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Electrochemical synthesis of 1,3,4-thiadiazol-2-ylthio-substituted catechols in aqueous medium

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ABSTRACT

Anodic oxidation of catechols **1a**–**e** in the presence of 5-methyl-2-mercapto-1,3,4-thiadiazole **2** has been studied in acetate buffer solution by cyclic voltammetry and controlled-potential electrolysis techniques. The effects of various electrolytic conditions (amount of passed charge, anodic materials, pH of the electrolytic solution, applied potential, and concentration of substrates) on the yield have also been investigated. The results showed that the position of the initial substituent of the starting catechol derivatives dominated the formation of monothiadiazol-2-ylthio-substituted or/and dithiadiazol-2-ylthio-substituted products. For 4-substituted catechols **1a**–**b**, monothiadiazol-2-ylthio-substituted products (**3a**–**b**) were exclusively produced in high to excellent yields. However, in the cases of catechol itself (**1c**) and 3-substituted catechols (**1d**–**e**), both monothiadiazol-2-yl-substituted (**3c**–**e** and **5d**–**e**) and dithiadiazol-2-ylthio-substituted products (**4c**–**e**) were isolated. In addition, the nature of the initial substituent of the starting 3-substituted catechols (**1d** and **1e**) affected the relative ratio of the two monothiadiazol-2-ylthio-substituted isomers (**3d**–**e** vs **5d**–**e**).

1. Introduction

Construction of aromatic carbon–heteroatom bonds is one of the most important and challenging processes in synthetic organic chemistry. Among these reactions, formation of C (aryl)–S bond is much more important due to the fact that most of diaryl thioethers (especially the heteroaryl thioether) possess biological and pharmaceutical activities, or are molecular precursors for the development of materials.[1] Traditionally, synthesis of diaryl thioethers has been able to achieve through a direct displacement of aryl halides by nucleophiles (e.g., arylthiol or heteroarylthiol). Unfortunately, this type of reactions suffers from various problems, such as harsh conditions, long reaction time, low yields, as well as scarcity of starting materials. To overcome these problems, microwave induced technique[2] or transition-metal-mediated cross coupling approach[3] has been applied. However, the strong coordination of sulfur-containing substrates to the metal-based catalysts often makes the catalytic reaction ineffective and specially designed phosphine ligands are often required.[4] Moreover, for the active hydroxylated aromatics, a protection–deprotection process is required. Therefore, a convenient approach for the generation of polyhydroxylated diaryl thioethers is still desirable.

The dearomatization electrochemically of catechols and 1,4-dihydroxybenzenes forming benzoquinones may provide an alternative strategy for the synthesis of diaryl thioether due to the electrochemically generated cyclohexadienone motif serves as an electrophile, and would undergo successively a Michael addition reaction with mercapto molecules and a re-aromatization step to produce polyhydroxylated diaryl thioether. In this context, Nematollahi and others have achieved the synthesis of some heteroaryl thioethers.[5] For example, mercapto-substituted tetrazole, 1,2,4-triazole, and pyridine derivatives were treated with the electrochemically generated *o*-benzoquinones to afford the corresponding heteroaryl thioethers in good yields. Surprisingly, only monomercapto-substituted catechol derivatives were produced. Also, controlled experiments to determine optimal conditions have not yet conducted.

Considering the potential HIV integrase inhibitory activity of polyhydroxylated aromatics, such as catechols, caffeic, and gallic acid derivatives,[6] we have recently carried out a project to synthesize chemically or electrochemically polyhydroxylated aromatics as potential HIV integrase inhibitors.[7] In the present work, we investigated the anodic oxidation of catechol derivatives in the presence of 5-methyl-2-mercapto-1,3,4-thiadiazole in aqueous acetic buffer solutions, with a target to produce polyhydroxylated aryl thioether holding 1,3,4-thiadiazole moiety, due to the pharmacological importance of 1,3,4-thiadiazole derivatives.[8] In addition, effects of various electrolytic conditions, such as amount of passed

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electricity, electrode materials, pH of the electrolytic solution, applied potential, and concentration of substrates, on the yields of products have also been studied to optimize the reaction conditions. Our results demonstrated that the position and nature of the initial substituent of the starting catechols determine not only the formation of monothiadiazol-2-ylthio-substituted aryl thioether and dithiadiazol-2-ylthio-substituted derivatives, but also the ratio of the two monothiadiazol-2-ylthio-substituted isomers in the cases of 3-substituted catechols. These results further demonstrate the versatility of the electrochemically generated benzoquinones and their in-situ transformation for the synthesis of polyhydroxylated aromatics.

2. Results and discussion

2.1. Voltammetric studies of 1a–1e in the absence and presence of 2

Electrochemical behaviors of catechols (**1a**–**e**) in the absence and presence of **2** have been investigated by cyclic voltammetry (CV), at room temperature, in 2:1 (v:v) acetate buffer solution/acetonitrile (0.2 M, pH 6) as the supporting electrolyte system. The results are summarized in Table 1 and typical CVs of 4-*tert*-butylcatechol **1a** are shown in Figure 1.

As shown in curve a, Figure 1, on the initial anodic sweep of 4-*tert*-butylcatechol **1a**, one well-defined oxidation wave (A1) at +0.25 V (vs Ag/AgCl) was observed, which corresponded to the formation of corresponding *o*-benzoquinone derivative.[5,9] After scan reversal, a reversible cathodic peak at +0.07 V versus Ag/AgCl (C1) appeared. The ratio of the current amplitudes between the oxidation and reduction processes is equal to unity (Ip_{ox}/Ip_{red}), indicating that the *o*-benzoquinone produced at the surface of the electrode is stable under acetate buffer solution and that side reactions such as hydroxylation or dimerization reactions are too slow to be observed on the time scale of the cyclic voltammetry. Curve 'c' is the CV of 5-methyl-2-mercapto-1,3,4-thiadiazole **2**, showing a broad ill-defined anodic wave centered at about +0.35 V (vs Ag/AgCl).

