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A Facile Synthesis of α-Aryl α-Oxoheterocyclic Ketene N,N-Acetals Bearing an Electron-Rich Catechol Subunit–An Electrochemical Oxidative Approach

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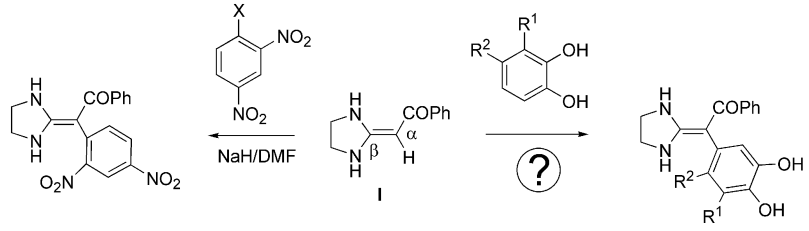
Heterocyclic ketene N,N-acetals are versatile building blocks for the synthesis of nitrogen-containing heterocyclic compounds. In the present work, the anodic oxidation of catechols **2a–f** in the presence of α-oxoheterocyclic ketene N,N-acetals **1a–d** has been investigated using cyclic voltammetry and controlled-potential electrolysis methods. These results indicate that α-oxoheterocyclic ketene N,N-acetals could undergo Michael addition to the anodically generated *o*-benzoquinones and produce α-carbon-arylated products in good yields. This approach provides effective and "green" access to the synthesis of α-aryl α-oxoheterocyclic ketene N,N-acetals containing an electron-rich aromatic ring. In addition, density functional theory calculations were performed to explain the exclusive formation of α-carbon-arylated products. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2009)

Introduction

During the past decades, much attention has been paid to the α-oxoheterocyclic ketene N,N-acetals (I, Scheme 1) due to their unique structure and various applications in the synthesis of nitrogen-containing heterocyclic compounds, especially the fused heterocyclic ones.[1] Structurally, α-oxoheterocyclic ketene N,N-acetals function as enaminones,[2] in which the electron-donating amino groups and electron-withdrawing carbonyl groups are conjugated and thus, the double bond is highly polarized, leading to the nucleophilicity of the α-carbon and the amino groups (the α- and β-carbons of the heterocyclic ketene N,N-acetals are marked in Scheme 1). Accordingly, two different electrophiles may be introduced at the same time through the respective substitution at or addition to the α-carbon and amino groups. Furthermore, one molecule with two electrophilic sites can be used to assemble a fused heterocyclic ring in one pot. For example, α-oxoheterocyclic ketene N,N-acetals can react smoothly with alkyl halides,[3] activated acetylenes,[4] electrophilic olefins[4] and 1,3-dipoles[5] to obtain various α-carbon-alkylated products.

Compared to the α-carbon alkylation of α-oxoheterocyclic ketene N,N-acetal derivatives, few studies involving their α-carbon arylation have been carried out.[6] To the best of our understanding, only one successful example was reported on the synthesis of a 2,4-dinitrobenzene derivative of an α-oxoheterocyclic ketene N,N-acetal using NaH as a base and 2,4-dinitrohalobenzenes as the reactants (Scheme 1, left). In this example, two nitro groups played a key role in achieving substitution, and no other aryl groups with moderate electron-withdrawing or electron-donating groups succeeded. Therefore, it is highly desirable to seek a complementary approach to obtain some α-aryl α-oxoheterocyclic ketene N,N-acetals bearing electron-rich groups, such as catechol analogues (Scheme 1, right).



Scheme 1. Synthetic approach toward electron-poor (left) and electron-rich (right) α-aryl α-oxoheterocyclic ketene N,N-acetals.

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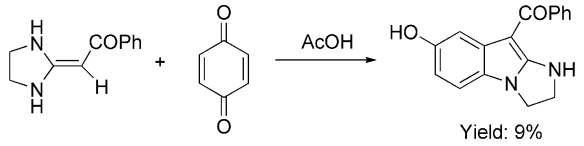
As part of our continuous efforts towards the electrochemical synthesis of polyhydroxylated aromatics as potential HIV-1 integrase inhibitors, we have investigated the electrochemical oxidation of catechols in the presence of nucleophiles and synthesized a variety of heterocyclic substituted catechols.[7] With this rationale in mind and in view of the nucleophilicity of the α-carbon of α-oxoheterocyclic ketene N,N-acetals, we hypothesized that the electrochemically in-situ-generated *o*-benzoquinones may be used as Michael addition acceptors and react with α-oxoheterocyclic ketene N,N-acetals to synthesize α-aryl α-oxoheterocyclic ketene N,N-acetals containing an electron-rich aromatic ring. The present work demonstrates that α-aryl α-oxoheterocyclic ketene N,N-acetals incorporating a catechol subunit can be synthesized in good to high yields using this electrochemical approach. This protocol provides an efficient way to obtain α-aryl α-oxoheterocyclic ketene N,N-acetals containing electron-rich aromatic rings.

It is worth noting that the reaction between *p*-benzoquinone and an α-oxoheterocyclic ketene N,N-acetal was previously reported using a conventional chemical approach. However, a 5-hydroxyindole derivative was formed in 9% yield, instead of the expected Michael addition product (Scheme 2).[8]



Scheme 2. Reaction of α-oxoheterocyclic ketene N,N-acetals and *p*-benzoquinone.

Results and Discussion

Electrochemical Investigation of Catechols in the Absence or Presence of α-Oxoheterocyclic Ketene N,N-Acetals by Cyclic Voltammetry

Before we performed the electrochemical coupling reaction of electron-rich aromatics and α-oxoheterocyclic ketene N,N-acetals, we needed to first study the electrochemical properties of the starting materials. Taking 4-methylcatechol (**2a**) as a example, we investigated the electrochemical behavior of catechols **2** by cyclic voltammetry (CV) in the absence or presence of α-oxoheterocyclic ketene N,N-acetals **1** at room temperature in water containing 0.2 M acetate buffer (pH = 7.0) as the supporting electrolyte. Due to the poor solubility of α-oxoheterocyclic ketene N,N-acetals in water, we added acetonitrile as a cosolvent.

