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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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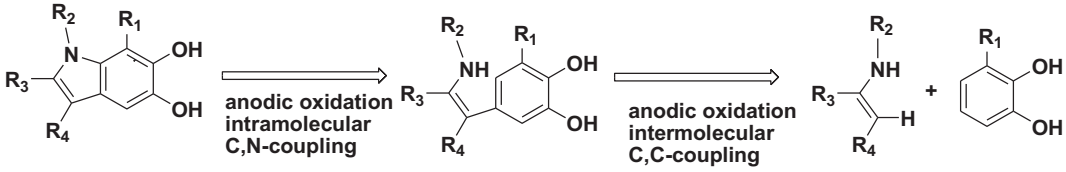
ABSTRACT

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).

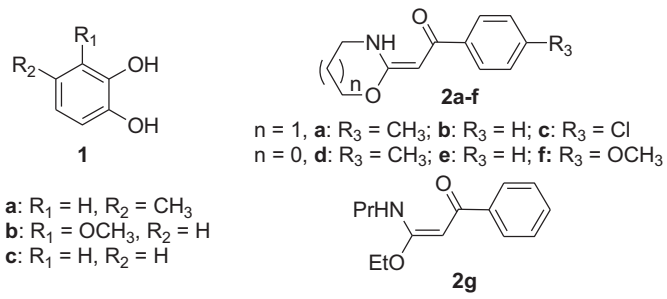


Fig. 1. The structure of starting catechols and ketene *N*,*O*-acetals.

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).

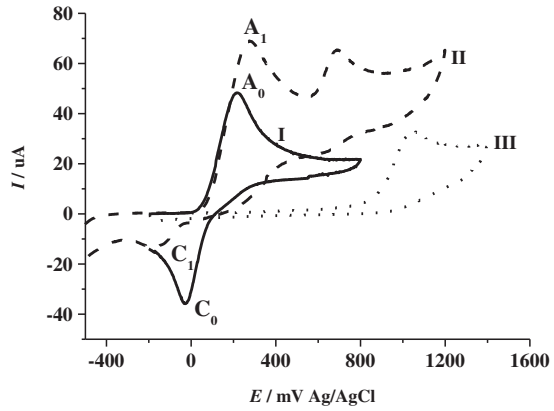
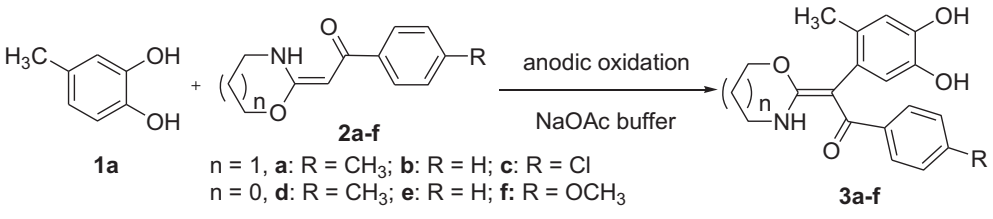


Fig. 2. Cyclic voltammograms of (I) 2 mM of 4-methylcatechol (**1a**), (II) a mixture of 2 mM of **1a** and 2 mM of ketene *N*,*O*-acetal **2a**, and (III) 2 mM of ketene *N*,*O*-acetal **2a**, at a glassy carbon working electrode, platinum wire counter electrode, and Ag/AgCl (0.1 M) reference electrodes, 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

Table 1
Anodic oxidation of catechols **1** in the presence of heterocyclic ketene *N*,*O*-acetals **2**

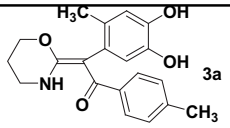
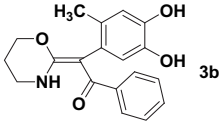
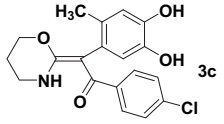
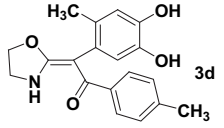
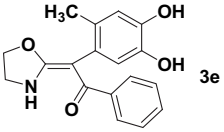
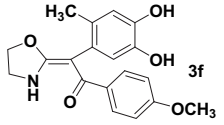
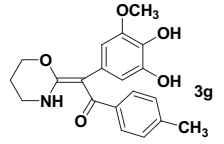
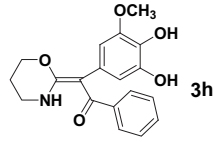
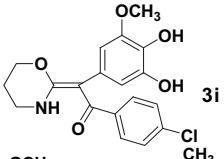
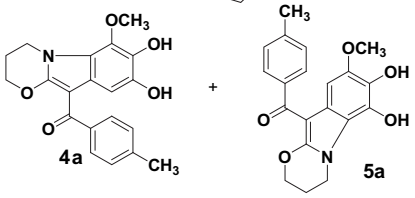
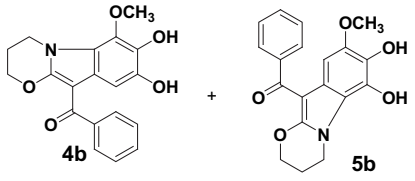
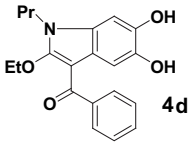
Entry	Catechol	Ketene acetal	Product	Ratio[a]	Yield[b] (%)
1[c]	**1a**	**2a**	 **3a**	—	75
2[c]	**1a**	**2b**	 **3b**	—	46
3[c]	**1a**	**2c**	 **3c**	—	78
4[c]	**1a**	**2d**	 **3d**	—	68
5[c]	**1a**	**2e**	 **3e**	—	56
6[c]	**1a**	**2f**	 **3f**	—	81
7[c]	**1b**	**2a**	 **3g**	—	56
8[c]	**1b**	**2b**	 **3h**	—	43
9[c]	**1b**	**2c**	 **3i**	—	75
10[d]	**1b**	**2a**	 **4a** + **5a**	2: 1	45
11[d]	**1b**	**2b**	 **4b** + **5b**	2: 1	25

