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# One-Pot Electrochemical Synthesis of Fused Indole Derivatives Containing Active Hydroxyl Groups in Aqueous Medium

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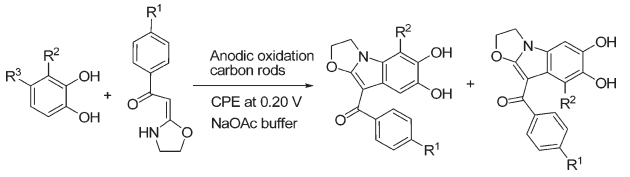


An novel and convenient electrochemical approach was developed for the synthesis of indole derivatives from catechols and α-oxoheterocyclic ketene *N*,*O*-acetals. This method provides an environmentally benign access to fused indole derivatives containing active hydroxyls and carbonyl under mild reaction conditions.

As one of the environmentally benign processes, organic electrochemical synthesis in aqueous medium[1] is attracting considerable attention from organic chemists and pharmacologists and is being applied to the synthesis of organic compounds with various biological properties or as key steps for the synthesis of complex natural products.[2,3]

Nitrogen-containing heterocycles, especially indole derivatives, constitute an important class of biologically active natural and unnatural compounds.[4] Some of them are used as anticancer,[5] antioxidant,[6] and HIV integrase inhibitors.[7] Consequently, the synthesis and functionalization of indoles have been the object of research for over 100 years, and a variety of well-established classical methods are now available.[8] Recently, due to the great advance in palladium-catalyzed Sonogashira coupling reactions of alkynes and aromatic iodide, 2-ethynylaniline derivatives can be easily produced in large scale and, therefore, the synthesis of indoles from 2-ethynylaniline derivatives by using transition metal catalysts has become the main context of indole synthetic chemistry.[9,10]

As part of our ongoing studies on the electrochemical synthesis of polyhydroxylated aromatics as potential HIV-1 integrase inhibitors, we have observed that the electrochemical oxidation of catechols in the presence of some types of mononucleophiles involves an ECEC mechanism (E = electrochemical and C = chemical step) to generate disubstituted catechols.[11,12] Following the same mechanism, benzofuran derivatives are also produced from electrochemically generated *o*-benzoquinones and 1,3-dicarbonyl compounds.[13,14] With this in mind, we hypothesized that the anodic oxidation of catechols in the presence of enamines as dinucleophile may also follow an ECEC process and undergo a C−C coupling and a C−N coupling sequence to generate indole derivatives. In the present work, we report on the electrochemical oxidation of catechols **1** in the presence of α-oxoheterocyclic ketene *N*,*O*-acetals **2**[15] to synthesize fused indole derivatives containing active hydroxyl groups. To the best of our knowledge, this is the first example of the formation of highly functionalized fused indole derivatives by a one-pot and transition metal-free electrochemical approach, where protection−deprotection of the two active hydroxyl groups is not required.

The electrochemical behaviors of catechols in the absence and presence of **2a**−**c** were first investigated by cyclic voltammetry (CV), at room temperature, in 0.2 M acetate buffer (pH 7). Taking **1b** as an example, its typical CVs are shown in Figure 1. Upon scanning anodically, catechol **1b** exhibits one well-defined oxidation wave (A1) at 0.34 V versus Ag/AgCl,

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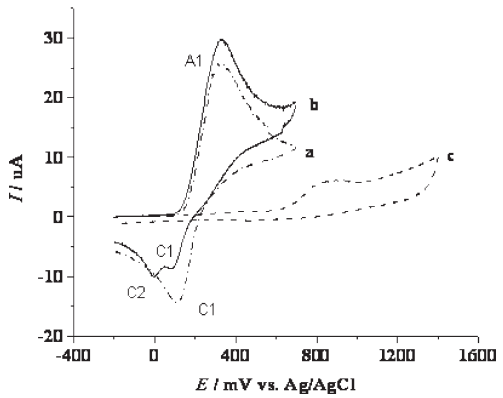
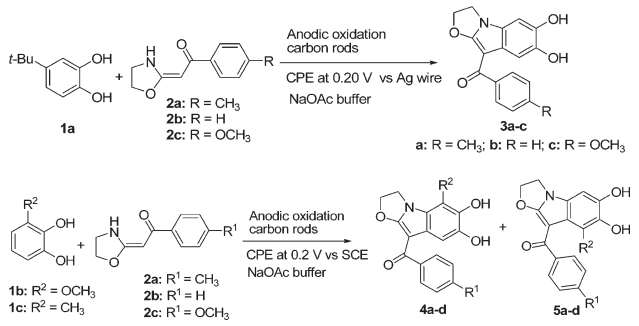