As shown in Figure 1, upon scanning anodically, 4-methylcatechol exhibited a well-defined quasireversible oxidation wave (peak A) at +0.30 V vs. Ag/AgCl (3 M) and a corresponding cathodic peak (C) at +0.08 V vs. Ag/AgCl (3 M), which we attributed to the oxidation of 4-methylcatechol to the corresponding *o*-benzoquinone and vice versa. The ratio of the current amplitudes between the oxidation and reduction processes was equal to unity (I_p^{ox}/I_p^{red}), indicating that the *o*-benzoquinone produced at the surface of the electrode was stable in pH = 7 acetate buffer and that side reactions such as hydroxylation or dimerization were too slow to be observed on the time scale of the cyclic voltammetry.[9] When we added 1 equiv. of α-oxoheterocyclic ketene N,N-acetal **1a**, the voltammogram of 4-methylcatechol exhibited one anodic peak (A_1) at +0.36 V vs. Ag/AgCl (3 M), whereas the cathodic counterpart of the anodic peak A_1 decreased (curve c, Figure 1). Moreover, the ratio of the anodic current to the cathodic current (I_p^{ox}/I_p^{red}) of the mixture of 4-methylcatechol and **1a** decreased with increasing potential sweep rate (Figure 2). Curve b in Figure 1 is the CV of α-oxoheterocyclic ketene N,N-acetal **1a**, where two irreversible anodic waves at 0.70 V and 1.17 V were observed. In addition, the positive anodic shifts of the anodic A_1 peak (0.36 V vs. 0.30 V) in the presence of **1a** we attributed to the formation of a thin film of product at the surface of the electrode, inhibiting to a certain extent the performance of the electrode process.[9a–9d]

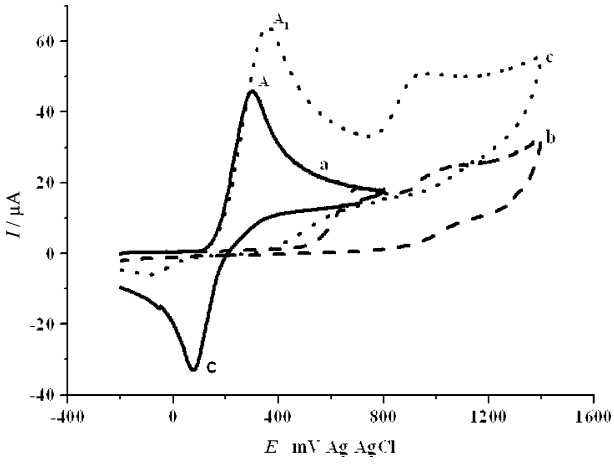


Figure 1. CVs of a) 2 mM 4-methylcatechol (**2a**), b) 2 mM α-oxoheterocyclic ketene N,N-acetal **1a** and c) a mixture of 2 mM **2a** and 2 mM **1a** with a glassy carbon working electrode, a platinum wire counter and Ag/AgCl reference electrodes in 2:1 (v/v) acetate buffer/acetonitrile (0.2 M, pH = 7) at a scan rate of 50 mV/s.

On the basis of the CVs described above for catechols in the absence or presence of α-oxoheterocyclic ketene N,N-acetals, we assumed that a chemical step occurred between the electrochemically generated *o*-benzoquinone (at A) and the α-oxoheterocyclic ketene N,N-acetals **1**, and therefore, Michael addition products may be synthesized upon the anodic oxidation of a mixture of a catechol and a α-oxoheterocyclic ketene N,N-acetal **1** when the electrolysis potential is controlled by modulating the anodic potentials of the corresponding catechols. We hypothesized that the undesired oxidation of α-oxoheterocyclic ketene N,N-acetals would not take place due to their significantly higher anodic potentials.

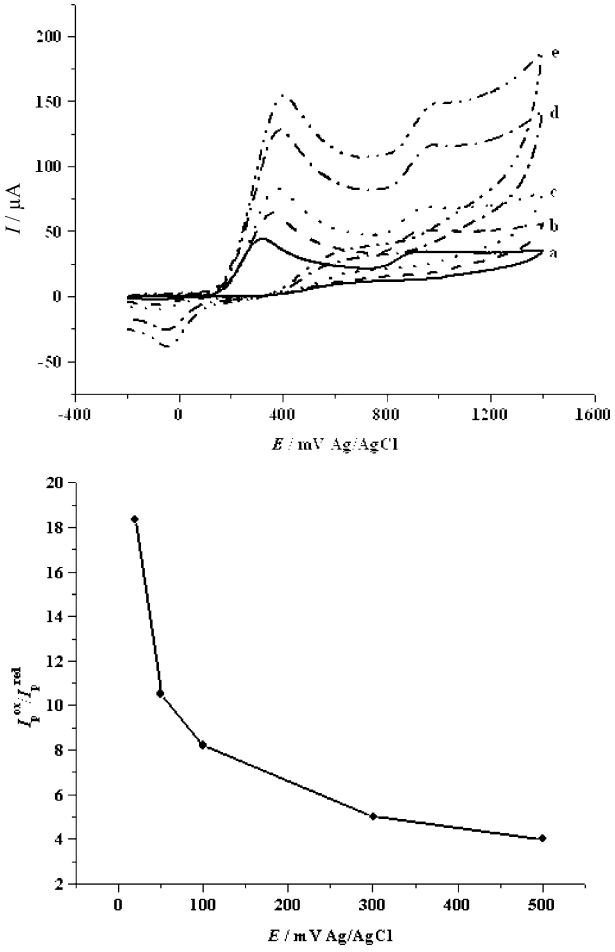
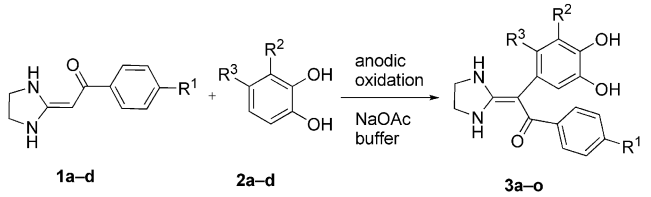


Figure 2. Top: CVs of a mixture of 2 mM **2a** and 2 mM **1a** at a scan rate of: a) 20 mV/s, b) 50 mV/s, c) 100 mV/s, d) 300 mV/s and e) 500 mV/s. Bottom: variation of peak current ratio I_p^{ox}/I_p^{red} vs. scan rate.



Scheme 3. Anodic oxidation of catechols **2** and α-oxoheterocyclic ketene N,N-acetals **1**.

Electrochemical Synthesis of 3a–o

We employed controlled-potential electrolysis (CPE) in a divided cell to perform the α-carbon arylation of α-oxoheterocyclic ketene N,N-acetals, and the results are summarized in Table 1. As shown in Table 1 and Scheme 3, according to our reported conditions,[7] we electrolyzed an equivalent amount of 4-methylcatechol (**2a**) and α-oxoheterocyclic ketene N,N-acetal **1a** at a controlled potential of 0.3 V vs. Ag wire in acetate buffer. During the reaction, the solution turned from yellow to brown, and a white powder precipitated. After 4-methylcatechol was consumed (the passed charge was approximately 2.5 F/mol), we filtered the resulting powder, washed it with water and characterized it as the desired **3a** in 79% yield on the basis of its spectral and analytical data (Table 1, Entry 1).

When we subjected 4-*tert*-butylcatechol (**2b**) and caffeic acid (**2c**) to anodic oxidation in the presence of **1a** under the same conditions, we achieved the desired products **3b** and **3c** in 50% and 48% yield, respectively (Table 1, Entries 2 and 3).