The anodic oxidation of **1a** in the presence of 5-methyl-2-mercapto-1,3,4-thiadiazole **2** has also been studied by cyclic voltammetry method. As shown in Figure 1 (curve b), the anodic current increased dramatically. Simultaneously, cathodic current decreased and a second new peak C2 (0.16 V vs Ag/AgCl) emerged, which indicated that a chemical reaction took place between the electrochemically generated *o*-benzoquinone (at A1) and **2**.

The electrochemical behavior of **1d** in the presence of **2**, under the same conditions, proceeded similarly to that of **1a**. However, in these cases of **1b**, **1c**, and **1e**, no obvious new cathodic peak appeared, which may stem from the close reductive potential of the starting catechol and its corresponding product. Actually, the product by itself is also catechol derivative. Thus, what we observed is an average reductive wave consisting of both product and starting material.[7b]

Table 1
Peak potentials of starting compounds **1** in the absence and presence of **2**[a]

Starting materials	Peak potential at GC[b]		Peak potential at GC[c]		
	Ep_{ox}	Ep_{red}	Ep_{ox}	Ep_{red1}	Ep_{red2}
1a	0.25	0.07	0.29	0.04	0.16
1b	0.26	0.03	0.30	—	—
1c	0.32	0.08	0.41	0.07	—
1d	0.26	0.04	0.29	0.05	0.11
1e	0.28	0.02	0.33	0.04	—

[a] Cyclic voltammetry measurements were performed in 2:1 (v:v) acetate buffer solution/acetonitrile (0.2 M, pH 6); glassy carbon (GC) working electrode; scan rate 50 mV/s. Reference electrode: Ag/AgCl.
[b] 2 mM of **1** in the absence of **2**.
[c] 2 mM of **1** in the presence of 2 mM of **2**.

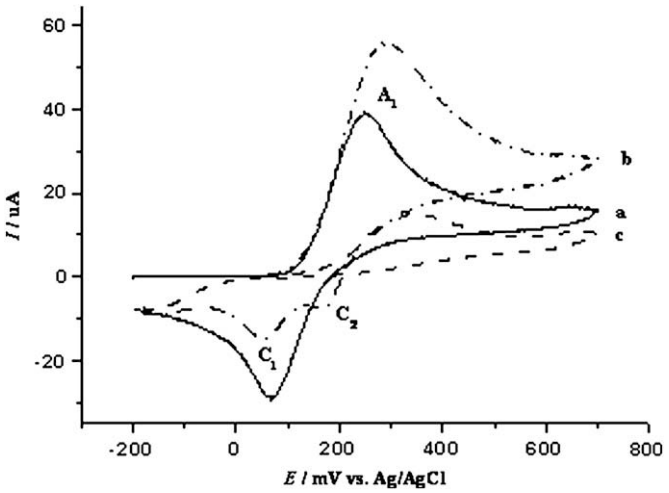


Figure 1. Cyclic voltammogram of (a) 2 mM of 4-*tert*-butylcatechol, (b) a mixture of 2 mM of 4-*tert*-butylcatechol and 2 mM of 5-methyl-2-mercapto-1,3,4-thiadiazole, (c) 2 mM of 5-methyl-2-mercapto-1,3,4-thiadiazole, at a glassy carbon electrode, platinum net counter, and Ag/AgCl reference, in 2:1 (v:v) acetate buffer solution/acetonitrile (0.2 M, pH 6); scan rate: 50 mV/s.

The electrochemical behaviors of 4-*tert*-butylcatechol at different working electrodes were also investigated. As shown in Figure 2, a well-defined reversible redox couple was obtained on glassy carbon anode. However, under the same conditions, the anodic potential on Pt and Au electrode shifted positively to 0.50 V and 0.46 V, respectively, along with lower anodic current. Such outcomes indicated that higher electro-oxidation activity could be achieved using glassy carbon.

2.2. Optimization of electrolytic condition using 1a as a model compound

Different from conventional chemical approach, electrochemical parameters, such as electrode materials, amount of passed electricity, solvents, supporting electrolytes, sorts of cell (divided cell or undivided cell), and mode of electrolysis (controlled potential or

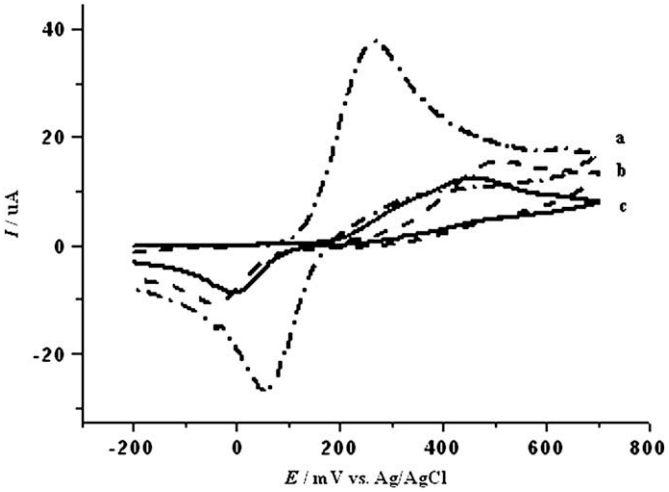


Figure 2. Cyclic voltammogram of 2 mM of 4-*tert*-butylcatechol at (a) glassy carbon, (b) Pt and (c) gold electrodes, platinum net counter and Ag/AgCl reference, in 2:1 (v:v) acetate buffer solution/acetonitrile (0.2 M, pH 6); scan rate: 50 mV/s.

constant current), significantly affect the electrochemical results. Therefore, 4-*tert*-butylcatechol was first chosen as a model compound to investigate the appropriate conditions and then applied the optimized conditions to other catechols. In this work, the effects of passed charge, electrode materials, pH, applied potential, and concentration of substrates were studied, respectively.