**FIGURE 1.** Cyclic voltammogram of (a) 2 mM 3-methoxycatechol **1b**, (b) a mixture of 2 mM 3-methoxycatechol and 2 mM heterocyclic ketene *N*,*O*-acetal **2a**, and (c) 2 mM heterocyclic ketene *N*,*O*-acetal **2a**, at a glassy carbon electrode, platinum wire counter and Ag/AgCl reference, in 4:1 (v/v) acetate buffer solution/acetronitrile (0.2 M, pH 7); scan rate 50 mV/s.

presumably corresponding to the formation of *o*-benzoquinone derivative involving a simultaneous 2e process,[13,14] which was reduced in the cathodic sweep at 0.10 V (C1), back to **1a** (curve a). 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 under pH 7 acetate buffer. To get further information on the transformation of the in situ generated *o*-benzoquinone in the presence of **2** as dinucleophile, the anodic oxidation of **1b** in the presence of **2a** has also been studied by the cyclic voltammetry method. As shown in curve b, when an equivalent amount of **2a** was added, the anodic potential slightly shifts positively to 0.36 V and a new cathodic peak (C2) at 0.00 V appears. Simultaneously, the current amplitude of the initial cathodic peak (C1) obviously decreased. Curve c is the CV of α-oxoheterocyclic ketene *N*,*O*-acetal **2a** with a not well-defined anodic peak centered at 0.89 V. This behavior indicates that a chemical reaction occurs between the electrochemically generated *o*-benzoquinone (at A1) and the α-oxoheterocyclic ketene *N*,*O*-acetal **2a**, and therefore Michael addition products may be synthesized upon anodic oxidation of the mixture of catechol and α-oxoheterocyclic ketene *N*,*O*-acetals when the electrolyzed potential was controlled at the anodic potential of catechol (0.34 V versus Ag/AgCl for **1b**), where, undesired oxidation of ketene *N*,*O*-acetals will not take place due to their significantly higher anodic potentials.

On the basis of the above CV analysis of catechols in the absence and presence of heterocyclic ketene *N*,*O*-acetals **2**, we first carried out the controlled-potential electrolysis (CPE) of a mixture of 4-*tert*-butylcatechol and **2a**. Thus, according to our reported conditions,[11,12] an equivalent amount of **2a** and **1a** in a divided cell was electrolyzed at 0.20.V vs. Ag wire in acetate buffer. After the consumption of starting 4-*tert*-butylcatechol, a brown powder was finally isolated by column chromatography and its structure was characterized by $^1$H NMR, $^{13}$C NMR, IR, and HRMS. Surprisingly, no *tert*-butyl signal was observed in its $^1$H NMR spectrum, which exhibits two triplets (at $\delta$ 3.98 and 4.32 ppm) and two singlets (at $\delta$ 9.08 and 9.22 ppm) attributed to the $NCH_2CH_2O$

**SCHEME 1. One-Pot Synthesis of Fused Indole Derivatives 3, 4, and 5 with Anodic Oxidation**




subunit and two hydroxyl groups, respectively. In addition, there are two singlets residing at 6.98 and 7.42 ppm, assigned to the signals of two protons of the catechol unit, apart from two doublets (AA′BB′ system of the benzene ring of *p*-methylbenzoyl subunit) in the aromatic region. All this information along with other spectral and analytical data (see the Experimental Section) demonstrate that what we obtained was a fused indole derivative **3a**.