Subsequently, we applied the reaction to 3-substituted catechols such as 3-methoxycatechol (**2d**), 3-methylcatechol (**2e**) and catechol (**2f**) with a view to investigate the scope of the reaction. In a similar way, we performed electrochemical oxidation of **2d** and **2e** in the presence of **1a** and obtained the expected products **3d** and **3e** in 36 and 27% yield, respectively (Table 1, Entries 4 and 5). In the case of catechol itself, no solid precipitated, although TLC showed a major product formed in the electrolytic solution. Upon modification of the electrolytic component (the volume ratio of acetate buffer to acetonitrile), the desired **3f** precipitated, and we isolated a 21% yield after simple filtration. Obviously, the chemical yields in the cases of **2d**–**f** were a little lower than those of 4-substituted catechols **2a**–**c**.

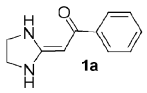
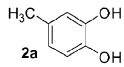
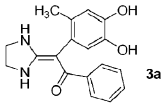
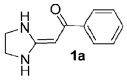
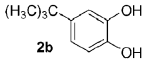
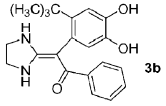
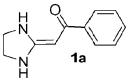
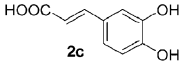
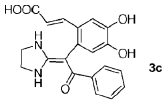
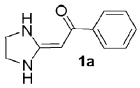
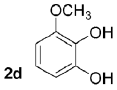
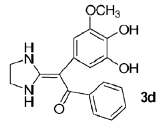
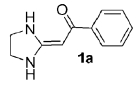
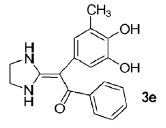
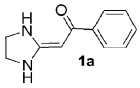
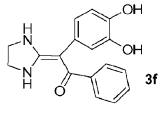
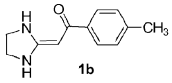
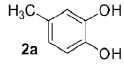
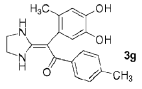
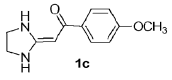
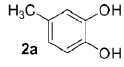
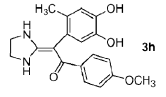
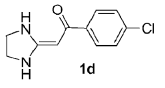
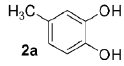
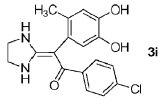
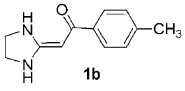
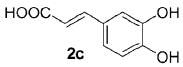
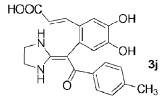
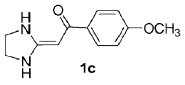
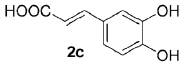
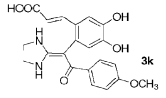
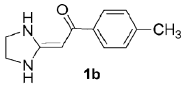
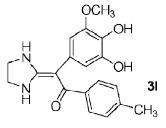
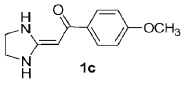
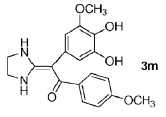
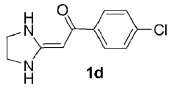
In order to demonstrate the versatility of the reaction, we turned our studies to other α-oxoheterocyclic ketene N,N-acetals. Thus, the electrochemical oxidation of 4-methylcatechol (**2a**) in the presence of 2-(*p*-methylbenzoylmethylene)-imidazolidine (**1b**), 2-(*p*-methoxybenzoylmethylene)imidazolidine (**1c**) and 2-(*p*-chlorobenzoylmethylene)imidazolidine (**1d**) also proceeded smoothly under the previously described conditions, yielding the desired **3g**–**i** in respective 73%, 50% and 79% yields (Table 1, Entries 7–9). We also obtained similar results when we electrochemically oxidized caffeic acid (**2c**), 3-methoxycatechol (**2d**) or 4-*tert*-butylcatechol in the presence of **1b**–**d**, and we isolated the corresponding α-arylated heterocyclic ketene N,N-acetals **3j**–**o** in moderate to high yields (Table 1, Entries 10–15).

We determined the structures of **3a**–**o** by using ^{1}H NMR, ^{13}C NMR, IR and ESI-MS. Taking **3a** as an example, its ^{1}H NMR spectrum exhibited one singlet at δ = 1.85 ppm, which we attributed to the methyl group. The two singlets at δ = 6.37 and 6.45 ppm are the signals of the two aromatic protons of the catechol unit. The two OH proton signals of the catechol unit were located at δ = 8.40 and 8.47 ppm, respectively. Interestingly, the two N–H groups were quite different, as one N–H resonated at δ = 5.97 ppm, while the other resonated at δ = 10.05 ppm due to its intramolecular H-bonding with the neighboring carbonyl group. The ^{13}C NMR spectrum of **3a** exhibited 18 signals.

Reaction Mechanism

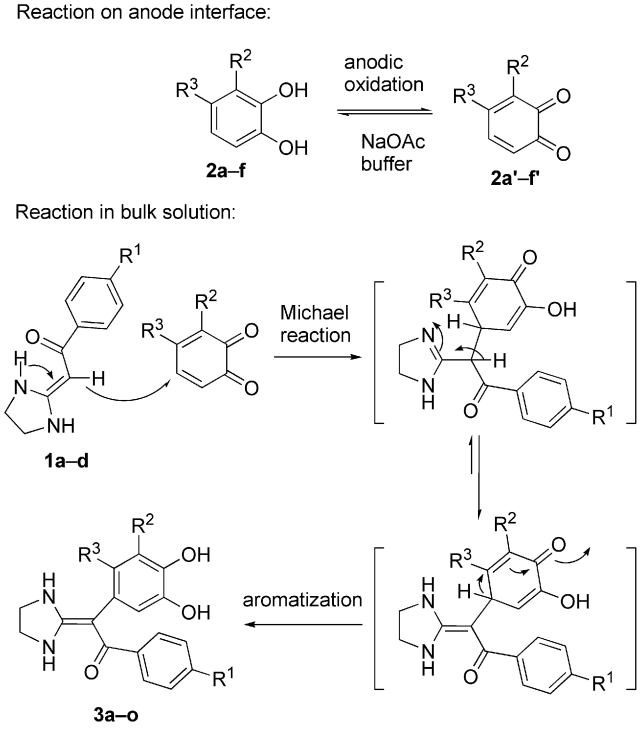
As the reaction mechanism is concerned, it is well documented[9] that the anodic oxidation of catechol and its derivatives in an aqueous medium leads to the formation of the corresponding *o*-benzoquinone intermediates. These intermediates are converted to other intermediates or prod-

Table 1. Electrochemical synthesis of α-aryl α-oxoheterocyclic ketene N,N-acetals containing a catechol subunit.

