Tetrahedron 69 (2013) 658–663

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Electrochemical oxidation of aminophenols in the presence of benzenesulfinate

Huan-Lan Xiao [a], Cheng-Wen Yang [a], Ni-Tao Zhang [a], Cheng-Chu Zeng [a,*], Li-Ming Hu [a], Hong-Yu Tian [b], R. Daniel Little [c]

[a] College of Life Science & Bioengineering, Beijing University of Technology, Beijing 100124, China
[b] School of Food Chemistry, Beijing Technology and Business University, Beijing 100048, China
[c] Department of Chemistry & Biochemistry, University of California Santa Barbara, Santa Barbara, CA 93106, USA

ARTICLE INFO

Article history:
Received 16 July 2012
Received in revised form 10 October 2012
Accepted 2 November 2012
Available online 8 November 2012

Keywords:
Electrochemical synthesis
Aminophenol
S-Nucleophiles
Michael addition

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**)

* Corresponding author. Fax: +86 10 67392001; e-mail address: zengcc@bjut.edu.cn (C.-C. Zeng).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.11.005

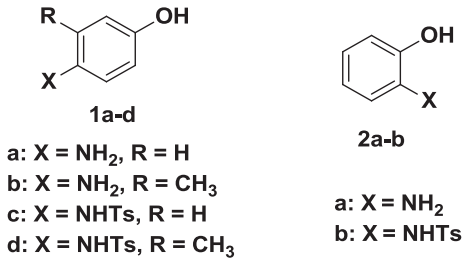

Fig. 1. Structures of starting aminophenols **1a**–**d** and **2a**,**b**.

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.

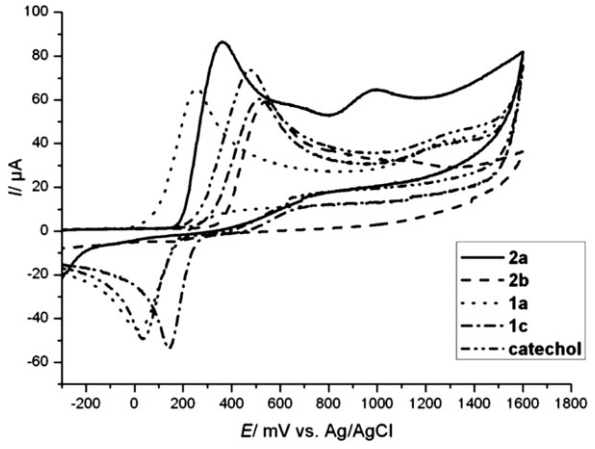

Fig. 2. Cyclic voltammograms of 2 mM of *o*-aminophenol (**2a**), *N*-(2-hydroxyphenyl)-4-methylbenzenesulfonamide (**2b**), *p*-aminophenol (**1a**), *N*-(4-hydroxyphenyl)-4-methylbenzenesulfonamide (**1c**) and catechol at a glassy carbon working electrode, platinum wire counter and Ag/AgCl reference 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

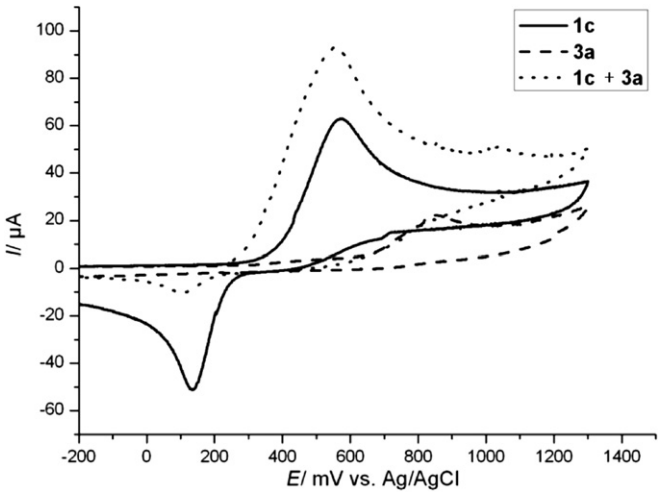

Fig. 3. Cyclic voltammograms of *N*-(4-hydroxyphenyl)-4-methylbenzenesulfonamide (**1c**), 2 mM of sodium benzenesulfinate (**3a**) and a mixture of 2 mM of **1c** and 2 mM of **3a**, at a glassy carbon working electrode, platinum wire counter and Ag/AgCl (3.0 M) reference electrodes, in a mixed solution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