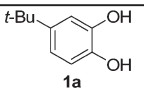
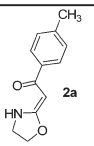
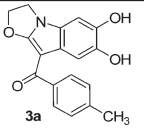
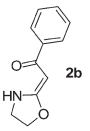
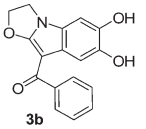
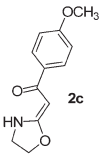
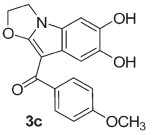
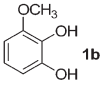
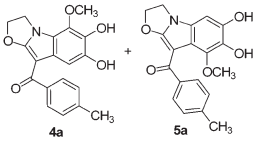
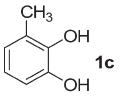
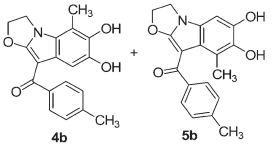
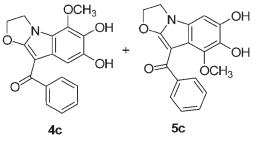
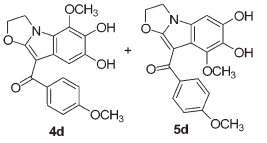
Prompted by the successful synthesis of indole derivative **3a**, we then examined the scope of different catechols and ketene *N*,*O*-acetals **2** and the results are summarized in Table 1. As shown in Scheme 1 and Table 1, we first extended this reaction to **2b** and **2c** with a view to investigate the scope of heterocyclic ketene *N*,*O*-acetals. Therefore, electrochemical oxidation of 4-*tert*-butylcatechol in the presence of **2b** and **2c** was performed and produced the expected products **3b** and **3c** in 56% and 48% yields, respectively.

To further extend the scope of this reaction, we then investigated the flexibility of catechols. Thus, 3-methoxycatechol (**1b**) and 3-methylcatechol (**1c**) were subjected to anodic oxidation under identical conditions. After simple filtration, indole derivatives **4a** and **5a** as a mixture of regioisomers in the ratio of 2:1 were obtained in 71% yield from the anodic oxidation of **1b** in the presence of **2a** (Scheme 1). In the case of 3-methylcatechol (**1c**), the regioisomers of **4b** and **5b** in a ratio of 1:1 were also isolated in 62% yield.

A similar trend was observed when 3-methoxycatechol (**1b**) was oxidized anodically in the presence of **2b** or **2c**. Under identical conditions, the corresponding mixtures of regioisomers (**4c** and **5c**, **4d** and **5d**) were accomplished in 51% and 40% yields, respectively. This result indicates that indole derivatives could indeed be synthesized by reaction between catechols and enamine derivatives (such as compound **2a**) on the electrochemical oxidation conditions.

Mechanistically, Nematollahi et al.[13,14] have proposed the formation of benzofurans from anodic oxidation of catechols in the presence of 1,3-dicarbonyl compounds employing the ECEC mechanism. Obviously, we can assume that a similar process may take place to generate the final indole derivatives from catechols and ketene *N*,*O*-acetals. Therefore, as shown in Scheme 2, the anodic oxidation of 4-*tert*-butyl catechol **1a** transforms to the corresponding *o*-benzoquinones **6a**, which are highly reactive and undergo Michael reaction with ketene *N*,*O*-acetals, to generate intermediates **7** due to the greater nucleophilicity of the α-C of ketene *N*,*O*-acetals. The initially formed intermediate **7**, by itself