Entry	Ketene N,N-acetal	Catechol	Product	Yield
1	 1a	 2a	 3a	79
2	 1a	 2b	 3b	50
3	 1a	 2c	 3c	48
4	 1a	 2d	 3d	36
5	 1a	 2e	 3e	27
6	 1a	 2f	 3f	21
7	 1b	 2a	 3g	73
8	 1c	 2a	 3h	50
9	 1d	 2a	 3i	79
10	 1b	 2c	 3j	52
11	 1c	 2c	 3k	52
12	 1b	 2d	 3l	75
13	 1c	 2d	 3m	40
14	 1d	2d	3n	81
15	1b	2b	3o	25[a]

[a] The yield increased to 82% after 2.24 F/mol of charge was passed through the mixture when the CPE was carried out at 0 °C instead of room temperature (about 25 °C).

ucts, following a pattern of an EC or an ECEC mechanism, depending on the nature of the nucleophiles and structures of the starting catechols. Accordingly, it is safe to speculate that the α-arylation of α-oxoheterocyclic ketene N,N-acetals to generate products **3** also follows a similar mechanism. As illustrated in Scheme 4, the initial step is an electrochemical process that involves the oxidation of catechols **1** on the anodic electrode surface and generates the corresponding *o*-benzoquinones. Subsequently, a chemical reaction in the bulk electrolytic solution occurs, wherein the active *o*-benzoquinone intermediates undergo a Michael addition to the α-carbon of the α-oxoheterocyclic ketene N,N-acetals **1** followed by aromatization, leading to products **3**.



Scheme 4. A plausible mechanism for the reaction between catechols **2** and heterocyclic ketene N,N-acetals **1**.

We note that very recently, we electrolyzed a mixture of catechol derivatives **2** and α-oxoheterocyclic ketene N,O-acetals **6** (the analogues of N,N-acetals **1**) and achieved the one-pot electrochemical synthesis of fused indole derivatives **7** and **8** in the range of 37–71% yields (Scheme 5).[10] This reaction may involve the over oxidation of the initially formed intermediates followed by enamine-imine tautomerization, imine-enamine tautomerization, intramolecular Michael addition and aromatization. Similarly, compounds of type **3** are typical catechol derivatives, with oxidation potentials close to that of the starting catechols **2**, (such as 0.30 V for **1a** and 0.35 V for **3a** vs. Ag/AgCl, Figure 3). Therefore, over oxidation and further intramolecular Michael addition may also occur and cause the formation of corresponding indole derivatives. However, we observed the exclusive formation of α-aryl α-oxoheterocyclic ketene N,N-acetals **3**. Their selective formation may have resulted from the poor solubility of products **3a**–**o** in the given electrolytic system, which prevented their over oxidation, although the nature of the starting α-oxoheterocyclic ketene acetals (N,N-acetal or N,O-acetal) may also have played a key role.[11]

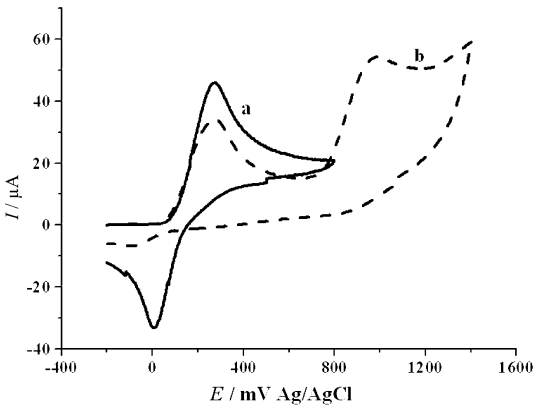
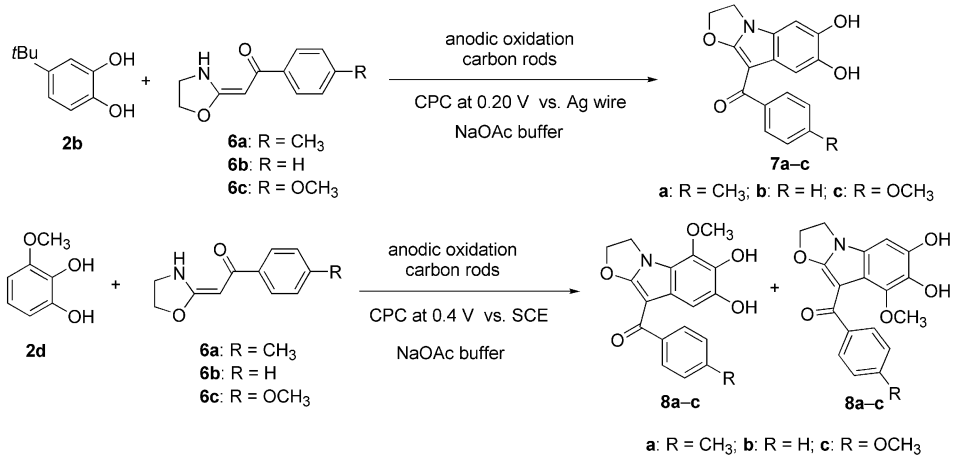
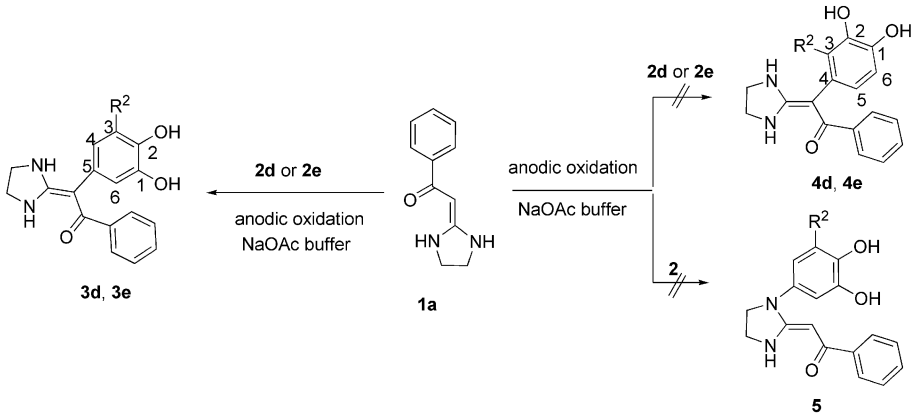


Figure 3. CVs of (a) 2 mM 4-methylcatechol (**2a**) and (b) 2 mM **3a** with a glassy carbon working electrode, a platinum wire counter and Ag/AgCl reference electrodes in 1:1 (v/v) acetate buffer/acetonitrile (0.2 M, pH = 7) at a scan rate of 50 mV/s.



Scheme 5. One-pot synthesis of fused indole derivatives from catechols and α-oxoheterocyclic ketene N,O-acetals.



Scheme 6. The possible reaction products of **1a** in the presence of **2**.

We noted that the asymmetry of 3-substituted catechols, such as 3-methoxycatechol and 3-methylcatechol, may cause the formation of two isomers because the nucleophilic attack of the α-carbon of α-oxoheterocyclic ketene N,N-acetals upon the electrochemically generated 3-substituted *o*-benzoquinone may take place at the C-5 or C-4 of the benzene ring, leading to **3** or their isomers **4**, respectively (Scheme 6).[10] In our case, we introduced the α-oxoheterocyclic ketene N,N-acetal subunits in the C-5 position of the catechol scaffold, which led exclusively to products **3d** and **3e**.