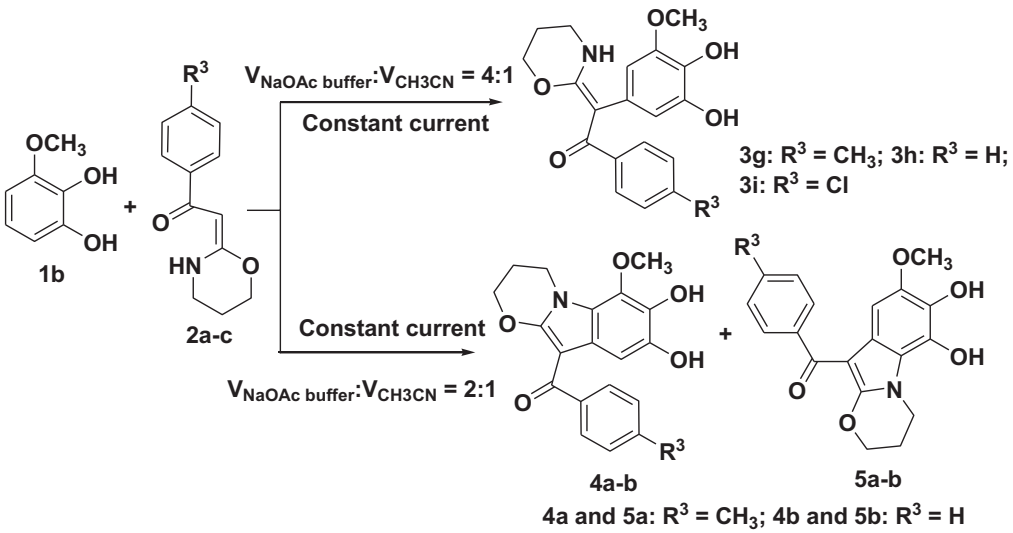
Table 1 (*continued*)

Entry	Catechol	Ketene acetal	Product	Ratio[a]	Yield[b] (%)
12[d]	**1c**	**2g**	 **4d**		23

[a] Ratio of regioisomers determined by ^{1}H NMR.
[b] Isolated yield.
[c] Experimental conditions: room temperature, 1 mmol of catechol **1** and 1 mmol of **2** in 50 mL of 0.2 M acetate buffer and acetonitrile (4:1=v/v), an assembly of seven graphite rods anode, Pt plate (2 cm^2) cathode, divided cell; Constant current: 15 mL (~3 mA/cm); Charge passed: 2.24 F/mol.
[d] Experimental conditions: 1.5 mmol of catechol **1b** and 1 mmol of **2** in 100 mL of 0.2 M acetate buffer and acetonitrile (2:1=v/v), charge passed: 4.0 F/mol, other conditions were identical to the above.

addition, heterocyclic ketene acetals **2d**–**f** containing an oxazolidine ring afforded adducts **3d**, **3e**, and **3f** in yields of 68%, 56%, and 81%, respectively, under similar reaction conditions (Scheme 2 and entries 4–6).

Attention was next turned toward exploring the possible utility of 3-substituted catechols. To this end, 3-methoxycatechol was examined (Scheme 3).[11] As shown in Table 1, under identical conditions, products **3g**–**i** were obtained after simple filtration in 56%, 43%, and 75% yield, respectively (Scheme 3 and entries 7–9, Table 1). remained unchanged. After 2.24 F/mol of current was passed, **3g** was detected by TLC, along with the formation of another compound. Also, no precipitate formed. When a total of 4.39 F/mol of charge was passed, a yellow powder precipitated, which was filtered and identified. Spectroscopic methods demonstrated that the precipitate was a 2:1 mixture of regioisomers **4a** and **5a**, formed in a 45% yield (entry 10). Efforts to separate the polyhydroxylated indoles **4a** and **5a** failed using conventional methods, due to 'identical' polarity of **4a** and **5a** (Scheme 3).



