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Electrode Instead of Catalyst and Enzyme. A Greener Protocol for the Synthesis of new 2-Hydroxyacetamide Derivatives Containing γ-lactone ring†

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Electrochemical synthesis of some 2-hydroxyacetamides containing a γ-lactone ring was carried out by anodic oxidation of 3,5-di-*tert*-butylcatechol in the presence of primary aliphatic amines at the surface of carbon electrode. This transformation was triggered by extradiol ring cleavage of electrogenerated *o*-benzoquinone followed by lactonization and amide bond formation lead to 2-hydroxyacetamide derivatives. In this work, some new 2-hydroxyacetamides in a single step without any enzyme, catalyst and activator in good to high yields, without toxic reagents at a carbon electrode using a sustainable method, are provided.

The degradation of aromatic compounds often involves a sequence of reactions in which oxidative cleavage of catecholic intermediates is a pivotal step.[1] These cleavages are performed by catechol dioxygenases with the incorporation of oxygen molecules. These enzymes are classified on the basis of the position of the catechol ring cleavage into intradiol and extradiol cleavage enzymes.[2] Some metal complexes such as Co(II),[3] Cu(II),[4] RU(II),[5] and V(IV)[6] complexes and some reagents like KO_2,[7] hydrogen peroxide and peracetic acid,[8] have also been reported to catalyze oxidative cleavage of catechol.

On the other hand, the amides are important functional groups in chemical intermediates, polymers, pharmaceuticals and natural products.[9] Hence considerable advances have been attained in the amide bond formation. Traditionally, an amide bond is formed by the reaction of a pre-activated carboxylic acid with an amine.[9c,10] Several alternative methods such as reaction of thiocarboxylic acids with azides,[11] condensation of carboxylic acids with aryl isocyanates,[12] addition of formamides to alkenes or alkynes,[13] solid-phase strategies,[9b,14] mesoporous-nanocatalyzed amidation[15] and many other techniques which often need harsh reaction conditions have been developed for the amide bond synthesis.

In addition, lactones are not only recognized as useful building blocks in organic synthesis, but also are important structural motif in many natural products and drugs. These findings have prompted many researchers to synthesize a number of these compounds by different methods.[16] Despite the success in the synthesis of amides and lactones, there is still room for improvement. Accordingly, we envisaged that the polyfunctional structures containing both lactone and amide moieties may have some promising applications in chemical and biological fields.

Here we report an electrochemical method for the synthesis of 2-hydroxyacetamides with an unsaturated γ-lactone ring. In the strategy presented herein, 3,5-di-*tert*-butylcatechol (**1**) was chosen as a model compound to afford the best conditions for the oxidative cleavage. The presence of two *tert*-butyl groups at the catechol ring of **1** prevent coupled chemical reactions such as Michael addition which often occur after oxidation of catechols.[17] According to this idea, we investigate electrochemical oxidation of **1** in the presence of some primary amines **9**-**17**) and propose a novel protocol for the synthesis of some new 2-hydroxyacetamide-γ-lactone derivatives. This procedure that avoids metal-based reagents, enzymes, catalysts, and stoichiometric oxidants is carried out in a simple cell using carbon electrodes in a single step with high atom economy in ambient conditions.

Cyclic voltammogram of **1** in water (carbonate buffer, c = 0.2 M, pH 11.0)/acetonitrile mixture (60:40, v:v) shows one anodic peak (A_1) and a corresponding cathodic peak (C_1), which corresponds to the transformation of **1** to 3,5-di-*tert*-butyl-1,2-benenzoquinone (**2**) and vice-versa within a quasi-reversible two-electron process (Fig. 1a).[17e,f] The peak current ratio (I_{pC1}/I_{pA1}) is almost unity confirms the stability of **2** under the experimental time scale. This also confirms that any side reactions are too slow to be observed on the time scale of cyclic voltammetry. It is a favorable condition for the study of probable homogeneous reactions coupled with electrochemical process. The oxidation of **1** in the presence of *n*-butylamine (**9**) was also studied. Cyclic voltammogram of **1** in the presence of **9** has been shown in Fig. 1b. The occurrence of a chemical reaction after electrochemical process is supported by the decrease in I_{pC1} during

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†Electronic Supplementary Information (ESI) available: Detailed experimental procedure, Crystallography data of **9a** and ^{1}H NMR, ^{13}C NMR, FT-IR, MS of all compounds.. See DOI: 10.1039/x0xx00000x

the reverse scan, which could indicate that **2** is partially consumed by a chemical reaction.