*2.2.1. Effect of passed electricity on the yield of product **3a***

The reaction process was firstly monitored by HPLC chromatography. To a beaker-type undivided cell were added 0.11 mmol of 4-*tert*-butylcatechol and 0.10 mmol of **2** in 65 mL of 0.1 M acetate buffer and acetonitrile (v:v=2:1). The electrolytic solution was electrolyzed at 0.4 V versus SCE using graphite rod anode. With the proceeding of electrolysis, the starting colorless electrolytic solution slowly turned to pink, then brown. To investigate the effect of passed electricity on the reaction, the reaction solution was directly subjected to HPLC analysis. As shown in Figure 3, with the starting **2** and **1a** continuously consumed, a new compound appeared and its yield increased continuously. This new compound was demonstrated to be compound **3a** after isolation and identification. When 6 F/mol of electricity was passed, the starting **2** disappeared and, simultaneously, more than 95% of **3a** was obtained. However, when charge was continuously passed, the yield of **3a** decreased. For example, the yield of **3a** decreased to 25% when 16 F/mol charge passed. This outcome demonstrated that, in parallel to the oxidation of starting **1a**, product **3a** also underwent oxidation and decomposed to other by-products. The parallel oxidation of **3a** is not surprised because **3a** by itself is also catechol derivative and its oxidation potential is close to the starting **1a**. Therefore, passing 4–6 F/mol electricity would be the suitable condition.

*2.2.2. Effect of anodic materials on the yield of product **3a***

Among all the electrochemical parameters, the anodic material is of importance. Therefore, the effects of different anodic materials (platinum, glassy carbon and graphite) on the yield of **3a** were also investigated. As shown in Table 2, excellent yield (95%) of **3a** could be achieved by using graphite rod as anodic material after passing 6 F/mol of electricity. Under the same conditions, **3a** was also produced in good yield (78%) with glassy carbon anode. However, after passing 9 F/mol electricity, only 11% of **3a** was obtained and most of the starting **2** (62%) and **1a** were still existent when platinum plate was used as anodic material (in this case, the initial anodic current shifted to as high as 2 A in a few minutes). Obviously, graphite rod appears preferable for such a reaction. Such

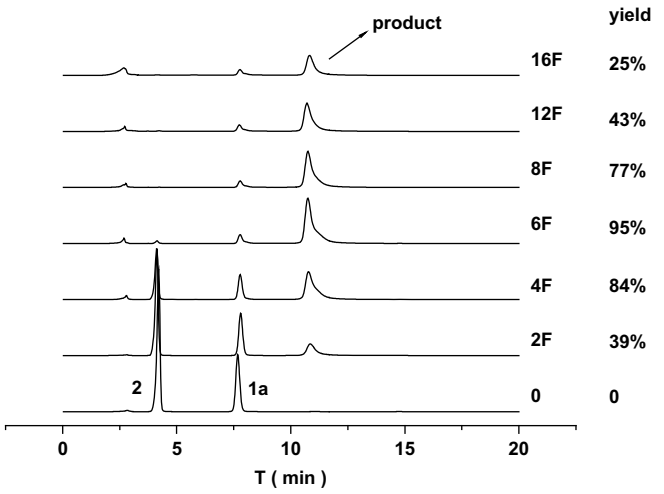


Figure 3. HPLC chromatograms of the solution obtained when different amounts of charge were passed.

Table 2
The effect of anodic materials on the yield of product **3a**[a]

Anodic materials	Recovered **2**[b] (%)	Yield[b] (%)
Platinum plate[c] (4 cm^2)	62	11
Glassy carbon (4 cm^2)	6	78
Graphite rods (4 cm^2)	0	95

[a] Experimental condition: room temperature, 0.11 mmol of 4-*tert*-butylcatechol and 0.10 mmol of 5-methyl-2-mercapto-1,3,4-thiadiazole in 65 mL of 0.1 M acetate buffer and acetonitrile (2:1=v:v), Pt plate (2 cm^2) cathode, undivided cell; controlled potential: 0.4 V versus SCE; passed charge: 6 F/mol.
[b] The yield based on the starting 5-methyl-2-mercapto-1,3,4-thiadiazole.
[c] When platinum plate was used as anode electrode, the initial current increased to as high as 2 A in a few minutes. Passed charge: 9 F/mol (repeating two times).

results consist with those of CVs using different working electrodes because the anodic potentials of **1a** and **2** at Pt and Au working electrode are very close (Fig. 2), not only the starting **1a**, but also the nucleophile would be oxidized and resulted into decrease of the yield of corresponding product. Hereafter, the effects of the other electrolytic conditions were studied by using the graphite rods as anodic electrode.

*2.2.3. Effect of pH of electrolytic solution on the yield of product **3a***

Effect of pH of the electrolytic solution on the yield of **3a** was also studied and summarized in Table 3. It is evident that the desired reaction prefers mild acidic or neutral condition. After passing 6 F/mol of electricity, more than 95% of **3a** was obtained in pH 6 acetate buffer solution. Also, good yield (87%) could be achieved when electrolysis was performed in pH 7.3 acetate buffer solution. On the contrary, in acidic condition, after passing same amount of electricity, only moderate yields of **3a** were generated. For instance, only 49% of **3a** was obtained in pH 3 acetate buffer solution.

In addition, the results in Table 3 further demonstrated that 6 F/mol of charge appeared preferable for the electrolysis. For example, in acidic buffer solution (pH 3–6 range), **3a** was obtained in lower yield after only passing 4 F/mol electricity. Simultaneously, 12–29% of the starting **2** was recovered. However, on electrolysis in pH 7.3 buffer, 4 F/mol of electricity consumption was better and 93% of **3a** was obtained, in comparison to 87% of yield in the case of 6 F/mol. Therefore, achievement of highest yield would depend on the combination of pH and electricity consumption.