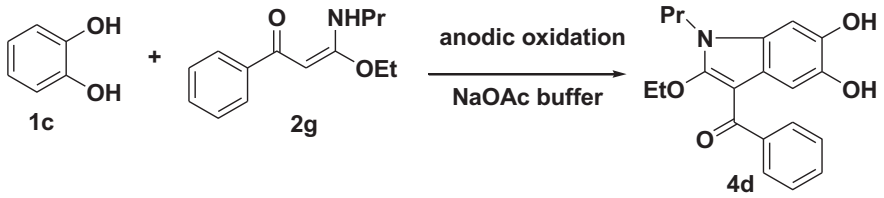
Scheme 3. Anodic oxidation of 3-methoxycatechol (**1b**) in the presence of ketene *N*,*O*-acetals **2a**–**c**.

Since we have reported the formation of the indole ring from 3-methoxycatechol **1b** and heterocyclic ketene *N*,*O*-acetals **2d**–**f** using anodic oxidation, we expected that indole formation would also take place when *N*,*O*-acetals **2a**–**c** were examined. However, in the present instances, only the α-arylated products **3g**–**i** were produced. Perhaps the presence of a six-membered oxazinane ring of ketene *N*,*O*-acetals prevented intramolecular Michael addition from generating the indole ring. Another rationale suggests that the initially formed products **3g**–**i** do not dissolve and further oxidation and intramolecular Michael addition is thus terminated. If the second reason is true, then indole derivatives should be attainable by modifying the electrolytic solution to ensure solubility of the initially formed materials **3g**–**i**.

To test this hypothesis, we examined the reaction of **1b** and **2a**. We changed the composition of the electrolytic solution from 1:4 to a 1:2 ratio of acetonitrile to acetate buffer solution and repeated the electrochemical oxidation. Other reaction conditions, such as applied current, the nature of the electrode material and cell type

To further explore our hypothesis, the electrochemical oxidation of 3-methoxycatechol (**1b**) in the presence of **2b** was also carried out under the modified conditions. After conventional workup and column chromatography, a 2:1 mixture of regioisomers **4b** and **5b** was obtained in 25% yield, along with the isolation of 14% yield of α-arylation product **3h** (Scheme 3 and entry 11). It is worth noting that the corresponding indoles **4c** and **5c** did not form from the reaction of **1b** and **2c** under the modified conditions. Once again, it is because of the low solubility of **3i**. For example, **3i** precipitated when 2 F/mol charge was passed and did not disappear after the consumption of 4 F/mol of charge. After conventional workup, α-arylation product **3i** was obtained in a 73% yield (Scheme 3 and entry 11).

Finally, noncyclic ketene *N*,*O*-acetal **2g** was designed and synthesized to examine whether the ring structure of the ketene *N*,*O*-acetal would influence the selective formation of indole or α-arylation product. As shown in Table 1, the anodic oxidation of a mixture of **1c** and **2g** under identical conditions afforded corresponding **4d** in 23% yield (Scheme 4 and entry 12, Table 1).



Scheme 4. Anodic oxidation of catechol in the presence of ketene *N*,*O*-acetals **2g**.

It is noteworthy that these polyhydroxylated α-arylation product and indoles were quite difficult to separate by silica gel column chromatography because they adhered so strongly to the chromatographic support.[12] Therefore, somewhat lower yields of **4d** were obtained when it was isolated using column chromatography, compared with that of **4a**, which was isolated via simple filtration, although almost quantitative of conversion was observed via TLC in both cases.

On the basis of the above results and our previous examination of the anodic oxidation of catechols in the presence of ketene *N*,*N*-acetals,[9] we conclude that the structure of the starting benzoyl-substituted ketene *N*,*O*-acetals ketene plays a key role in determining the formation of α-arylation products or indoles, although the exact reason behind such results is not clear.

