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Electrochemical oxidation of catechols in the presence of ketene *N*,*O*-acetals: indole formation versus α-arylation

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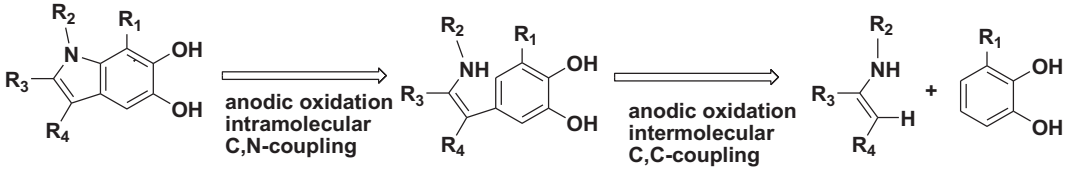
ABSTRACT

Anodic oxidation of catechols has been investigated in the presence of ketene *N*,*O*-acetals using cyclic voltammetry and constant current electrolysis methods. The results show that in the presence of ketene *N*,*O*-acetals, the anodic oxidation of 4-methylcatechol affords α-arylated products in satisfactory yields. Meanwhile, indoles can be synthesized from simple 3-substituted catechols or catechol itself following an ECEC mechanism. In addition, either α-arylation or indole formation could be the dominant pathway by simply modifying the composition of the electrolyte solution.

1. Introduction

The anodic oxidation of a catechol generates a reactive *o*-benzoquinone that can be used to trigger a number of interesting reactions. Typically, the in situ electro-generated *o*-benzoquinone serves as a dienophile and is trapped with a diene[1] to generate an enone derivative. More often, this type of intermediate serves as a Michael receptor to react with a *C*-,[2] an *N*-,[3] or a *S*-based[4] mono-nucleophile or a *C*,*O*-,[5] an *N*,*N*-based[6] doubly nucleophilic species to generate a variety of substituted catechols or fused catechols. Generally the nucleophile is introduced *para* to the initial hydroxyl groups of the catechol ring via a Michael addition.

As part of our ongoing studies on the electrochemical synthesis of polyhydroxylated aromatics,[4a,7] our attention has recently focused on polyhydroxylated indoles due to their potential HIV-1 integrase inhibitory activity.[8] It has been suggested that an ECEC mechanism (E=electrochemical and C=chemical step) is involved with the electrochemical synthesis of disubstituted catechols and benzofurans via the reaction of electro-generated *o*-benzoquinone and nucleophiles. In principle, the indole ring could be constructed in a similar manner from a catechol and an enamine by employing a sequential intermolecular C–C coupling followed by an intramolecular C–N coupling sequence (Scheme 1).



Scheme 1. Retrosynthetic analysis of polyhydroxylated indoles.

Recently, we reported the electrochemical oxidation of catechols **1** in the presence of ketene *N*,*N*-acetals and found that the reaction stopped at the intermolecular C–C coupling step and generated exclusively α-arylated products of ketene *N*,*N*-acetals.[9] When the enamine substrates are replaced by *N*,*O*-acetals containing a five-membered oxazolidine ring, indole derivatives did

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form.[10] Obviously, the nature of the starting ketene acetals (*N*,*N*-acetal or *N*,*O*-acetal) plays a key role in the formation of indole or α-arylated products. Herein we report the full details of the anodic oxidation of catechols in the presence of heterocyclic ketene *N*,*O*-acetals or noncyclic ketene *N*,*O*-acetal (Fig. 1).

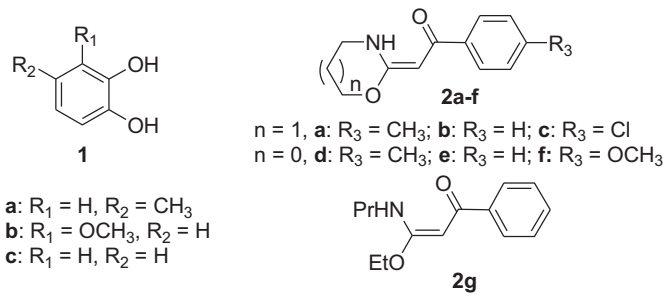


Fig. 1. The structure of starting catechols and ketene *N*,*O*-acetals.

2. Results and discussion

2.1. Cyclic voltammetric studies

Before the preparative scale electrolysis was performed, the electrochemical behavior of catechols in the absence and presence of enamine **2** was first examined by cyclic voltammetry (CV), at room temperature, in 0.2 M acetate buffer (pH 7). The CV curve of **1a** is typical of each of the catechols; it is shown in Fig. 2. Upon scanning anodically, catechol **1a** exhibits one well-defined oxidation wave (A_1) at 0.22 V, corresponding to a cation radical that ultimately leads to the formation of an *o*-benzoquinone derivative, which was reduced in the cathodic sweep at −0.03 V (C_1), back to **1a** (curve I). The ratio of the current amplitudes between the oxidation and reduction processes is equal to unity (I_p^{ox}/I_p^{red}), indicating that the *o*-benzoquinone produced at the surface of the electrode is stable in the pH 7 acetate buffer solution. To obtain further information concerning the transformation of the in situ generated *o*-benzoquinone, the anodic oxidation of **1a** in the presence of **2a** was studied by cyclic voltammetry. As shown in curve II of Fig. 2, when an equivalent amount of **2a** was added, the anodic potential shifts slightly to 0.27 V and a new anodic wave centered at 0.68 V appears. Simultaneously, the current amplitude of the initial cathodic peak (C_1) decreased. Curve III is that of the ketene *N*,*O*-acetal **2a** itself; it shows a well-defined anodic peak centered at 1.05 V (Fig. 2).