In order to further elucidate these results, we performed density functional theory (DFT) calculations [using B3LYP/6-311+g(d,p) base] of atomic polar tensor (APT) charges of **1a**–**d** and electro-generated intermediates **2d′** and **2e′** (Figure 4). As shown in Table 2, the APT charge of C-5 in **2d′** and **2e′** were 0.351 and 0.166, respectively. These values were higher than those of C-4 (–0.275 for **2d′** and –0.018 for **2e′**), which indicated that α-oxoheterocyclic ketene N,N-acetals **1a**–**d** were easily introduced at the C-5 position of the catechol scaffolds by nucleophilic attack. The steric hindrance of C-4 may also have played a key role in controlling the generation of regioisomers **4d** and **4e**. Both factors led to the exclusive formation of **3** instead of **4**.

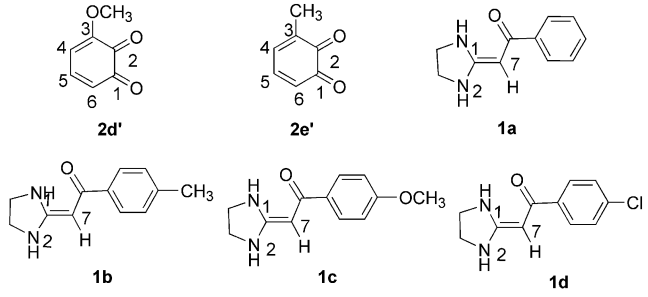


Figure 4. Atomic labeling of selective atoms.

The DFT calculation results also shed light on the formation of α-carbon-substituted derivatives of α-oxoheterocyclic ketene N,N-acetals **1**, forming *C*-substituted **3** instead of the corresponding *N*-substituted **5** (Scheme 6). As shown in Table 2, the α-carbon of heterocyclic ketene N,N-acetals exhibited a higher atomic charge than that of the two amino groups (N-1 and N-2). For example, the APT charge of C-7 of **1a** was –1.020; however, the APT charges of N-1 and N-2 were –0.793 and –0.801, respectively. Therefore, we exclusively formed *C*-substituted compounds.

Table 2. APT charges of selected atoms in **1a**–**d**, **2d′** and **2e′**.

Entry		C-4	C-5	C-6	N-1	N-2	C-7
1	**2d′**	–0.275	0.351	–0.313	–	–	–
2	**2e′**	–0.018	0.166	–0.217	–	–	–
3	**1a**	–	–	–	–0.793	–0.801	–1.020
4	**1b**	–	–	–	–0.805	–0.811	–1.041
5	**1c**	–	–	–	–0.224	–0.198	–0.396
6	**1d**	–	–	–	–0.803	–0.814	–1.052

Conclusion

In summary, the electrochemical behavior of catechols **2** in the absence or presence of α-oxoheterocyclic ketene N,N-acetals **1** have been investigated by CV. The CVs of the catechols exhibited one well-defined oxidation wave and a corresponding cathodic peak. However, when 1 equiv. of **1** was added, the cathodic wave disappeared or decreased depending on the nature of the initial substituent on the catechol ring. Based on relative CVs data, the anodic oxidation of catechols **2** in the presence of α-oxoheterocyclic ketene N,N-acetals **1** were conducted to synthesize α-aryl ketene N,N-acetals **3** in moderate to good yields. Thus, this process provides an alternative access to α-aryl α-oxoheterocyclic ketene N,N-acetals containing a catechol subunit. The poor solubility of the products may have been responsible for their selective formation. In addition, DFT calculations were performed to explain the exclusive formation of α-carbon-arylated products. Such reactions further demonstrates that the anodic oxidation of catechol derivatives and their in-situ transformation can be utilized to synthesize a library of polyhydroxylated aromatics.

Experimental Section

Instruments and Reagents: CVs were measured with a 273A potentiostat/galvanostat equipped with electrochemical analysis software and a conventional three-electrode cell. The working electrode was a glassy carbon disk electrode (Ø ≈ 3 mm). The auxiliary and reference electrodes in these studies were Pt wire and saturated Ag/AgCl, respectively. The glassy carbon was polished with polishing cloth before each measurement. All electrodes for CV experiments were from CH Instruments, Inc., USA. Acetate buffer was prepared with NaAc and HOAc and monitored by a digital pH meter. The scan rate was 50 mV/s. The concentration of **1** and **2** were 2 mM, while that of the supporting electrolyte was 0.2 M.

For controlled-potential electrolysis (CPE), a 100 mL, H-type cell was equipped with a medium glass frit as a membrane. The anode compartment contained an assembly of seven graphite rods as the anode; the upper rims of the rods were wrapped with a copper wire, and a polished silver wire was the quasireference electrode, which was immersed in electrolyte solution in a glass cylinder with a fine glass frit at its end. A platinum plate (2 cm^2) as the counter electrode was immersed in the cathode compartment. The applied potential throughout CPE was 0.30 V vs. Ag wire and controlled by the 273A potentiostat/galvanostat. The passed charge for each experiment was recorded on a computer. During electrolysis, the mixture was stirred magnetically.

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

Catechols **2a**–**e** were of reagent-grade, purchased from Alfa Aesar, China (Tianjin) Co., Ltd. Compounds **1a**–**d** were synthesized according to ref.[12] Other chemicals and solvents were from Beijing Chemicals Co. and used without further purification. Doubly distilled deionized water was used for the preparation of the acetate buffer. All experiments were performed at room temperature and ambient pressure.

General Procedure for the Synthesis of 3a–o: In a typical procedure, a mixture of acetate buffer (50 mL, pH = 6) and acetonitrile (12 mL) was pre-electrolyzed at the chosen potential (0.30 V vs. Ag wire) in the H-type divided cell, which was kept in water at room temperature for 10 min (to remove impurities present in the electrolytic system). Subsequently, a catechol **2** (2 mmol) and a α-oxoheterocyclic ketene N,N-acetal **1** (2 mmol) were added to the anodic compartment, and electrolysis was continued. The electrolysis was terminated when the starting **2** was consumed (as determined by TLC). The passed charge was in the range of 2.3–3.5 F/mol. After electrolysis, the pH was adjusted to 7 with a few drops of acetic acid, and the precipitate was filtered and washed with water.

2-[Benzoyl(4,5-dihydroxy-2-methylphenyl)methylene]imidazolidine (3a): Yield 79% (489 mg); m.p. 245 °C (dec.). ^1H NMR (400 MHz, [D_6]DMSO): δ = 1.85 (s, 3 H, CH_3), 3.33 (t, J = 7.6 Hz, 2 H, CH_2), 3.67 (s, J = 7.6 Hz, 2 H, CH_2), 5.97 (br. s, 1 H, NH), 6.37 (s, 1 H, ArH), 6.45 (s, 1 H, ArH), 7.06–7.08 (m, 5 H, ArH), 8.40 (s, 1 H, OH), 8.47 (s, 1 H, OH), 10.05 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 19.6, 39.4, 39.8, 90.5, 117.6, 121.0, 127.2, 127.8, 127.9, 128.5, 129.2, 143.1, 144.2, 165.4, 184.43 ppm. IR (KBr): $\tilde{\nu}$ = 3404, 3107, 2899, 1590, 1575, 1526, 1477 cm^{-1}. ESI-MS: m/z = 311.0 $[M + 1]^+$, 308.7 $[M - 1]^-$.

