19}H_{17}NO_5S_2$ $[M]^+$ 403.0548, found 403.0550.

*4.2.2. N-[4-Hydroxy-3-(4-methylphenylsulfonyl)phenyl]-4-methylbenzenesulfonamide (**4b**).* Yield 53%; mp: 185–186 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 6H, CH_3), 6.70 (d, 1H, J=8.8 Hz, Ar–H), 7.14 (d, 2H, J=8.0, 2.4 Hz, Ar–H), 7.36 (d, 4H, J=8.0 Hz, Ar–H), 7.51 (d, 1H, J=8.4 Hz, Ar–H), 7.55 (d, 2H, J=8.4 Hz, Ar–H), 7.60 (d, 2H, J=8.0 Hz, Ar–H), 10.10 (br, 2H, OH and NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.4, 21.4, 118.8, 122.9, 126.8, 127.3, 128.2, 128.7, 129.7, 130.0, 130.4, 136.6, 138.6, 143.7, 144.2, 154.1; FT-IR (KBr): ν 3387, 3254, 1597, 1505, 1395, 1399, 1161, 1145 cm^{-1}; ESI-MS: m/z 415.8 $[M-H]^-$; HREI-MS: m/z calcd for $C_{20}H_{19}NO_5S_2$ $[M]^+$ 417.0705, found 417.0709.

*4.2.3. N-[4-Hydroxy-2-methyl-5-(phenylsulfonyl)phenyl]-4-methylbenzenesulfonamide (**4c**).* Yield 66%; mp: 243–245 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.03 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.65 (s, 1H, Ar–H), 7.28 (s, 1H, Ar–H), 7.40 (d, 2H, J=8.0 Hz, Ar–H), 7.54 (d, 2H, J=8.0 Hz, Ar–H), 7.58 (t, 2H, J=7.6 Hz, Ar–H), 7.65–7.70 (m, 3H, Ar–H), 9.45 (br, 1H, NH), 10.77 (br, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 21.48, 119.5, 124.3, 126.5, 127.4, 128.0, 128.5, 129.3, 130.1, 133.7, 137.4, 141.7, 143.7, 145.1, 154.6; FT-IR (KBr): ν 3338, 3256, 1606, 1508, 1450, 1159 cm^{-1}; ESI-MS: m/z 418 $[M+H]^+$, 834.7 $[2M+H]^+$; HREI-MS: m/z calcd for $C_{20}H_{19}NO_5S_2$ $[M]^+$ 417.0705, found 417.0710.

*4.2.4. N-[4-Hydroxy-2-methyl-5-(4-methylphenylsulfonyl)phenyl]-4-methylbenzenesulfonamide (**4d**).* Yield 72%; mp: 200–201 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.02 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.63 (s, 1H, Ar–H), 7.25 (s, 1H, Ar–H), 7.38 (d, 2H, J=8.8 Hz, Ar–H), 7.41 (d, 2H, J=9.2 Hz, Ar–H), 7.52 (d, 2H, J=8.0 Hz, Ar–H), 7.57 (d, 2H, J=8.0 Hz, Ar–H), 9.41 (br, 1H, NH), 10.73 (br, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 21.5, 119.5, 124.5, 126.2, 127.4, 128.1, 128.5, 129.7, 130.1, 137.4, 138.9, 143.6, 144.1, 144.9, 154.9; FT-IR (KBr): ν 3367, 3275, 1612, 1597, 1383, 1181 cm^{-1}; ESI-MS: m/z 431.9 $[M+H]^+$, 862.8 $[2M+H]^+$; HREI-MS: m/z calcd for $C_{21}H_{21}NO_5S_2$ $[M]^+$ 431.0861, found 431.0868.

*4.2.5. N-[2-Hydroxy-5-(phenylsulfonyl)phenyl]-4-methylbenzenesulfonamide (**4e**).* Yield 51%; mp: 105–106 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 6.89 (d, 1H, J=8.4 Hz, Ar–H), 7.29 (d, 2H, J=8.0 Hz, Ar–H), 7.51 (dd, 2H, J=8.4, 2.4 Hz, Ar–H), 7.56–7.78 (m, 8H, Ar–H), 9.64 (br, 1H, NH), 10.98 (br, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.4, 116.5, 122.6, 125.9, 126.1, 127.2, 127.2, 130.0, 130.1, 131.1, 133.7, 137.4, 142.4, 143.7, 154.7; FT-IR (KBr): ν 3557, 3485, 3237, 1587, 1508, 1461 cm^{-1}; ESI-MS: m/z 401.8 $[M-H]^-$, 425.7 $[M+Na]^+$; HREI-MS: m/z calcd for $C_{19}H_{17}NO_5S_2$ $[M]^+$ 403.0548, found 403.0552.

*4.2.6. N-[2-Hydroxy-5-(4-methylphenylsulfonyl)phenyl]-4-methylbenzenesulfonamide (**4f**).* Yield 56%; mp: 200–201 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.88 (d, 1H, J=8.4 Hz, Ar–H), 7.29 (d, 2H, J=8.0 Hz, Ar–H), 7.40 (d, 2H, J=8.0 Hz, Ar–H), 7.47 (dd, 2H, J=8.4, 2.4 Hz, Ar–H), 7.59 (d, 2H, J=8.4 Hz, Ar–H), 7.64 (d, 2H, J=8.4 Hz, Ar–H), 7.64 (d, 1H, J=2.4 Hz, Ar–H), 10.29 (br, 2H, OH and NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.4, 21.4, 116.4, 122.4, 125.8, 127.2, 127.3, 130.0, 130.5, 131.5, 137.4, 139.6, 143.7, 144.2, 154.6; FT-IR (KBr): ν 3360, 3269, 1595, 1507, 1446, 1399 cm^{-1}; ESI-MS: m/z 415.8 $[M-H]^-$, 439.9 $[M+Na]^+$; HREI-MS: m/z calcd for $C_{20}H_{19}NO_5S_2$ $[M]^+$ 417.0705, found 417.0710.

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