*2.2.4. Effect of applied potential on the yield of product **3a***

The yield is also highly dependent on applied potential in the controlled-potential electrolysis. Therefore, the effect of applied potential on the yield of **3a** was also studied in pH 6 acetate buffer solution. As seen in Table 4, the highest yield of **3a** was obtained when electrolysis was performed at 0.4 V versus SCE and after passing 6 F/mol of electricity. Interestingly, such reaction could tolerate a wide range of applied potentials. Good to excellent yield of **3a** could be achieved in the potential range from 0.2 V to 0.8 V versus SCE and only slightly affected by the potential. For example, 91% of **3a** was obtained when applied potential was controlled at

Table 3
Effect of pH on the yield of product (graphite rod anode)[a]

pH	Recovered **2**[b] (%)	Yield[b] (%)	Recovered **2**[c] (%)	Yield[c] (%)
3.0	25	48	1	49
4.0	29	61	2	68
5.0	12	75	0	78
6.0	22	84	0	95
7.3	16	93	1	87

[a] The electrolysis was carried out at the potential of 0.4 versus SCE, graphite was used as anode electrode.
[b] After passing 4 F/mol of electricity.
[c] After passing 6 F/mol of electricity.

Table 4
Effect of applied potential on the yield of the product **3a**[a]

Applied potential	Recovered **2**[b] (%)	Yield[b] (%)	Recovered **2**[c] (%)	Yield[c] (%)
0.2	10	>99	0	91
0.3	21	78	0	90
0.4	21	84	0	95
0.5	18	86	0	90
0.6	28	66	0	93
0.7	13	90	0	80
0.8	14	80	0	88
1.0	48	32[d]	34	46[d]
1.2	40	49[d]	17	73[d]

[a] The supporting electrolyte solution was acetate buffer (pH 6) and acetonitrile (v:v=2:1).
[b] After passing 4 F/mol of electricity.
[c] After passing 6 F/mol of electricity.
[d] The distance between anode and auxiliary was not well controlled, so the yield of the product is not in agreement with the potential very well, but in agreement well with the magnitude of initial current.

0.2 V versus SCE. Under the same conditions, 88% of **3a** was also produced if electrolysis was performed at 0.8 V versus SCE. However, when the reaction was carried out at 1.0 V and 1.2 V versus SCE, 46% and 76% of **3a** would be obtained, respectively, lower yield than that controlled at 0.2–0.8 V.

In addition, the outcome in Table 4 further demonstrates that passing 6 F/mol of electricity is preferable for the synthesis of **3a** in the potential range of 0.2–0.8 V versus SCE. For example, about 20% of starting **2** did not get consumed up and less than 90% of **3a** was generated when 4 F/mol of electricity was passed.

*2.2.5. Effect of substrate concentration on the yield of product **3a***

The results in Table 5 demonstrate that the concentration of starting materials affects the yield of corresponding **3a**. When the starting **2** was less than 5.0 mM, good to excellent yield of **3a** could generate after passing 4 F/mol or 6 F/mol of electricity. However, it dropped to 61% when the concentration of **2** increased to 46 mM. Therefore, higher concentration than 45 mM of starting materials is not preferable.

2.3. Controlled-potential electrolysis of other catechol derivatives (1b–e) in the presence of 5-methyl-2-mercaptothiadiazole

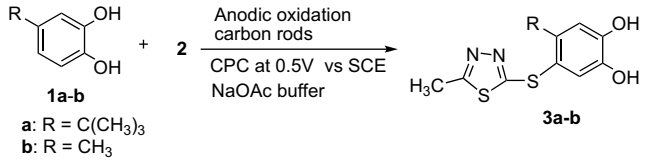
Based on the above investigations, the optimized conditions of anodic oxidation of **1a** in the presence of **2** for the synthesis of **3a** are summarized as follows: graphite rod anode, pH 6 acetate buffer solution, controlled potential at 0.5 V versus SCE, 6 F/mol passed charge in undivided cell. With this information in hand, we then applied to the anodic oxidation of other catechols in the presence of **2**. To the beaker-type cell equipped with 150 mL of pH 6 acetate buffer solution, 2 mmol of **1b–e** and 2 or 4 mmol of **2** were added and electrolyzed at controlled potential at 0.5 V versus SCE, using graphite rod anode. After passing 6 F/mol of electricity, the electrolytic solution was acidified and corresponding products were isolated after flash column chromatography.

Table 5
Effect of the concentration of starting **2** on the yield[a,b]

Concentration of **2** (mM)	Recovered **2**[c] (%)	Yield[c] (%)	Recovered **2**[d] (%)	Yield[d] (%)
1.5	18	84	0	95
5.0	10	85	0	94
15	10	87	0	64
46	25	61	0	—

[a] The electrolysis was carried out at the potential of 0.5 V versus SCE, graphite as anode electrode and the supporting electrolyte solution consisting of acetate buffer (pH 6) and acetonitrile (v:v=2:1).
[b] The sample injecting to HPLC system was prepared by diluting the electrolysis solution, with the same buffer, to the same concentration as that of the external calibrated standard solution of **3a**.
[c] 4 F/mol.
[d] 6 F/mol.

As shown in Scheme 1 and Table 6, in the presence of **2**, upon oxidation of 4-substituted catechols (**1a–b**), where one of the *para*-positions of the two OH groups was occupied, **3a** and **3b** were produced exclusively with excellent to good yield.

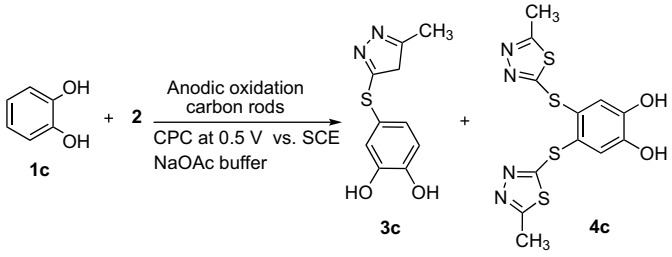


Scheme 1. Anodic oxidation of **1a–b** in the presence of **2**.