2.3. Reaction mechanism

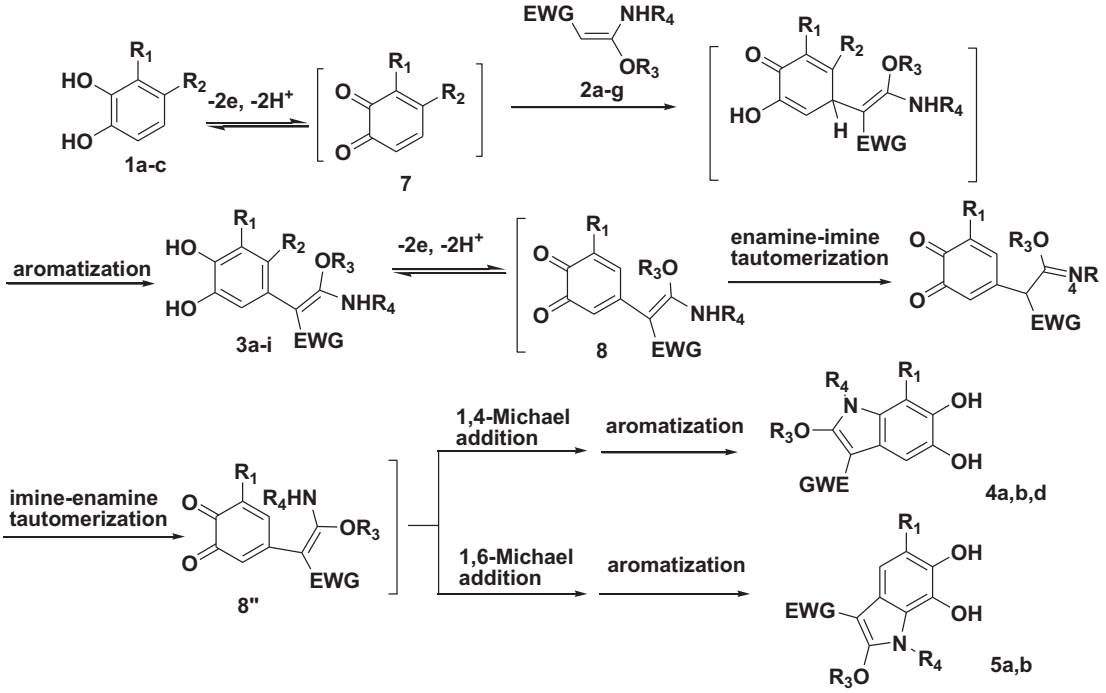
Nematollahi et al. have demonstrated the formation of benzofurans from the anodic oxidation of catechols in the presence of 1,3-dicarbonyl compounds and have suggested an ECEC mechanism. Obviously, we can assume that a similar sequence may take place to generate indole derivatives from catechols and ketene *N*,*O*-acetals. As shown in Scheme 5, we suggest that the anodic oxidation of catechol **1** transforms it to the corresponding highly reactive *o*-benzoquinones **7**, which then undergo Michael reaction with ketene *N*,*O*-acetals **2** to generate α-arylated products **3a**–**i**.

If the initially formed α-arylated products **3** do not dissolve in the electrolytic solution when the volume ratio of acetonitrile to acetate buffer is 1:4, then **3** precipitates, over-oxidation is avoided, and α-arylated products are produced exclusively. However, when the ratio of acetate buffer to acetonitrile is increased to 2:1, then the initially formed **3g** and **3h** can partially dissolve and further oxidation proceeds to generate the corresponding *o*-benzoquinone derivatives **8**. To achieve the geometry needed for the subsequent nucleophilic attack (see Scheme 5), an enamine-to-imine and an imine-to-enamine tautomerization is required to convert **8** to **8″**. From there, a Michael addition followed by aromatization to generate indole derivatives **4** or a 1,6-addtion leading to regioisomers **5** can occur.

It should be pointed out that, due to steric and electronic effects, the 1,4-addition pathway is preferable to 1,6-addition. This presumably accounts for the higher yield of **4** relative to **5** (the ratio of **4** to **5** is about 2:1 according to the ^{1}H NMR data).

3. Conclusion

The anodic oxidation of catechols has been investigated in the presence of heterocyclic and noncyclic ketene *N*,*O*-acetals. The results showed that α-arylated products can obtained from 4-substituted catechols and *N*,*O*-acetals, whereas, either α-arylated products or indoles could be generated from 3-substituted catechols. Also, the composition of the electrolyte solution plays a key



Scheme 5. Proposed mechanism for the conversion of catechols **1a**–**c** to indoles **4a**,**b**,**d** and **5a**,**b**.

role in ensuring that the reaction stops at the α-arylated products or proceeds leading to indole formation. In addition, we conclude that the nature of the ketene acetal is one of the predominant factors in determining whether or not the indole ring can be generated. Further investigation of the generality of this method for the formation of indoles is in progress.

4. Experimental

4.1. Instruments and reagents

Melting points were measured with a XT4A Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded with an AV 400 M Bruker spectrometer (400 MHz ^{1}H frequency, 100 MHz ^{13}C frequency). Chemical shifts are given as δ values (internal standard: TMS). The MS spectra (ESI) were recorded on a Bruker Esquire 6000 mass spectrometer.