2-[Benzoyl(4,5-dihydroxy-2-*tert*-butylphenyl)methylene]imidazolidine (3b): Yield 50% (352 mg); m.p. 256 °C (dec.). ^1H NMR (400 MHz, [D_6]DMSO): δ = 1.02 [s, 9 H, $C(CH_3)_3$], 3.28–3.36 (m, 2 H, CH_2), 3.62–3.66 (m, 2 H, CH_2), 5.78 (br. s, 1 H, NH), 6.45 (s, 1 H, ArH), 6.74 (s, 1 H, ArH), 7.02–7.20 (m, 3 H, ArH), 7.22 (dd, J = 8.4, 1.2 Hz, 2 H, ArH), 8.55 (s, 1 H, OH), 8.60 (s, 1 H, OH), 10.22 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 32.5, 36.0, 42.8, 44.2, 94.1, 116.3, 123.8, 126.7, 127.1, 128.0, 128.9, 140.9, 143.0, 143.8, 144.3, 165.9, 182.2 ppm. IR (KBr): $\tilde{\nu}$ = 3456, 3961, 1587, 1574, 1525, 1476 cm^{-1}. ESI-MS: m/z = 353.1 $[M + 1]^+$, 350.8 $[M - 1]^-$, 702.4 $[2M - 1]^-$.

(*E*)-3-[4,5-Dihydroxy-2-(1-imidazolidin-2-ylidene)-2-oxo-2-phenylethyl]phenylacrylic Acid (3c): Yield 48% (351 mg); m.p. 196–197 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 3.35–3.68 (m, 4 H, NCH_2CH_2N), 5.87 (d, J = 16.0 Hz, 1 H, CH=CH), 6.19 (br. s, 1 H, NH), 6.48 (s, 1 H, ArH), 6.95–7.07 (m, 6 H, ArH), 7.54 (d, J = 16.0 Hz, 1 H, CH=CH), 10.04 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 42.8, 44.1, 88.8, 113.1, 114.8, 121.1, 126.5, 127.3, 127.8, 132.4, 143.8, 144.0, 144.9, 148.3, 165.2, 168.6, 185.2 ppm. IR (KBr): $\tilde{\nu}$ = 3520, 3429, 3298, 1591, 1529, 1474 cm^{-1}. ESI-MS: m/z = 366.9 $[M + 1]^+$, 388.8 $[M + Na]^+$, 405.0 $[M + K]^+$, 364.8 $[M - 1]^-$, 730.9 $[2M - 1]^-$.

2-[Benzoyl(3,4-dihydroxy-5-methoxyphenyl)methylene]imidazolidine (3d): Yield 36% (234 mg); m.p. 210–211 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 3.32–3.63 (m, 4 H, NCH_2CH_2N), 3.51 (s, 3 H, OCH_3), 6.01 (d, J = 2.0 Hz, 1 H, ArH), 6.07 (d, J = 2.0 Hz, 1 H, ArH), 6.30 (br. s, 1 H, NH), 7.06–7.08 (m, 5 H, ArH), 7.91 (br. s, 1 H, OH), 8.53 (br. s, 1 H, OH), 10.05 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 39.9, 40.6, 56.0, 92.7, 108.7, 113.5, 127.3, 127.7, 128.2, 129.1, 132.5, 144.4, 145.7, 148.3, 165.4, 185.2 ppm. IR (KBr): $\tilde{\nu}$ = 3373, 2963, 2934, 1585, 1573, 1543, 1519, 1460 cm^{-1}. ESI-MS: m/z = 326.9 $[M + 1]^+$, 348.9 $[M + Na]^+$, 324.7 $[M - 1]^-$, 650.8 $[2M - 1]^-$.

2-[Benzoyl(3,4-dihydroxy-5-methylphenyl)methylene]imidazolidine (3e): Yield 27% (167 mg); m.p. 247 °C (dec.). ^1H NMR (400 MHz, [D_6]DMSO): δ = 1.92 (s, 3 H, CH_3), 3.40–3.59 (br. m, 4 H, NCH_2CH_2N), 6.17 (br. s, 1 H, NH), 6.23 (d, J = 1.6 Hz, 1 H, ArH), 6.25 (d, J = 1.6 Hz, 1 H, ArH), 7.04–7.13 (m, 5 H, ArH), 7.89 (br. s, 1 H, OH), 8.84 (br. s, 1 H, OH), 10.07 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 16.6, 39.9, 40.6, 92.5, 117.8, 124.3, 125.7, 127.3, 127.7, 128.4, 129.2, 141.7, 144.2, 144.8, 165.6, 184.7 ppm. IR (KBr): $\tilde{\nu}$ = 3439, 1585, 1541, 1476 cm^{-1}. ESI-MS: m/z = 310.9 $[M + 1]^+$, 332.8 $[M + Na]^+$, 308.7 $[M - 1]^-$, 619.0 $[2M - 1]^-$.

2-[Benzoyl(3,4-dihydroxyphenyl)methylene]imidazolidine (3f): Yield 21% (124 mg); m.p. 247 °C (dec.). ^1H NMR (400 MHz, [D_6]-DMSO): δ = 3.42–3.57 (br. m, 4 H, NCH_2CH_2N), 6.22 (br. s, 1 H, NH), 6.25 (d, J = 8.0 Hz, 2 H, ArH), 6.40 (s, J = 1.2 Hz, 1 H, ArH), 6.50 (d, J = 8.0 Hz, 2 H, ArH), 7.07 (s, 5 H, ArH), 8.57 (br. s, 2 H, OH), 10.06 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 39.9, 40.6, 92.4, 115.9, 120.3, 124.0, 127.3, 127.7, 128.4, 130.0, 143.6, 144.2, 145.1, 165.5, 184.9 ppm. IR (KBr): $\tilde{\nu}$ = 3435, 1584, 1538, 1478 cm^{-1}. ESI-MS: m/z = 296.8 $[M + 1]^+$, 318.8 $[M + Na]^+$, 294.6 $[M - 1]^-$, 590.9 $[2M - 1]^-$.

2-[(4-Methylbenzoyl)(4,5-dihydroxy-2-methylphenyl)methylene]imidazolidine (3g): Yield 73% (473 mg); m.p. 192–193 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 1.84 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 3.34 (t, J = 7.6 Hz, 2 H, CH_2), 3.65 (t, J = 7.6 Hz, 2 H, CH_2), 5.91 (br. s, 1 H, NH), 6.37 (s, 1 H, ArH), 6.46 (s, 1 H, ArH), 6.85 (d, J = 8.0 Hz, 2 H, ArH), 6.98 (d, J = 8.0 Hz, 2 H, ArH), 8.40 (s, 1 H, OH), 8.47 (s, 1 H, OH), 10.06 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 19.6, 21.2, 42.8, 44.1, 90.4, 117.7,

121.0, 127.8, 128.0, 128.7, 129.1, 137.1, 141.4, 143.1, 144.2, 165.3, 184.4 ppm. IR (KBr): ṽ = 3430, 2920, 1587, 1522, 1475, 1454 cm^{-1}. ESI-MS: *m*/*z* = 325.1 [M + 1]$^+$, 347.0 [M + Na]$^+$, 322.7 [M – 1]$^-$.