Table 6
Isolated yield of reaction of different catechols and **2**

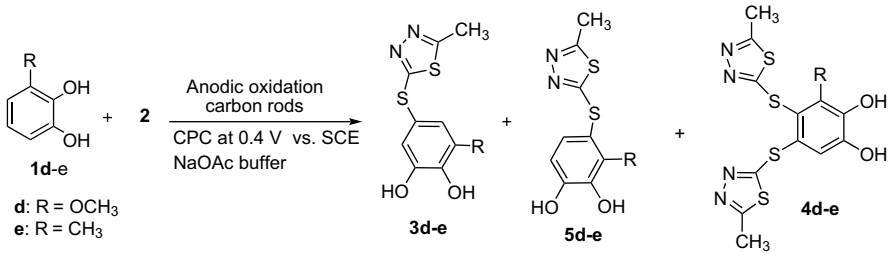
Starting catechols	Products	Yield (%)
4-*tert*-Catechol (**1a**)	**3a**	92
4-Methylcatechol (**1b**)	**3b**	65
Catechol (**1c**)	**3c**	31
	4c	33
3-Methoxycatechol (**1d**)	**3d**	31
	4d	16
3-Methylcatechol (**1e**)	**5e**	20
	4e	13

However, the anodic oxidation of catechol itself (**1c**) and 3-substituted catechols (**1d–e**) is different, where the two *para*-positions of the two hydroxyl groups are free and able to be attacked by nucleophiles. Therefore, not only mono- but also di-substituted derivatives were expected to be produced. In previous reports, however, only mono-substituted products formed.[5] In our cases, we did isolate mono- and di-substituted products simultaneously. Thus, for catechol **1c**, mono-substituted catechol derivative **3c** was produced in 31% isolated yield, simultaneously, compound **4c** with two thiadiazole moieties was also isolated in 33% of yield (Scheme 2).



Scheme 2. Anodic oxidation of **1c** in the presence of **2**.

Similar to the manner of **1c**, the oxidation of **1d** and **1e** in the presence of **2** also produced mono- and di-substituted compounds (Scheme 3). However, the asymmetry of these compounds might lead to two monothiadiazol-2-yl-substituted isomers because the nucleophilic addition of the first nucleophilic molecule to the 3-substituted *o*-benzoquinone (formed from the oxidation of corresponding 3-substituted catechols) may take place in the C-4 or C-5 of the benzene ring. Also, due to the steric hindrance as well as the less electropositive feature of C-4, usually, the substituted group is introduced in the C-5 position.[5] Actually, in our experiments, the electrochemical oxidation of **1d** and **1e** in the presence of **2** afforded an inseparable mixture of two regioisomers **3d–e** and **5d–e** and



Scheme 3. Anodic oxidation of **1d–e** in the presence of **2**.

their ratio could be calculated from the integration of signal in ^{1}H NMR spectrum (Fig. 4). Interestingly, the nature of the initial substituted group of the starting 3-substituted catechols (methyl or methoxy) dominated the related yield of the couple of isomers. For example, after anodic oxidation of **1d** in the presence of **2**, products **3d** and **5d** were detected and their ratio of **3d** to **5d** was about 10:0.8–1.2 during two repeated experiments, along with 16% yield of **4d**. Because both of them have very close polarity and could not be separated by column chromatography, following by recrystallization, **3d** with high purity could be finally obtained in 31% yield. However, in the case of **1e**, the ratio of **3e** to **5e** is about 1:10 and finally **5e** was obtained in 20% yield.

It is noteworthy that, when 2-mercapto pyrimidines were used as nucleophiles,[7c] similar to 5-methyl-2-mercaptothiadiazole, in the cases of **1a–b**, monopyrimidinethio-substituted catechols were produced exclusively; and both mono- and dipyrimidinethio-substituted catechols were isolated for **1d–e**, however, only monopyrimidinethio-substituted catechol isomers were detected and the pyrimidinethio groups were introduced into the C-5 position. On the other hand, when 6-mercaptopurine[7d] was used as nucleophile, only one mercapto-group was introduced into the C-5 position, independent of the nature and position of the initial substituents of the starting catechols. These outcomes also indicated that the nature of the nucleophiles, although being mercapto molecules, in some extents, affects the formation of corresponding products.

The structures of **3–5** were characterized by using ^{1}H NMR, ^{13}C NMR, IR, and ESI-MS. Taking **3a** as an example, its ^{1}H NMR spectrum exhibited two singlets at 1.2 and 2.6 ppm, attributed to the *tert*-butyl and methyl groups, respectively. The AB splitting system at aromatic region with coupling constant of 2.4 Hz is the signal of two protons of benzene ring. The two OH protons are located at 9.2 and 9.6 ppm, respectively. The ^{13}C NMR spectrum of compound **3a** exhibits 11 signals. It should be pointed out that the differentiation of the couples of regioisomer **3** and **5** is achieved by ^{1}H NMR. For example, in the ^{1}H NMR of compound **3d**, the two proton signals showed an AB system with coupling constant of 2.0 Hz due to the ^4J coupling, while it is 8.4 Hz for compound **5d** due to the ^3J coupling.

2.4. Reaction pathway

We now turn to discuss the reaction pathway of anodic oxidation of catechols **1a–e** in the presence of 5-methyl-2-mercaptothiadiazole **2**. Tabakovic[9] and Nematollahi[5] reported that the anodic oxidation of catechol and its derivatives in aqueous medium leads to the corresponding *o*-benzoquinone intermediates. In the presence of nucleophiles, the electrochemically generated *o*-benzoquinones are converted to other intermediates or products, following a pattern of an EC or an ECEC mechanism, depending on the nature of the nucleophiles and structures of the starting catechols. In the present cases, similar processes may take place to generate types **3** and **5** compounds. For 4-substituted catechols **1a** and **1b**, in which one of the *para*-positions of the two hydroxyl groups in the benzene ring was occupied and only the left position can be attacked by nucleophilic molecule, then, the EC processes may take place to produce compounds of **3a–b**. Therefore, as shown in Scheme 4, the anodic oxidation of catechols **1a–b** generates the corresponding *o*-benzoquinones, which are highly active and undergo the Michael addition reaction with **2** anion to generate products **3a–b**, respectively.