Catechols **1a** and **1b** were reagent-grade and obtained from Alfa Aesar China (Tianjin) Co. Ltd. Compounds **2a**–**f** and **2g** were synthesized by following known procedures.[13] Other chemicals and solvents were obtained from Beijing Chemicals Co. and used without further purification. All electrodes for CV experiments were from CH Instruments, Inc. USA. Doubly distilled de-ionized water was used for the preparation of the aqueous acetate buffer. All experiments were performed at room temperature and ambient pressure.

4.2. Cyclic voltammetry

Cyclic voltammograms were measured by using a 273A Potentiostat/Galvanostat equipped with an electrochemical analysis software, using a conventional three-electrode cell. The working electrode was a glassy carbon disk electrode (ca. ϕ=3 mm). The auxiliary and reference electrodes in these studies were Pt wire and saturated Ag/AgCl (in 3 M KCl), respectively. Glassy carbon was polished with polishing cloth before each measurement. Acetate buffer solutions were prepared from NaOAc and HOAc and were monitored by a digital pH meter. The scan rate was 50 mV/s. The concentration of **1** and **2** were 2 mmol L^{-1}, while that of the supporting electrolyte was 0.2 mol L^{-1}.

4.3. General procedure for the synthesis of compounds 3a–f

An H-type cell equipped with a medium porosity of glass frit as a membrane was maintained in water bath at room temperature. The anode compartment contained an anode assembly consisting of seven graphite rods whose upper rims were wrapped by a copper wire; a platinum plate (2 cm^2) served as the counter electrode and was immersed in the cathode compartment. The applied current throughout electrolysis was 15 mA ($\sim$3 mA/cm) and was controlled by a direct current power source. During the course of electrolysis, a magnetic stirrer stirred the mixture.

In a typical procedure, to the anode compartment was added a mixture of 50 mL 0.2 M acetate buffer/acetonitrile (the volume ratio is 4:1). Subsequently, 1 mmol catechols **1** and 1 mmol **2** were added to the anodic compartment and the solution was electrolyzed. The electrolysis was terminated after 2.24 F/mol of charge was passed. The formed precipitate was filtered, washed with water (3×10 mL), and dried to obtain the corresponding product, **3**.

*4.3.1. (E)-2-(4,5-Dihydroxy-2-methylphenyl)-2-(1,3-oxazinan-2-ylidene)-1-p-tolylethanone (**3a**).* Yield 75%; mp 227–228 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86 (s, 3H, CH_3), 1.97 (t, 2H, CH_2), 2.18 (s, 3H, CH_3), 3.47 (t, 2H, J=4.0 Hz, N–CH_2), 4.19 (t, 2H, J=5.2 Hz, O–CH_2), 6.26 (s, 1H, Ar–H), 6.41 (s, 1H, Ar–H), 6.87 (d, 2H, J=8.0 Hz, Ar–H), 6.97 (d, 2H, J=8.0 Hz, Ar–H), 8.27 (s, 1H, OH), 8.41 (s, 1H, OH), 13.16 (s, br, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.8, 21.0, 21.2, 37.3, 66.0, 94.1, 117.1, 121.4, 127.8, 127.9, 128.0, 129.3, 137.5, 140.5, 142.6, 143.9, 166.0, 185.4 ppm. IR (KBr): ν 3427, 2919, 1606, 1520 cm^{-1}. ESI-MS: m/z 339.7 [M+1]$^+$, 361.7 [M+Na]$^+$, 337.8 [M−1]$^-$, 676.9 [2M−1]$^-$.

*4.3.2. (E)-2-(4,5-Dihydroxy-2-methylphenyl)-2-(1,3-oxazinan-2-ylidene)-1-phenylethanone (**3b**).* Yield 46%; mp 232–234 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87 (s, 3H, CH_3), 1.98 (t, 2H, J=4.4 Hz, CH_2), 3.48 (s, 2H, CH_2), 4.20 (t, 2H, J=4.8 Hz, O–CH_2), 6.27 (s, 1H, Ar–H), 6.41 (s, 1H, Ar–H), 7.09 (m, 5H, Ar–H), 8.26 (s, 1H, OH), 8.40 (s, 1H, OH), 13.14 (s, br, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.8, 21.0, 37.3, 66.1, 94.2, 117.1, 121.4, 127.4, 127.6, 127.9, 128.2, 129.3, 142.6, 143.3, 143.9, 166.1, 185.5 ppm. IR (KBr): ν 3482, 1619, 1507, 1438 cm^{-1}. ESI-MS: m/z326.0 [M+1]$^+$, 347.9 [M+Na]$^+$, 673.0 [2M+Na]$^+$, 323.6 [M−1]$^-$, 648.7 [2M−1]$^-$.