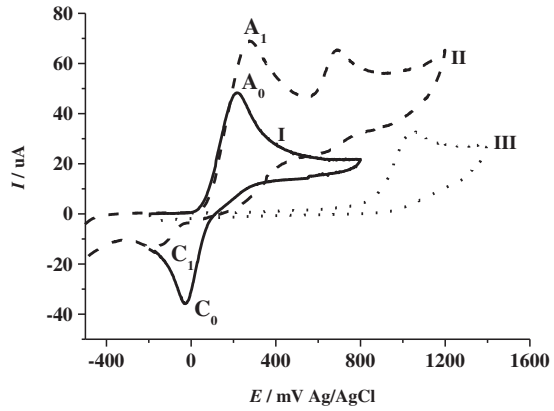
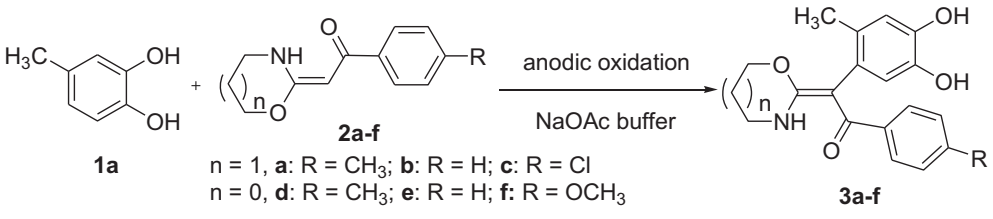


Fig. 2. Cyclic voltammograms of (I) 2 mM of 4-methylcatechol (**1a**), (II) a mixture of 2 mM of **1a** and 2 mM of ketene *N*,*O*-acetal **2a**, and (III) 2 mM of ketene *N*,*O*-acetal **2a**, at a glassy carbon working electrode, platinum wire counter electrode, and Ag/AgCl (0.1 M) reference electrodes, in 1:1 (v/v) acetate buffer/acetonitrile (0.2 M, pH 7) solution; scan rate: 50 mV/s.

The voltammetric behavior indicates that a chemical reaction occurs between the electrochemically generated intermediate (at A_1) and the α-oxoheterocyclic ketene *N*,*O*-acetal **2a** and suggest that Michael addition products may be produced if anodic oxidation of the mixture of a catechol and an α-oxoheterocyclic ketene *N*,*O*-acetal is carried out at the potential of catechol (0.27 V vs Ag/AgCl (0.1 M) AgCl for **1a**), or under constant current conditions where the undesired oxidation of ketene *N*,*O*-acetal will not take place due to the differing oxidation potentials between catechol and *N*,*O*-acetals (for example, 0.22 V for **1a** vs 1.05 V for **2a**).

2.2. Electrochemical oxidation of substituted catechols in the presence of ketene *N*,*O*-acetals

Based upon the CV analysis of the catechols in the absence and presence of heterocyclic ketene *N*,*O*-acetals acetals **2**, we first carried out the anodic oxidation of 4-methylcatechol (**1a**) in the presence of **2a**–**c** containing a six-membered oxazinane ring and also ketene *N*,*O*-acetals **2d**–**f** containing a five-membered oxazolidine ring (Scheme 2). The initial nucleophilic substrate was (*E*)-2-(1,3-oxazinan-2-ylidene)-1-*p*-tolylethanone (**2a**). The conditions employed for the synthesis were the optimized ones developed earlier for the reaction of catechols in the presence of ketene *N*,*N*-acetals.[9] They consisted of an anode made from an assembly of seven graphite rods held together with copper wire, a Pt cathode, 0.2 M sodium acetate in acetonitrile/acetate buffer (volume ratio of acetonitrile to acetate buffer was 1:4) electrolyte solution, and in an H-type divided cell. The reaction was conducted at a constant current of ~3 mA/cm^2. In the course of electrolysis, a brown powder precipitated. After the consumption of starting material **1a** (2.24 F/mol charge), the α-arylated product **3a**, stemming from the Michael addition of **1a** to the electro-generated *o*-benzoquinone was obtained in 75% yield after simple filtration (Scheme 2 and entry 1, Table 1).



Scheme 2. Anodic oxidation of 4-methylcatechol (**1a**) in the presence of ketene *N*,*O*-acetals **2a**–**f**.

A similar outcome was observed when **2b** or **2c** were used as Michael donors. As shown in Table 1, additives **3b** or **3c** were obtained in 46% and 78% yields, respectively (entries 2 and 3). In