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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**.

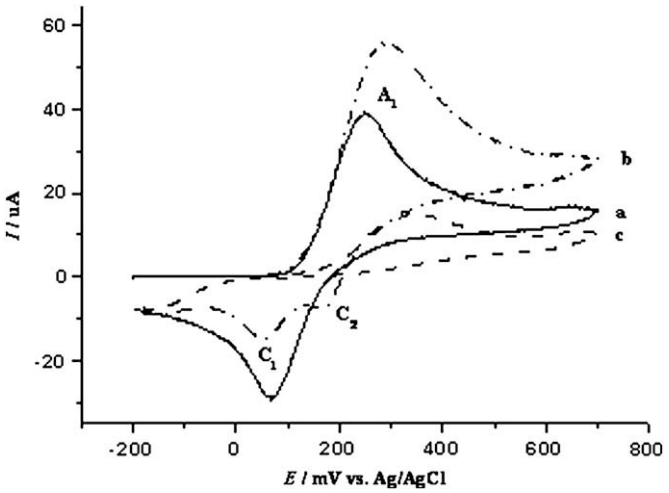

Figure 1. Cyclic voltammogram of (a) 2 mM of 4-*tert*-butylcatechol, (b) a mixture of 2 mM of 4-*tert*-butylcatechol and 2 mM of 5-methyl-2-mercapto-1,3,4-thiadiazole, (c) 2 mM of 5-methyl-2-mercapto-1,3,4-thiadiazole, at a glassy carbon electrode, platinum net counter, and Ag/AgCl reference, in 2:1 (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

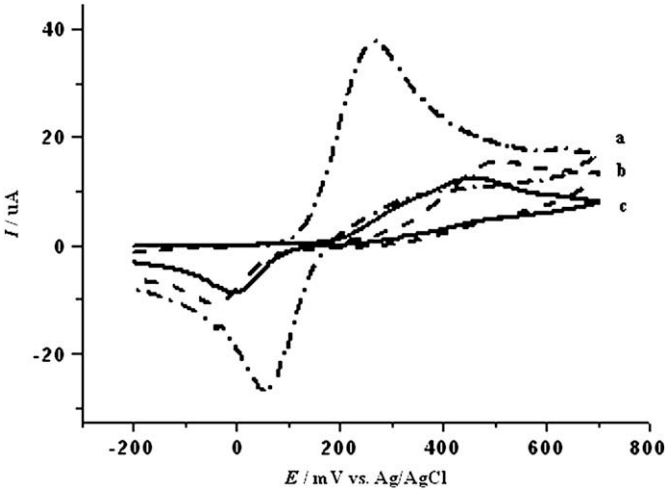

Figure 2. Cyclic voltammogram of 2 mM of 4-*tert*-butylcatechol at (a) glassy carbon, (b) Pt and (c) gold electrodes, platinum net counter and Ag/AgCl reference, in 2:1 (v:v) acetate buffer solution/acetonitrile (0.2 M, pH 6); scan rate: 50 mV/s.