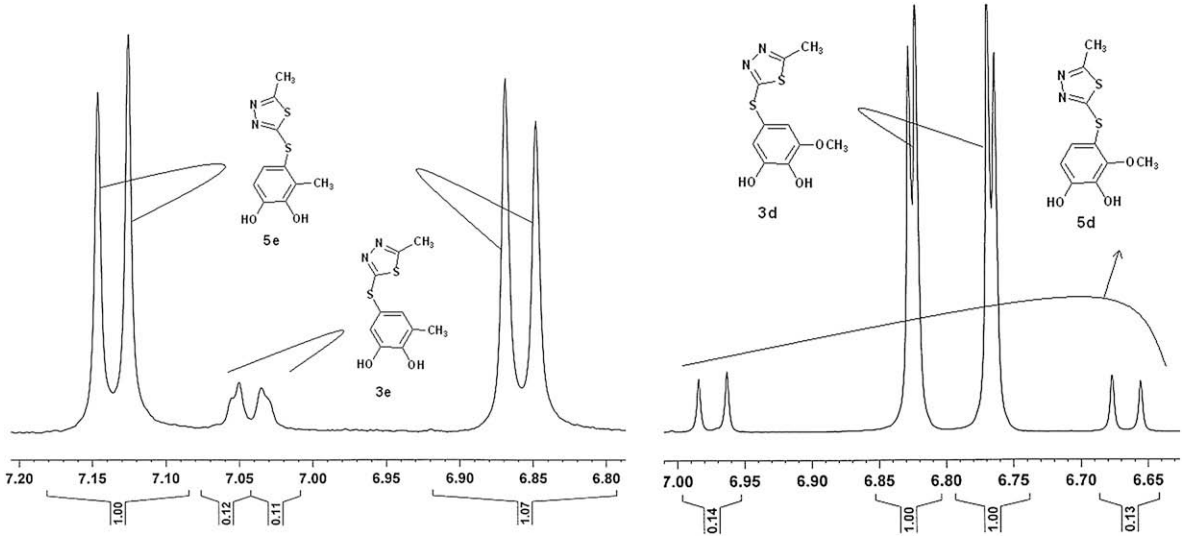
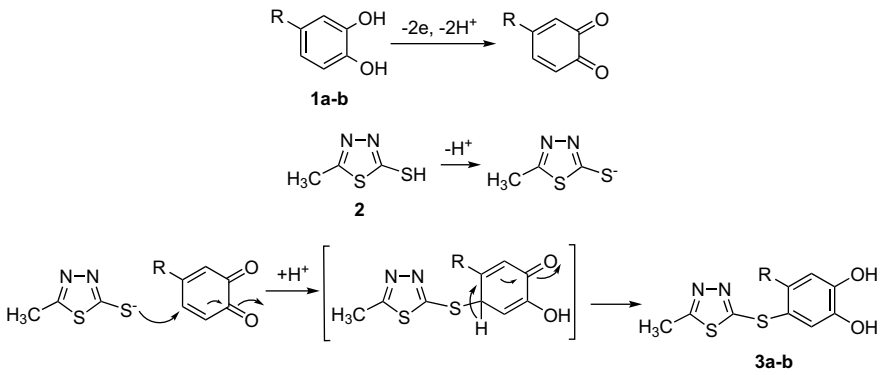


Figure 4. Partial ^{1}H NMR spectra of two couples of regioisomer mixtures **3d**, **5d** and **3e**, **5e**, showing the ratio of the isomers.

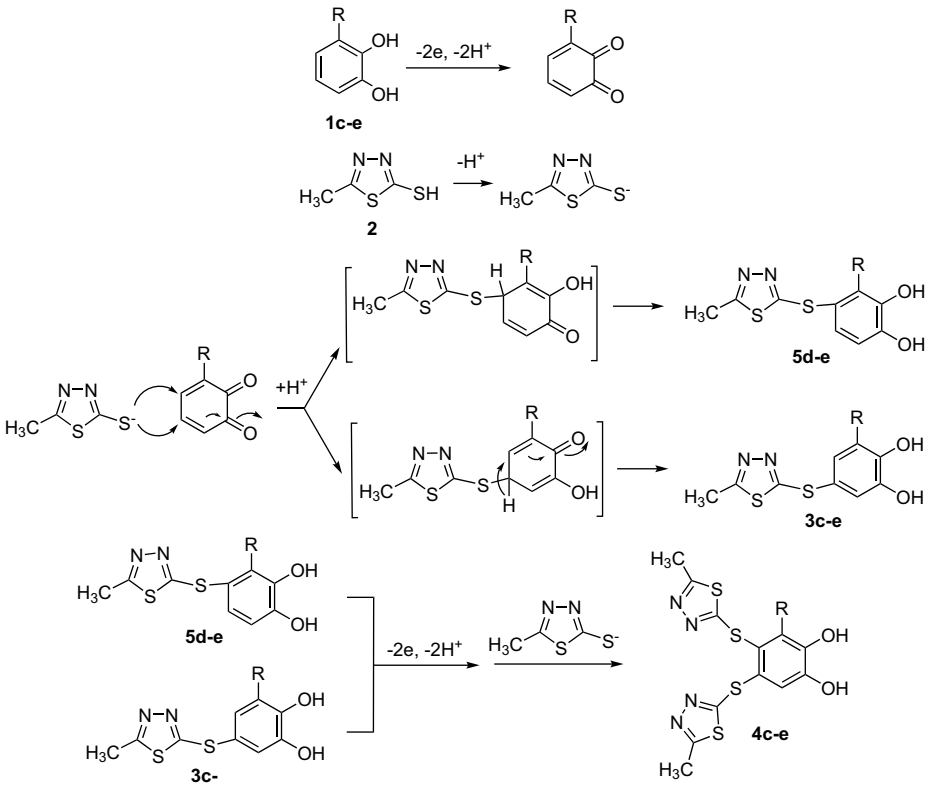


Scheme 4. A plausible mechanism between 4-substituted catechols and 5-methyl-2-mercaptothiadiazole.