*4.3.3. (E)-1-(4-Chlorophenyl)-2-(4,5-dihydroxy-2-methylphenyl)-2-(1,3-oxazinan-2-ylidene)ethanone (**3c**).* Yield 78%; mp 248–249 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86 (s, 3H, CH_3), 1.98 (t, 2H, J=4.0 Hz, CH_2), 3.49 (t, 2H, J=4.0 Hz, N–CH_2), 4.21 (t, 2H, J=4.8 Hz, O–CH_2), 6.26 (s, 1H, Ar–H), 6.43 (s, 1H, Ar–H), 7.05 (d, 2H, J=8.4 Hz, Ar–H), 7.13 (d, 2H, J=8.0 Hz, Ar–H), 8.30 (s, 1H, OH), 8.46 (s, 1H, OH), 13.03 (s, br, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.7, 20.9, 37.3, 66.2, 94.2, 117.2, 121.4, 127.2, 127.4, 129.2, 129.7, 132.8, 142.1, 142.7, 144.1, 166.2, 183.9 ppm. IR (KBr): ν 3414, 2919, 2875, 2700, 2586, 1606, 1572, 1520, 1506 cm^{-1}. ESI-MS: m/z 359.8 [M+1]$^+$, 381.7 [M+Na]$^+$, 357.8 [M−1]$^-$, 716.8 [2M−1]$^-$.

*4.3.4. (E)-2-(4,5-Dihydroxy-2-methylphenyl)-2-(oxazolidin-2-ylidene)-1-p-tolylethanone (**3d**).* Yield: 68%; mp: 225–226 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.78 (t, 2H, N–CH_2), 4.38 (t, 2H, O–CH_2), 6.33 (s, 1H, Ar–H), 6.44 (s, 1H, Ar–H), 6.91 (d, 2H, J=8.0 Hz, Ar–H), 7.04 (d, 2H, J=8.0 Hz, Ar–H), 8.34 (s, 1H, OH), 8.47 (s, 1H, OH), 10.55 (s, br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.7, 21.2, 43.9, 67.8, 90.8, 117.2, 120.9, 127.5, 128.1, 128.2, 128.9, 138.3, 139.9, 142.8, 144.1, 168.9, 187.3; IR (KBr): ν 3414, 2921, 1603, 1567, 1518, 1463; ESI-MS: m/z 325.9 [M+1]$^+$, 323.7 [M−1]$^-$, 648.8 [2M−1]$^-$.

*4.3.5. (E)-2-(4,5-Dihydroxy-2-methylphenyl)-2-(oxazolidin-2-ylidene)-1-phenylethanone (**3e**).* Yield: 56%; mp: 229–230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84 (s, 3H, CH_3), 3.80 (t, 2H, N–CH_2), 4.39 (t, 2H, O–CH_2), 6.33 (s, 1H, Ar–H), 6.43 (s, 1H, Ar–H), 7.08–7.18 (m, 5H, Ar–H), 8.32 (s, 1H, OH), 8.46 (s, 1H, OH), 10.55 (s, br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.7, 43.9, 67.9, 90.8, 117.2, 120.9, 127.3, 127.4, 128.0, 128.8, 128.9, 142.7, 142.8, 144.1, 168.9, 187.5; IR (KBr): ν 3424, 1599, 1520, 1488; ESI-MS: m/z 309.6 [M−1]$^-$.

*4.3.6. (E)-2-(4,5-Dihydroxy-2-methylphenyl)-1-(4-methoxyphenyl)-2-(oxazolidin-2-ylidene)ethanone (**3f**).* Yield: 81%; mp: 151–152 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.79 (m, 2H, N–CH_2), 4.38 (m, 2H, O–CH_2), 6.35 (s, 1H, Ar–H), 6.46 (s, 1H, Ar–H), 6.66 (d, 2H, J=8.8 Hz, Ar–H), 7.13 (d, 2H, J=8.8 Hz, Ar–H), 8.37 (s, 1H, OH), 8.50 (s, 1H, OH), 10.54 (s, br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.7, 43.9, 55.4, 67.8, 90.6, 112.8, 117.3, 120.8, 127.7, 128.8, 130.1, 134.9, 142.8, 144.1, 159.9, 168.8, 186.4; IR (KBr): ν 3436, 1602, 1576, 1469; ESI-MS: m/z 341.9 [M+1]$^+$, 363.8 [M+Na]$^+$, 339.7 [M−1]$^-$.