For more data, controlled-potential coulometry was performed in water/acetonitrile mixture containing **1** and **9** at 0.05 V versus Ag/AgCl. The monitoring of electrolysis progress was carried out by linear sweep voltammetry (Fig. 2).

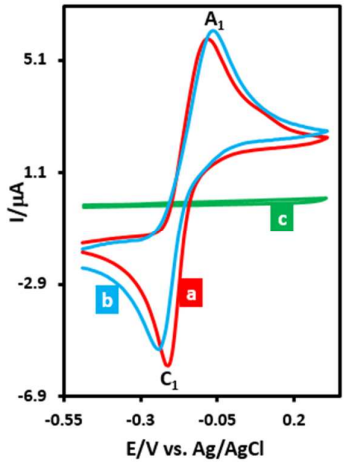


Fig. 1 Cyclic voltammograms of **1** (1.0 mM): (a) in the absence, (b) in the presence of *n*-butylamine (**9**) (5.0 mM) and (c) **9** (5.0 mM) in the absence of **1**, at glassy carbon electrode, in water (carbonate buffer, *c* = 0.2 M, pH 11.0)/acetonitrile mixture (60:40, v:v). Scan rate: 50 mV s^{-1}. Temperature: 25 ± 1 °C..

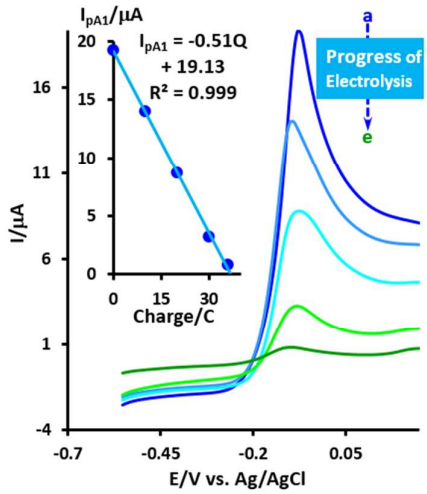
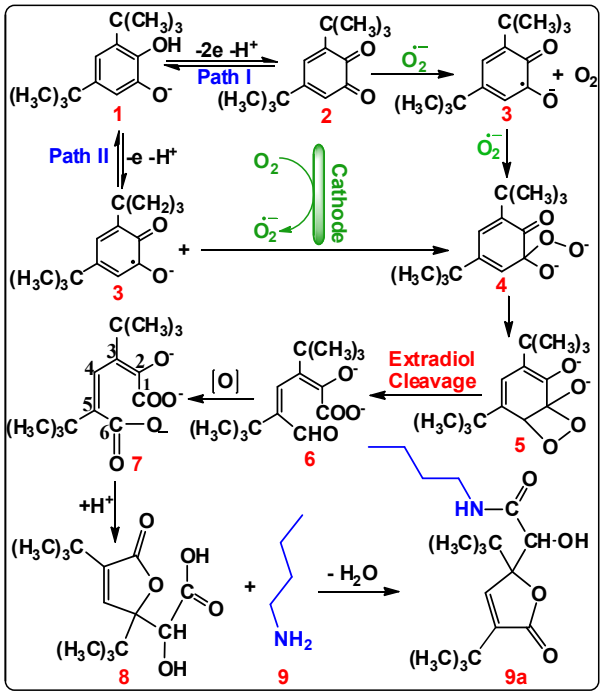


Fig. 2 Linear sweep voltammograms of **1** (0.2 mmol) in the presence of **9** (0.2 mmol) obtained at 100 mV s^{-1} during controlled potential coulometry at 0.05 V versus Ag/AgCl, after consumption of: (a) 0, (b) 10, (c) 20, (d) 30 and (e) 36 C. Inset: Variation of peak current (I_{pA1}) versus charge consumed. Temperature: 25 ± 1 °C.