In the case of catechol **1c** and 3-substituted catechols **1d**–**e**, where two *para*-positions of the two hydroxyl groups in the benzene ring are free and ECEC mechanism pattern is expected to follow. Therefore, upon oxidation of **1c**–**e**, the mercapto anion enters 4- or 5-position of benzene ring to form mono-(1,3,4-thiadiazol-2-ylthio)-catechols **3c**–**e** and **5d**–**e**. Due to their solubility in the aqueous CH_3CN, as well as the close oxidation potential with starting catechols, such initial addition products performed further oxidation and subsequent addition of the second mercapto anion to transfer into bis-(1,3,4-thiadiazol-2-ylthio)-catechols **4c**–**e** (Scheme 5).

3. Conclusions

In summary, the electrochemical behaviors of catechols **1** in the absence and presence of nucleophile **2** have been investigated by cyclic voltammetry method. CVs of catechols exhibited one well-defined oxidation wave and a corresponding cathodic peak. However, when equivalent mole of **2** was added, the cathodic wave disappeared or decreased depending on the nature of the initial substituent on the ring of catechol unit. Based on the relative CV data, 4-*tert*-butylcatechol was used as a mode compound to investigate the effects of different electrochemical parameters, including passed charge, electrode materials, pH, applied potential, and concentration of substrates, on the yield of corresponding **3a** and then applied the optimized conditions to other catechols. It was found that the anodic oxidation of **1a**–**b** in the presence of **2** afforded monothiadiazole-substituted catechol derivatives in good to excellent yield. However, for catechol **1c** and 3-substituted catechols **1d**–**e**, mono- and dithiadiazole-substituted catechols were isolated. Such reaction further demonstrates that the anodic oxidation of catechol derivatives and their in-situ transformation can be utilized to synthesise a library of polyhydroxylated aromatics.



Scheme 5. A plausible mechanism between catechol or 3-substituted catechols and 5-methyl-2-mercaptothiadiazole.

4. Experimental

4.1. General

Cyclic voltammograms were measured by a 273A Potentiostat/Galvanostat equipped with an electrochemical analysis software, using a conventional three-electrode cell. The working electrode was a glassy carbon disk (ca.=3 mm), Pt disk (ca.=2 mm) or Au disk (ca.=2 mm) electrodes. The auxiliary and reference electrodes in these studies were Pt net and Ag/AgCl (in 3 M KCl), respectively. All electrodes for CV experiments were from CH Instruments, Inc., USA. Mixed solution of acetate buffer (pH=6.0) and acetonitrile (v:v=2:1) was used as a supporting electrolyte system. The concentrations of substrates were 2 mmol L^{-1}, while those of the supporting electrolyte was 0.2 mol L^{-1}. Controlled-potential electrolyses were conducted in a 250 mL beaker-type cell (undivided) equipped with a platinum plate (2.0 cm^2) cathode and an assembly of 7-carbon rod (ca. 8 mm diameter and 60 mm length) anode, which were connected to the 273A Potentiostat/Galvanostat.

Catechols **1a**–**e** and 5-methyl-2-mercaptothiadiazole **2** were reagent grade from 'Alfa Aesar China (Tianjin) Co., Ltd'. Other chemicals and solvents were from Beijing Chemicals Co. These chemicals were used without further purification. Doubly distilled de-ionized water was used for preparation of acetate buffer. All experiments were performed at room temperature and ambient pressure.

Melting points (mp) were determined on an XT4A Electrothermal apparatus equipped with a microscope and were uncorrected. Infrared spectra (IR) were recorded as thin films on KBr plates on a Bruker IR spectrophotometer and are expressed in ν (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were obtained using an AV 400M Bruker spectrometer in solvent (DMSO-d_6 or acetone-d_6) with TMS as internal reference. The MS data (ESI) were recorded on a Bruker esquire 6000 mass spectrometer.

4.2. General procedure for the synthesis of compounds 3–5

To a 250 mL of undivided beaker-type cell were added a mixture of 100 mL of 0.1 mol/L acetate buffer solution (pH=6.0) and 50 mL of acetonitrile, which were pre-electrolyzed (to remove impurities present in the electrolytic system) at 0.50 V (vs SCE). Subsequently, 2 mmoL of catechols and 2 mmoL of 5-methyl-2-mercaptothiadiazole **2** were added to the cell and continued to electrolysis. After electrolysis, the solvent was acidified to pH=1 with 1 mol/L aqueous HCl and then extracted by ethyl acetate (3×20 mL) and washed with water (20 mL). The separated organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on silica gel and eluted with a mixture of petroleum ether and acetone (v:v=1:1).

*4.2.1. 5-tert-Butyl-4-(5-methyl-1,3,4-thiadiazol-2-ylthio)benzene-1,2-diol (**3a**)*

Yield 92%; mp 172–174 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 1.22 (s, 9H, C(CH_3)$_3$), 2.58 (s, 3H, CH_3), 6.95 (d, 1H, J=2.4 Hz, Ar-H), 6.99 (d, 1H, J=2.4 Hz, Ar-H), 9.17 (br s, 1H, O*H*), 9.61 (br s, 1H, O*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.6, 31.6, 34.3, 115.9, 116.0, 122.3, 143.1, 144.9, 146.3, 165.9, 169.0; IR (KBr): ν 3482, 2967, 1647, 1479, 1400, 1288 cm^{-1}; ESI-MS: m/z 297 (M^++1), 319 (M^++Na), 615 ($2M^+$+Na).