*4.3.7. (E)-2-(3,4-Dihydroxy-5-methoxyphenyl)-2-(1,3-oxazinan-2-ylidene)-1-p-tolylethanone (**3g**).* Yield 56%; mp 210–211 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.99 (t, 2H, J=5.2 Hz, CH_2), 2.19 (s, 3H, CH_3), 3.48 (s, 2H, N–CH_2), 3.48 (s, 3H, OCH_3), 4.23 (t, 2H, J=4.8 Hz, O–CH_2), 5.97 (d, 1H, J=1.6 Hz, Ar–H), 6.08 (d, 1H, J=1.6 Hz, Ar–H),

6.89 (d, 2H, J=8.0 Hz, Ar–H), 7.00 (d, 2H, J=8.0 Hz, Ar–H), 7.89 (s, 1H, OH), 8.45 (s, 1H, OH), 13.06 (s, br, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.9, 21.2, 37.3, 56.2, 66.0, 96.1, 109.7, 114.4, 127.8, 127.9, 128.3, 129.0, 129.6, 132.5, 137.3, 140.8, 145.2, 147.8, 166.1, 186.2 ppm. IR (KBr): ν 3372, 2969, 22,939, 2700, 2869, 1607, 1573, 1528, 1501, 1447 cm^{-1}. ESI-MS: m/z 355.9 $[M+1]^+$, 393.8 $[M+K]^+$.

*4.3.8. (E)-2-(3,4-Dihydroxy-5-methoxyphenyl)-2-(1,3-oxazinan-2-ylidene)-1-phenylethanone (**3h**).* Yield 43%; mp 211–212 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.00 (t, 2H, J=5.2 Hz, CH_2), 3.45 (s, 3H, OCH_3), 3.48(s, 2H, CH_2), 4.24 (t, 2H, J=4.8 Hz, O–CH_2), 5.93 (s, 1H, Ar–H), 6.10 (s, 1H, Ar–H), 7.09 (m, 5H, Ar–H), 7.88 (s, 1H, OH), 8.45 (s, 1H, OH), 13.02 (s, br, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.87, 37.3, 56.11, 66.1, 96.2, 109.7, 114.3, 127.4, 127.6, 127.9, 128.1, 132.4, 143.6, 145.1, 147.8, 166.1, 186.4 ppm. IR (KBr): ν 3468, 1615, 1532, 1504 cm^{-1}. ESI-MS: m/z 341.8 $[M+1]^+$, 361.8 $[M+Na]^+$, 704.9 $[2M+Na]^+$, 339.8 $[M-1]^-$.

*4.3.9. (E)-1-(4-Chlorophenyl)-2-(3,4-dihydroxy-5-methoxyphenyl)-2-(1,3-oxazinan-2-ylidene)ethanone (**3i**).* Yield 75%; mp: 237–239 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.01 (m, 2H, CH_2), 3.48 (s, 2H, N–CH_2), 3.48 (s, 3H, OCH_3), 4.25 (t, 2H, J=5.2 Hz, O–CH_2), 5.95 (d, 1H, J=1.6 Hz, Ar–H), 6.09 (d, 1H, J=1.6 Hz, Ar–H), 7.09 (d, 2H, J=8.4 Hz, Ar–H), 7.16 (d, 2H, J=8.4 Hz, Ar–H), 7.97 (s, 1H, OH), 8.52 (s, 1H, OH), 12.93 (s, br, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.8, 37.4, 56.1, 66.2, 96.3, 109.5, 114.3, 127.3, 127.5, 130.2, 132.5, 132.6, 142.4, 145.3, 147.9, 166.2, 186.7 ppm. IR (KBr): ν 3435, 1612, 1530, 1508, 1484 cm^{-1}. ESI-MS: m/z 375.8 $[M+1]^+$, 397.8 $[M+Na]^+$, 373.8 $[M-1]^-$, 748.7 $[2M-1]^-$.

4.4. Procedure for the synthesis of compounds 4a and 5a

The setups were identical to that for the synthesis of **3a**–**3f**. To the anode compartment was added a mixture of 100 mL of 0.2 M acetate buffer and acetonitrile (the volume ratio is 2:1). Subsequently, 1.5 mmol of catechols **1b** and 1.5 mmol of **2a** were added to the anodic compartment and the solution was electrolyzed. The electrolysis was terminated after 4.0 F/mol of charge was passed. The precipitate was filtered, washed with water (3×10 mL) and dried to obtain the desired products **4a** and **5a**.