**TABLE 1. Anodic Oxidation of Catechols 1 in the Presence of Reaction of Heterocyclic Ketene *N,O*-Acetals 2**

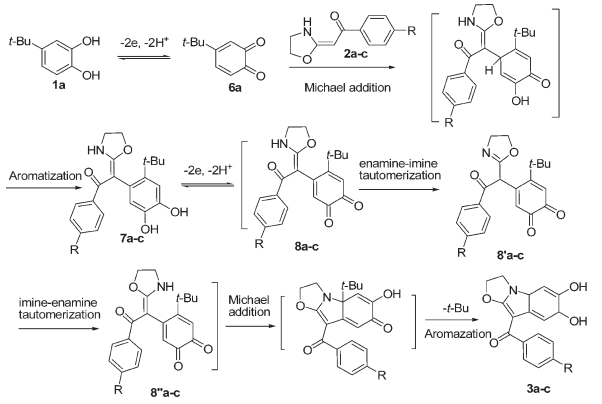
| Entry | Catechol | N,O-acetal | Products | Ratio[a] | Yield(%)[b] |
|---|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **3a** | | 37 |
| 2 | **1a** |  **2b** |  **3b** | | 56 |
| 3 | **1a** |  **2c** |  **3c** | | 48 |
| 4 |  **1b** | **2a** |  **4a** **5a** | 2:1 | 71 |
| 5 |  **1c** | **2a** |  **4b** **5b** | 1:1 | 62 |
| 6 | **1b** | **2b** |  **4c** **5c** | 2:1 | 51 |
| 7 | **1b** | **2c** |  **4d** **5d** | 2:1 | 40 |

[a]Ratio of region−isomers by $^1$H NMR. [b]Isolated yield.

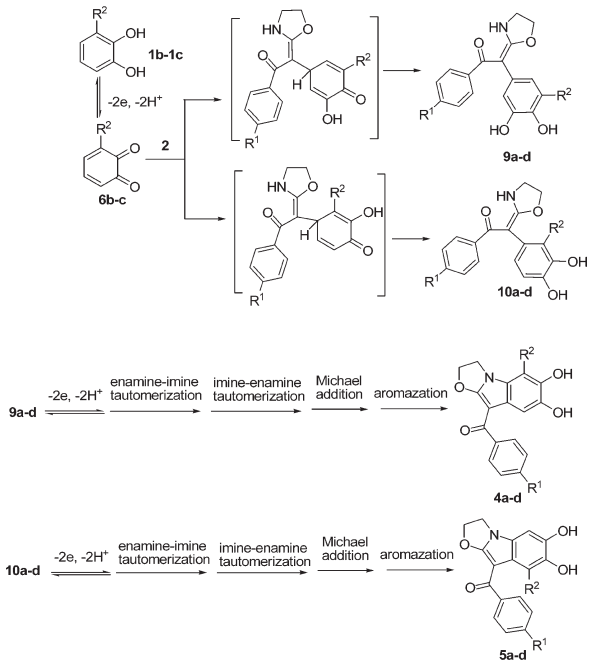
a catechol derivative, is further oxidized to the corresponding *o*-benzoquinone derivatives **8**. To take a preferable configuration for further nucleophilic attack, an enamine−imine and an imine−enamine tautomerization process are required, which led to the formation of **8″**. After the Michael addition reaction and subsequent loss of a *tert*-butyl carbonium followed by aromatization, indoles **3a**−**c** were finally generated.

The electrochemical oxidation of 3-substituted catechol **1b** and **1c** in the presence of **2a**−**c** proceeded in a similar manner. However, the asymmetry of 3-substituted catechol led to two indole isomers **4** and **5** because the initial nucleophilic addition of the carbine C of ketene *N,O*-acetals to the 3-substituted *o*-benzoquinone (formed from the oxidation of corresponding 3-substituted catechols) can occur in the C-4 and C-5 of the benzene ring, leading to the formation of intermediates **9** and **10**. Upon anodic oxidation, enamine−imine tautomerization, imine−enamine tautomerization, the Michael feature of addition, and the aromazation process, indole derivatives **4** and **5** were finally generated. It should be pointed out that, due to the steric hindrance as well as the less electropositive C-4, the initial Michael addition on the C-5 position is preferable to that on the C-4 position, which results in the yield of **4** being higher than that of **5** (the ratio of **4** to **5** is about 2:1 according to the $^1$H NMR data). Both of

**SCHEME 2. A Plausible Mechanism for the Synthesis of Indoles 3**




**SCHEME 3. A Plausible Mechanism for the Synthesis of Indoles 4 and 5**




them have very similar polarity and could not be separated (Scheme 3).

In conclusion, we have developed a novel and convenient electrochemical approach for the synthesis of indole derivatives from heterocyclic ketene *N*,*O*-acetals and catechols. This method provides an environmentally benign access to fused indole derivatives with multiactive functional groups for further derivatization under mild reaction conditions. The commonly known process of protection−deprotection of the two active hydroxyl groups is not required here and the use of metal catalyst and ligand is avoided. Moreover, the electrochemical formation of indole derivatives extends the application of electrochemical synthesis of *o*-benzoquinone and its in situ transformation. Further investigation for other indoles and the generality of this method are in progress.