2-[(4-Methoxybenzoyl)(4,5-dihydroxy-2-methylphenyl)methylene]-imidazolidine (3h): Yield 50% (340 mg); m.p. 200 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.85 (s, 3 H, CH$_3$), 3.66 (s, 3 H, OCH$_3$), 3.48–3.83 (br. m, 4 H, NCH$_2$CH$_2$N), 5.97 (br. s, 1 H, NH), 6.39 (s, 1 H, ArH), 6.49 (s, 1 H, ArH), 6.61 (d, *J* = 8.8 Hz, 2 H, ArH), 7.07 (d, *J* = 8.8 Hz, 2 H, ArH), 8.45 (br. s, 1 H, OH), 8.50 (br. s, 1 H, OH), 10.08 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 19.6, 39.9, 40.6, 55.3, 90.3, 112.5, 117.8, 120.9, 128.8, 129.1, 129.7, 136.4, 143.2, 144.2, 159.2, 165.4, 183.5 ppm. IR (KBr): ṽ = 3435, 2966, 1583, 1535, 1475 cm^{-1}. ESI-MS: *m*/*z* = 340.9 [M + 1]$^+$, 338.8 [M – 1]$^-$, 678.9 [2M – 1]$^-$.

2-[(4-Chlorobenzoyl)(4,5-dihydroxy-2-methylphenyl)methylene]imidazolidine (3i): Yield 79% (543 mg); m.p. 242–244 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.85 (s, 3 H, CH$_3$), 3.35 (s, 3 H, OCH$_3$), 3.35 (br. s, 2 H, NCH$_2$CH$_2$N), 3.69 (br. s, 2 H, NCH$_2$CH$_2$N), 6.07 (br. s, 1 H, NH), 6.37 (s, 1 H, ArH), 6.48 (s, 1 H, ArH), 7.06 (d, *J* = 8.8 Hz, 2 H, ArH), 7.12 (d, *J* = 8.8 Hz, 2 H, ArH), 8.45 (br. s, 1 H, OH), 8.54 (br. s, 1 H, OH), 10.00 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 19.6, 39.9, 40.6, 90.6, 117.7, 121.0, 127.3, 128.1, 129.1, 129.8, 132.4, 143.0, 143.3, 144.4, 165.4, 182.8 ppm. IR (KBr): ṽ = 3248, 1638, 1582 cm^{-1}. ESI-MS: *m*/*z* = 344.7 [M + 1]$^+$, 342.7 [M – 1]$^-$.

(*E*)-3-{4,5-Dihydroxy-2-[1-(imidazolidin-2-ylidene)-2-oxo-2-*p*-tolylethyl]phenyl}acrylic Acid (3j): Yield 52% (395 mg); m.p. 195–196 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.13 (s, 3 H, CH$_3$), 3.31–3.64 (m, 4 H, NCH$_2$CH$_2$N), 5.86 (d, *J* = 15.6 Hz, 1 H, CH=CH), 6.12 (br. s, 1 H, NH), 6.44 (s, 1 H, ArH), 6.81 (d, *J* = 8.0 Hz, 2 H, ArH), 6.87 (d, *J* = 8.0 Hz, 2 H, ArH), 6.99 (s, 1 H, ArH), 7.51 (d, *J* = 16.0 Hz, 1 H, CH=CH), 10.02 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.2, 42.8, 44.1, 88.7, 113.2, 114.9, 121.1, 126.5, 126.6, 127.9, 128.9, 132.6, 137.1, 141.2, 143.8, 144.9, 148.3, 165.2, 168.6 ppm. IR (KBr): ṽ = 3419, 1586, 1529, 1474 cm^{-1}. ESI-MS: *m*/*z* = 380.7 [M + 1]$^+$, 379.0 [M – 1]$^-$, 759.0 [2M – 1]$^-$.

(*E*)-3-{4,5-Dihydroxy-2-[1-(imidazolidin-2-ylidene)-2-(4-methoxyphenyl)-2-oxoethyl]phenyl}acrylic Acid (3k): Yield 52% (411 mg); m.p. 198–200 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.33–3.67 (m, 4 H, NCH$_2$CH$_2$N), 3.65 (s, 3 H, OCH$_3$), 5.90 (d, *J* = 16.0 Hz, 1 H, CH=CH), 6.08 (br. s, 1 H, NH), 6.48 (s, 1 H, ArH), 6.59 (d, *J* = 8.8 Hz, 2 H, ArH), 6.98 (d, *J* = 8.8 Hz, 2 H, ArH), 7.52 (d, *J* = 16.0 Hz, 1 H, CH=CH), 10.07 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 42.8, 44.1, 55.3, 88.6, 112.6, 113.3, 115.0, 121.0, 126.5, 129.7, 132.7, 136.2, 143.8, 144.9, 148.4, 159.1, 165.2, 168.6, 184.3 ppm. IR (KBr): ṽ = 3427, 1601, 1574, 1525, 1475 cm^{-1}. ESI-MS: *m*/*z* = 396.9 [M + 1]$^+$, 418.9 [M + Na]$^+$, 435.0 [M + K]$^+$, 394.7 [M – 1]$^-$, 790.9 [2M – 1]$^-$.

2-[(4-Methylbenzoyl)(3,4-dihydroxy-5-methoxyphenyl)methylene]-imidazolidine (3l): Yield 75% (510 mg); m.p. 245 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.18 (s, 3 H, CH$_3$), 3.40–3.61 (m, 4 H, NCH$_2$CH$_2$N), 3.56 (s, 3 H, OCH$_3$), 6.06 (s, 2 H, ArH), 6.25 (br. s, 1 H, NH), 6.88 (d, *J* = 8.0 Hz, 2 H, ArH), 7.02 (d, *J* = 8.0 Hz, 2 H, ArH), 7.93 (br. s, 1 H, OH), 8.55 (br. s, 1 H, OH), 10.08 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.2, 39.9, 40.6, 56.0, 92.7, 108.7, 113.6, 127.8, 128.3, 129.3, 132.6, 137.0, 141.5, 145.7, 148.3, 165.3, 185.0 ppm. IR (KBr): ṽ = 3397, 2962, 1588, 1528 cm^{-1}. ESI-MS: *m*/*z* = 341.0 [M + 1]$^+$, 363 [M + Na]$^+$, 338.7 [M – 1]$^-$.

2-[(4-Methoxybenzoyl)(3,4-dihydroxy-5-methoxyphenyl)methylene]-imidazolidine (3m): Yield 40% (284 mg); m.p. 229 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.58 (s, 3 H, OCH$_3$), 3.67 (s, 3 H, OCH$_3$), 3.33–3.67 (br. m, 4 H, NCH$_2$CH$_2$N), 6.08 (s, 1 H, ArH), 6.09 (s, 1 H, ArH), 6.22 (br. s, 1 H, NH), 6.64 (d, *J* = 8.8 Hz, 2 H, ArH), 7.10 (d, *J* = 8.8 Hz, 2 H, ArH), 7.97 (br. s, 1 H, OH), 8.59 (br. s, 1 H, OH), 10.09 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 39.9, 40.6, 55.4, 56.1, 92.5, 108.5, 112.5, 113.6, 129.5, 130.1, 132.6, 136.5, 145.8, 148.4, 159.1, 165.4, 184.2 ppm. IR (KBr): ṽ = 3439, 3386, 2964, 2934, 1605, 1590, 1573, 1522, 1480 cm^{-1}. ESI-MS: *m*/*z* = 356.9 [M + 1]$^+$, 354.8 [M – 1]$^-$, 710.9 [2M – 1]$^-$.