4.4.1. (7,8-Dihydroxy-6-methoxy-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indol-10-yl)-p-tolylmethanone and (6,7-dihydroxy-8-methoxy-3,4-dihydro-2H-[1,3]-oxazino-[3,2-a]indol-10-yl)-p-tolylmethanone.- Yield 45%; mp 151–152 °C; ^{1}H NMR of **4a** (400 MHz, DMSO-d_6): δ 1.81 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 3.32 (s, NCH_2), 3.77 (s, 3H, OCH_3), 4.24 (s, 2H, OCH_2), 6.03 (s, 1H, Ar–H), 7.36 (d, 2H, J=6.4 Hz, Ar–H), 7.53 (br, s, H, OH), 7.74 (d, 2H, J=7.2 Hz, Ar–H), 10.02 (br, s, H, OH); ^{1}H NMR of **5a** (400 MHz, DMSO-d_6): δ 1.80 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 3.32 (s, NCH_2), 3.77 (s, 3H, OCH_3), 4.24 (s, 2H, OCH_2), 5.99 (s, 1H, Ar–H), 7.36 (d, 2H, J=6.4 Hz, Ar–H), 7.44 (br, s, H, OH), 7.74 (d, 2H, J=7.2 Hz, Ar–H), 10.06 (br, s, H, OH) ppm. ^{13}C NMR of **4a** and **5a** (100 MHz, DMSO-d_6): δ 21.6, 21.7, 43.2, 43.3, 55.6, 55.8, 65.9, 107.0, 109.2, 129.4, 129.6, 130.0, 130.0, 132.7, 133.2, 134.9, 135.1, 138.8, 139.1, 144.8, 145.0, 150.7, 151.3, 152.4, 152.9, 154.7, 176.3, 176.4, 194.0, 194.2 ppm. IR (KBr): ν 3419, 3366, 3124, 2972, 2941, 2855, 1664, 1622, 1606, 1580, 1528, 1472, 1449, 1427 cm^{-1}. ESI-MS: m/z 354.0 $[M+1]^+$, 729.0 $[2M+Na]^+$, 351.7 $[M-1]^-$.

4.5. Procedure for the synthesis of compounds 4b, 5b and 4d

The setups were identical to that for the synthesis of **3a**–**3f**. To the anode compartment was added a mixture of 100 mL of 0.2 M acetate buffer and acetonitrile (the volume ratio is 2:1). Subsequently, 1.5 mmol of catechols **1b** and 1.5 mmol of **2b** were added to the anodic compartment and the solution was electrolyzed. The electrolysis was terminated after 4.0 F/mol of charge was passed. The solution was acidified to pH=1 with 1 mol/L aqueous HCl and then extracted using 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, eluted with a mixture of petroleum ether and acetone (v/v=2:1) to afford **4b** and **5b**.

4.5.1. (7,8-Dihydroxy-6-methoxy-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indol-10-yl)(phenyl)methanone and (6,7-dihydroxy-8-methoxy-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indol-10-yl)(phenyl)methanone. Yield 25%; mp 101–103 °C; ^{1}H NMR of **4b** (400 MHz, DMSO-d_6): δ 1.81 (m, 2H, CH_2), 3.43 (t, 2H, J=5.6 Hz, NCH_2), 3.77 (s, 3H, OCH_3), 4.26 (t, 2H, J=5.6 Hz, OCH_2), 6.05 (s, 1H, Ar–H), 7.53–7.86 (m, 5H, Ar–H), 10.05 (br, s, H, OH); ^{1}H NMR of **5b** (400 MHz, DMSO-d_6): δ=1.78 (m, 2H, CH_2), 3.41 (t, 2H, J=7.0 Hz, NCH_2), 3.45 (s, 3H, OCH_3), 4.22 (t, 2H, J=7.0 Hz, OCH_2), 7.57 (s, 1H, Ar–H), 7.53–7.86 (m, 5H, Ar–H), 10.05 (br, s, H, OH) ppm. ^{13}C NMR of **4b** and **5b** (100 MHz, DMSO-d_6): δ 21.6, 31.1, 43.3, 55.6, 55.8, 65.9, 107.0, 107.0, 109.1, 129.3, 129.4, 129.5, 133.0, 133.5, 134.2, 134.4, 137.3, 137.6, 138.5, 138.7 150.8, 151.4, 152.4, 153.0, 154.8, 176.3, 176.4, 194.5, 194.7 ppm. IR (KBr): ν 3434, 2931, 2856, 1640, 1534, 1448 cm^{-1}. ESI-MS: m/z 340.0 $[M+1]^+$, 362.0 $[M+Na]^+$, 337.7 $[M-1]^-$.

*4.5.2. (2-Ethoxy-5,6-dihydroxy-1-propyl-1H-indol-3-yl)(phenyl)methanone (**4d**).* Yield: 23%; mp: 215–216 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.84–0.91 (m, 6H, $2CH_3$), 1.68–1.73 (m, 2H, CH_2), 3.68 (q, 2H, J=6.8 Hz, NCH_2), 3.91 (q, 2H, J=6.8 Hz, OCH_2), 6.81 (s, 1H, Ar–H), 7.28 (s, 1H, Ar–H), 7.55 (m, 5H, Ar–H), 8.64 (s, 1H, OH), 8.77 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.7, 15.1, 22.7, 43.4, 73.5, 97.5, 99.5, 106.9, 118.0, 125.4, 128.4, 128.7, 131.3, 141.4, 142.8, 143.4, 154.8, 189.5; IR (KBr): ν 3434, 2963, 2923, 2853, 2373, 2344, 1603, 1584, 1553, 1517, 1473, 1433 cm^{-1}; ESI-MS: m/z 339.9 (M^++1), 361.8 (M^++Na^+), 337.9 (M^-−1), 677.0 ($2M^-$−1).

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