## Experimental Section

**General Procedure for the Synthesis of Compounds 3a−c.** In a typical procedure, 50 mL of sodium acetate solution (0.2 M, pH 7) was pre-electrolyzed at the chosen potential (0.20 V vs. Ag wire) in an H-type cell, which was kept in water at room temperature for 10 min to remove impurities present in the electrolytic system. Subsequently, 4-*tert*-butyl catechol (2 mmol) and α-oxoheterocyclic ketene *N*,*O*-acetal **2** (2 mmol) were added to the anodic compartment and electrolyzed. The typical working currents were in the range of 40−90 mA and the electrolysis was terminated when the starting **1** was consumed by TLC following the reaction process. After electrolysis, the anolyte was adjusted to pH 7 by a few drop of acetic acid. The reaction mixture was extracted by ethyl acetate (3 × 30 mL) and washed with water (2 × 30 mL). The separated organic layer was dried over $MgSO_4$, then filtered and evaporated. The crude product was purified by column chromatography on silica gel, eluted with a mixture of acetone−petroleum ether (v:v 1:3) to give indole derivatives **3**.

**(6,7-Dihydroxy-2,3-dihydrooxazolo[3,2-*a*]indol-9-yl)(4-methylphenyl)methanone (3a):** mp 220−222 °C; $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$ 2.36 (s, 3H, $CH_3$), 3.98 (t, 2H, $J$ = 9.2 Hz, $NCH_2$), 4.32 (t, 2H, $J$ = 9.2 Hz, $OCH_2$), 6.99 (s, 1H, Ar−H), 7.28 (d, 2H, $J$ = 8.0 Hz, Ar−H), 7.41 (s, 1H, ArH), 7.79 (d, 2H, $J$ = 8.0 Hz, Ar−H), 9.08 (s, 1H, OH), 9.22 (s, 1H, OH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$ 21.4, 54.8, 67.0, 98.1, 105.2, 106.9, 119.2, 127.6, 128.8, 129.2, 139.3, 143.9, 145.7, 148.0, 155.1, 159.6; IR (KBr) ($cm^{-1}$) $\nu$ max 3414, 2923, 1628, 1328; ESI-MS $m/z$ 307.6 ($M^+ - 1$); HRMS (EI) $m/z$ calcd for $C_{18}H_{14}NO_4$ 308.0923, found 308.0925.

**(6,7-Dihydroxy-2,3-dihydrooxazolo[3,2-*a*]indol-9-yl)(phenyl)methanone (3b):** mp 191−193 °C; $^1$H NMR (400 MHz, acetone-$d_6$, ppm) $\delta$ 4.04 (t, 2H, $J$ = 9.6 Hz, $NCH_2$), 4.37 (t, 2H, $J$ = 9.6 Hz, $OCH_2$), 7.05 (s, 1H, Ar−H), 7.43−7.49 (m, 3H, Ar−H), 7.59 (s, 1H, ArH), 7.99−8.01 (m, 2H, Ar−H); $^{13}$C NMR (100 MHz, acetone-$d_6$, ppm) $\delta$ 55.4, 67.3, 98.0, 106.6, 107.7, 120.7, 128.7, 129.5, 129.8, 131.4, 143.7, 145.8, 149.3, 156.0, 160.5; IR (KBr) ($cm^{-1}$) $\nu$ max 3468, 2928, 2871, 1624, 1566, 1482, 1315; ESI-MS $m/z$ 295.8 ($M^+$+1), 293.5 ($M^+ - 1$); HRMS (EI) $m/z$ calcd for $C_{17}H_{12}NO_4$ 294.0722, found 294.0711.

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**Supporting Information Available:** Electrochemical apparatus description and general procedure for the synthesis of **4a−d** and **5a−d** and spectral data for compounds **3c**, **4a−d**, and **5a−d**. This material is available free of charge via the Internet at http://pubs.acs.org.