It shows that during the coulometry experiment, the I_{pA1} decreases. This peak (A_1) disappears when the charge consumption becomes about 2e^- per molecule of **1**. The cyclic voltammetry results accompanied by the spectroscopic data of the product (**9a**) (see Supporting Information) allow us to propose a mechanism for the oxidation of **1** in the presence of **9** (Scheme 1).

Because of the triplet ground state and strong oxygen-oxygen bond, oxygen molecules are kinetically quite stable towards reaction at room temperature, and must be activated by enzymes containing active centers of metal ions such as substrate activating and dioxygen activating enzymes.[18] However, this work was undertaken without any catalyst or enzyme for dioxygen activation.

Since the electrochemical oxidation of **1** in the absence of amine does not lead to oxidative ring cleavage,[17e] it seems that amine plays a vital role in oxygen activation. In the absence of enzymes and catalysts, it seems that the dioxygen gains one electron from the electrolysis medium during the oxidation of **1** to form active superoxide radical anion which is a strong nucleophile. The presence of acetonitrile in electrolysis medium increases the stability of superoxide radical anion.[19] Rapid electron transfer from superoxide radical anion to quinones to generate corresponding anion radical has been reported by Poupko and Rosentha.[7,20] So, single electron transfer from generated superoxide to **2** converts it to **3** (path I).



Scheme 1 Proposed mechanism for the electrochemical oxidation of **1** in the presence of **9**.

In addition, direct generation of **3** via single electron transfer is probable (path II). The reaction of the unstable semi-quinone **3** with superoxide radical anion leads to the intermediate **4**. The intramolecular addition reaction of connected peroxidic oxygen to the C-6 in the next step, converts **4** to **5**, containing a four-membered dioxetane ring. Spontaneous cleavage of the dioxetane ring occurs to produce the acyclic intermediate **6** through extradiol cleavage that after oxidation easily leads to the formation of dicarboxylate **7**.[2c,d]

The intramolecular addition of the oxygen to the C-C double bond affords carboxylic acid **8** containing unsaturated γ-lactone ring. The formation of the stable γ-lactone is the driving force for the cyclization. This compound (**8**) due to α,β-unsaturated carbonyl is somewhat similar to that of the sesquiterpene lactones. However, unlike the sesquiterpene lactones that are often attacked by

nucleophiles from the β-carbon through Michael addition reactions,[21] **8** does not participate in the Michael addition reaction due to steric inhibition of the *tert*-butyl groups. The results show that due to the presence of *n*-butylamine (**9**) in the electrolysis medium, the amide bond formation between **8** and **9** leads to lactone-amide **9a** as the final product with the extrusion of a water molecule (Scheme 1). The structure of **9a** was further confirmed by single-crystal X-ray diffraction analysis (Fig. 3) (Section VI, Supporting Information).

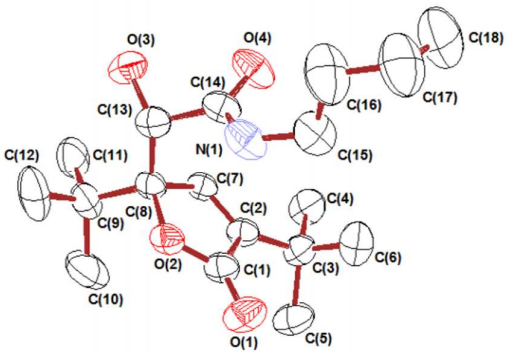
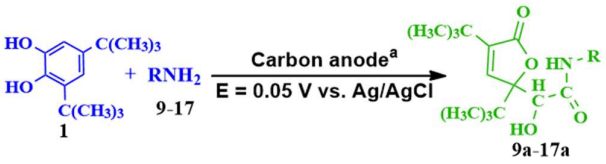


Fig. 3 ORTEP view of X-ray crystal structure of **9a**.