*4.2.2. 5-Methyl-4-(5-methyl-1,3,4-thiadiazol-2-ylthio)benzene-1,2-diol (**3b**)*

Yield 65%; mp 191–194 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.79 (s, 1H, Ar-*H*), 7.02 (s, 1H, Ar-*H*), 9.29 (br s, 1H, O*H*), 9.54 (br s, 1H, O*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.6, 19.9, 117.7, 118.8, 123.1, 133.6, 144.9, 149.0, 165.9, 170.6; IR (KBr): ν 3428, 2925, 2854, 1646, 1603, 1279 cm^{-1}; ESI-MS: m/z 255 (M^++1), 277 (M^++Na), 531 ($2M^+$+Na).

*4.2.3. 4-(5-Methyl-1,3,4-thiadiazol-2-ylthio)benzene-1,2-diol (**3c**)*

Yield 31%; mp 210–211 °C; ^1H NMR (400 MHz, acetone-d_6): δ 2.62 (s, 3H, CH_3), 6.95 (d, 1H, J=8.0 Hz, Ar-*H*), 7.08 (dd, 1H, J=8.4 Hz, J=1.6 Hz, Ar-*H*), 7.17 (d, 1H, J=1.6 Hz, Ar-*H*), 8.51 (br s, 2H, O*H*); ^{13}C NMR (100 MHz, acetone-d_6): δ 15.4, 117.5, 120.9, 122.4, 128.1, 147.2, 148.8, 166.2, 170.8; IR (KBr): ν 3412, 1596, 1511, 1286 cm^{-1}; ESI-MS: m/z 238.6 (M^+−1), 262.7 (M^++Na), 478.7 ($2M^+$−1), 502.7 ($2M^+$+Na).

*4.2.4. 4,5-Bis(5-methyl-1,3,4-thiadiazol-2-ylthio)benzene-1,2-diol (**4c**)*

Yield 33%; mp 219–221 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.63 (s, 6H, CH_3), 7.19 (s, 2H, Ar-*H*), 10.17 (s, 2H, O*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.8, 123.2, 124.4, 149.4, 167.1, 167.3; IR (KBr): ν 3435, 2925, 1637, 1385 cm^{-1}; ESI-MS: m/z 368.7 (M^+−1).

*4.2.5. 3-Methoxy-5-(5-methyl-1,3,4-thiadiazol-2-ylthio)benzene-1,2-diol (**3d**)*

Yield 31%; mp 179–180 °C; ^1H NMR (400 MHz, acetone-d_6): δ 2.58 (s, 3H, CH_3), 3.77 (s, 1H, OCH_3), 6.76 (d, 1H, J=2.4 Hz, Ar-*H*), 6.82 (s, 1H, J=2.4 Hz, Ar-H), 8.97 (s, 1H, Ar-OH), 9.45 (s, 1H, Ar-OH); ^{13}C NMR (100 MHz, acetone-d_6): δ 15.6, 19.9, 117.7, 118.8, 123.1, 133.6, 144.9, 149.0, 165.9, 170.6; IR (KBr): ν 3415, 1650, 1294 cm^{-1}; ESI-MS: m/z 269 (M^+−1).

*4.2.6. 3-Methoxy-4,5-bis(5-methyl-1,3,4-thiadiazol-2-ylthio)benzene-1,2-diol (**4d**)*

Yield 16%; mp 195–196 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.59 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 7.00 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, DMSO-d_6): 15.7, 15.8, 61.3, 117.4, 118.0, 126.0, 142.0, 150.9, 151.2, 166.0, 166.5, 167.6, 168.4; IR (KBr): ν 3434, 1639, 1389, 1310 cm^{-1}; ESI-MS: m/z 399 (M^+−1), 799 ($2M^+$−1).

*4.2.7. 3-Methyl-4-(5-methyl-1,3,4-thiadiazol-2-ylthio)benzene-1,2-diol (**5e**)*

Yield 20%; mp 184–185 °C; ^1H NMR (400 MHz, acetone-d_6): δ 2.37 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 6.85 (d, 1H, J=8.4 Hz, Ar-*H*), 7.12 (d, 1H, J=8.4 Hz, Ar-*H*); ^{13}C NMR (100 MHz, acetone-d_6): δ 14.1, 15.4, 114.4, 121.4, 128.8, 129.9, 145.7, 148.3, 165.9, 171.1; IR (KBr): ν 3411, 1646, 1290 cm^{-1}; ESI-MS: m/z 253 (M^+−1), 507 ($2M^+$−1).

*4.2.8. 3-Methyl-4,5-bis(5-methyl-1,3,4-thiadiazol-2-ylthio)benzene-1,2-diol (**4e**)*

Yield 13%; mp 203–204 °C; ^1H NMR (400 MHz, acetone-d_6): δ 2.47 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 7.21 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, acetone-d_6): δ 14.3, 14.6, 14.7, 118.2, 124.2, 128.0, 131.9, 146.3, 147.6, 165.2, 166.2, 166.6, 167.5; IR (KBr): ν 3429, 1640, 1390, 1295 cm^{-1}; ESI-MS: m/z 383 (M^+−1).

4.3. Yield determination by HPLC method

Similar to the preparative-scale electrolysis, 0.11 mmol of catechols **1** and 0.1 mmol of **2** were added to the beaker-type cell and were electrolyzed under different conditions (amount of passed charge, anodic material, pH, applied potential, concentration of **1** and **2**). After reaction, the electrolytic solution was diluted and subjected to HPLC analysis. HPLC analysis conditions were: Diamond (250×4.6 mm) C18 column (Dikma Technologies), an eluent with 2:3 CH_3OH+H_2O at 1.0 mL/min, a Waters 2487 UV detector with detection at 270 nm. Typically, un-reacted starting material **1** and the corresponding products were checked by an HPLC comparison with the authentic samples, which were isolated and characterized by ^1H NMR, ^{13}C NMR, MS, and IR. The yields of the products and the amount of un-reacted starting **2** were determined

by a calibration curve of external standard consisting of the products of the reaction, **3**, **4**, **5** or starting **2**.

Acknowledgements

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