2-[(4-Chlorobenzoyl)(3,4-dihydroxy-5-methoxyphenyl)methylene]-imidazolidine (3n): Yield 81% (583 mg); m.p. 243–244 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.56 (s, 3 H, OCH$_3$), 3.51–3.61 (br. m, 4 H, NCH$_2$CH$_2$N), 6.05 (d, *J* = 2.0 Hz, 1 H, ArH), 6.07 (d, *J* = 2.0 Hz, 1 H, ArH), 6.40 (br. s, 1 H, NH), 7.11 (d, *J* = 8.8 Hz, 2 H, ArH), 7.15 (d, *J* = 8.8 Hz, 2 H, ArH), 7.98 (br. s, 1 H, OH), 8.59 (br. s, 1 H, OH), 10.02 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 39.9, 40.6, 56.1, 92.8, 108.6, 113.6, 127.3, 128.7, 130.1, 132.3, 132.7, 143.1, 145.8, 148.4, 165.4, 183.4 ppm. IR (KBr): ṽ = 3514, 3365, 1586, 1583 cm^{-1}. ESI-MS: *m*/*z* = 360.9 [M + 1]$^+$, 358.6 [M – 1]$^-$.

2-[(4-Methylbenzoyl)(4,5-dihydroxy-5-*tert*-butylphenyl)methylene]-imidazolidine (3o): Yield 25% (183 mg); m.p. 244–246 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.03 [s, 9 H, (CH$_3$)$_3$], 2.17 (s, 3 H, CH$_3$), 3.27–3.67 (m, 4 H, NCH$_2$CH$_2$N), 5.72 (br. s, 1 H, NH), 6.43 (s, 1 H, ArH), 6.75 (s, 1 H, ArH), 6.85 (d, *J* = 8.8 Hz, 2 H, ArH), 7.11 (d, *J* = 8.8 Hz, 2 H, ArH), 8.54 (br. s, 1 H, OH), 8.59 (br. s, 1 H, OH), 10.22 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.1, 32.4, 36.0, 39.9, 40.6, 94.0, 116.3, 123.8, 127.0, 127.7, 129.0, 137.3, 140.9, 1401.0, 143.0, 144.2, 165.84, 182.1 ppm. IR (KBr): ṽ = 3435, 2955, 1706, 1582, 1532 cm^{-1}. ESI-MS: *m*/*z* = 367.0 [M + 1]$^+$, 364.9 [M – 1]$^-$.

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[1] For a review of the synthesis and application of heterocyclic ketene N,N-acetals, see: a) H. Junjappa, H. ILa, C. V. Asokan, *Tetrahedron* **1990**, *46*, 5423–5506; b) Z. T. Huang, M. X. Wang, *Heterocycles* **1994**, *37*, 1233–1264; c) M. X. Wang, Z. T. Huang, *Prog. Nat. Sci.* **2002**, *12*, 249–257.
[2] For a review of enaminone chemistry, see: A. A. Elassar, A. A. El-Khair, *Tetrahedron* **2003**, *59*, 8463–8480.
[3] Z. T. Huang, Z. R. Liu, *Chem. Ber.* **1989**, *122*, 95–100.
[4] Z. T. Huang, Z. R. Liu, *Heterocycles* **1986**, *24*, 2247–2254.
[5] a) J. H. Zhang, M. X. Wang, Z. T. Huang, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2087–2094; b) J. H. Zhang, M. X. Wang, Z. T. Huang, *Tetrahedron Lett.* **1998**, *39*, 9237–9240.
[6] W. Y. Zhao, Z. T. Huang, *J. Chem. Soc. Perkin Trans. 2* **1991**, 1967–1970.
[7] a) C. C. Zeng, C. F. Liu, J. Zeng, R. G. Zhong, *J. Electroanal. Chem.* **2007**, *608*, 85–90; b) C. C. Zeng, D. W. Ping, S. C. Zhang, R. G. Zhong, J. Y. Becker, *J. Electroanal. Chem.* **2008**, *622*, 90–96; c) C. C. Zeng, F. J. Liu, D. W. Ping, Y. L. Cai, R. G. Zhong, J. Y. Becker, *J. Electroanal. Chem.* **2009**, *625*, 131–137; d) C. C. Zeng, F. J. Liu, D. W. Ping, L. M. Hu, Y. L. Cai, R. G. Zhong, *Tetrahedron* **2009**, *65*, 4505–4512.
[8] V. Aggarwai, A. Kumar, H. Ila, H. Junjappa, *Synthesis* **1981**, 157–158.

[9] a) D. Nematollahi, M. Rafiee, *Green Chem.* **2005**, *7*, 638–644; b) D. Nematollahi, D. Habibi, M. Rahmati, M. Rafiee, *J. Org. Chem.* **2004**, *69*, 2637–2640; c) A. R. Fakhari, D. Nematollahi, M. Shamsipur, S. Makarem, S. S. H. Davarani, A. Alizadeh, H. R. Khavasi, *Tetrahedron* **2007**, *63*, 3894–3898; d) S. S. H. Davarani, D. Nematollahi, M. Shamsipur, N. M. Najahi, L. Masoumi, S. Ramyar, *J. Org. Chem.* **2006**, *71*, 2139–2142; e) F. Zhang, G. Dryhurst, *J. Electroanal. Chem.* **1995**, *398*, 117–128; f) X.-M. Shen, G. Dryhurst, *J. Med. Chem.* **1996**, *39*, 2018–2029; g) R. Xu, X. Huang, K. J. Kramer, M. D. Hawley, *Bioorg. Chem.* **1996**, *24*, 110–126; h) X. Huang, R. Xu, M. D. Hawley, T. L. Hopkins, K. J. Kramer, *Arch. Biochem. Biophys.* **1998**, *352*, 19–30; i) A. Felim, A. Urios, A. Neudorffer, G. Herrera, M. Blanco, M. Largeron, *Chem. Res. Toxicol.* **2007**, *20*, 685–693.

[10] C. C. Zeng, F. J. Liu, D. W. Ping, L. M. Hu, Y. L. Cai, R. G. Zhong, *J. Org. Chem.* **2009**, *74*, 6386–6389.

[11] In several controlled experiments, we increased the volume of acetonitrile and ensured that all formed products were dissolved. However, indole derivatives derived from further oxidation and intramolecular Michael addition were not detected.

[12] Z. T. Huang, P. C. Zhang, *Chem. Ber.* **1989**, *122*, 2011–2016.

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