Despite the abundant literature on the amide bond formation between carboxylic acid and amine functional groups, that have shown that the reaction doesn't happen at ambient temperature and without activation of carboxylic acid,[9-15] however, in this work, the amide bond formation between **8** and **9** occur at room temperature without any catalyst and activator.

Under constant potential electrolysis, the scope of the reaction was studied using different starting amines as presented in Scheme 2. These results indicate that various primary alkyl amines (**9**-**13**) and cycloalkyl amines (**14**-**17**) were converted successfully to the corresponding 2-hydroxyacetamides **9a**-**17a** in good to high yields.



Entry	Amine	Product	Mp (°C)	Yield[b] (%)
1	NH_2 (9)	9a	135-136	68
2	NH_2 (10)	10a	172-174	65
3	NH_2 (11)	11a	182-184	75
4	NH_2 (12)	12a	167-168	55
5	NH_2 (13)	13a	126-127	70
6	NH_2 (14)	14a	126-128	72
7	NH_2 (15)	15a	138-139	65
8	NH_2 (16)	16a	117-118	68
9	NH_2 (17)	17a	136-138	75

[a]Reaction condition: **1** (1.0 mmol), **9-17** (1.0 mmol), carbonate buffer, pH = 11.0 (24 ml), acetonitrile (36 ml). [b]Yields refer to the pure isolated products.
Scheme 2. Overall reaction and scope.

Electrolysis process was also investigated by constant current method (galvanostatic studies). Constant-current electrolysis afforded 2-hydroxyacetamides **9a**-**17a** in lower yields (Table S1, Supporting Information), indicating that the precise control of oxidation potential is an important factor of the transformation.

The oxidation of catechols can also be performed by the common oxidizing agents such as potassium ferricyanide.[22] However, our efforts towards the synthesis of 2-hydroxyacetamides using potassium ferricyanide failed to afford the desired products.

In summary, for the first time, we reported a sustainable method of electrochemical synthesis of novel 2-hydroxyacetamides containing unsaturated γ-lactone ring from 3,5-di-*tert*-butylcatechol and primary aliphatic amines. Moreover, a mechanism for the anodic oxidation of 3,5-di-*tert*-butylcatechol in the presence of these amines has been presented. The successful achievement of oxidative ring cleavage, oxygen activation, lactonization and amide bond formation without any catalyst, enzyme and reagent in ambient conditions at room temperature and atmospheric pressure are the most prominent features of this one-pot process. Performing an alternative chemical method for this transformation that can compete with the anodic oxidation is difficult. The development of this electrochemical strategy using the anodic oxidation of 3,5-di-*tert*-butylcatechol in the presence of diamines is currently underway in our laboratory.

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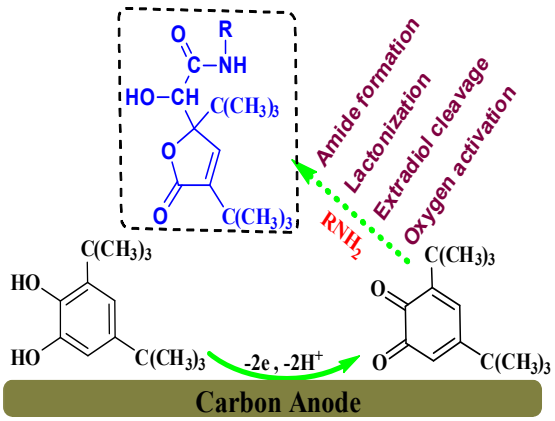
Graphical Abstract

Electrode instead of catalyst and enzyme: Electrochemical synthesis of novel 2-hydroxyacetamides was performed by the anodic oxidation of 3,5-di-*tert*-butylcatechol in the presence of primary amines. It is the first example of a one-pot protocol including oxygen activation, extradiol cleavage, lactonization and amide bond formation sequence without any catalyst and enzyme.



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