

Letter

# Scalable Electrochemical Dehydrogenative Lactonization of C(sp<sup>2</sup>/sp<sup>3</sup>)-H Bonds

Sheng Zhang,<sup>\*,†®</sup> Lijun Li,<sup>†</sup> Huiqiao Wang,<sup>†</sup> Qian Li,<sup>†</sup> Wenmin Liu,<sup>†</sup> Kun Xu,<sup>\*,†,‡®</sup> and Chengchu Zeng<sup>\*,‡®</sup>

<sup>†</sup>College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang 473061, China <sup>‡</sup>Beijing Key Laboratory of Environmental and Viral Oncology, College of Life Science & Bioengineering, Beijing University of Technology, Beijing 100124, China

Supporting Information

**ABSTRACT:** A practical, electrochemical method is developed for the direct dehydrogenative lactonization of  $C(sp^2/sp^3)$ -H bonds under external oxidant- and metal-free conditions, delivering diverse lactones, including coumarin derivatives with excellent regioselectivity. The scalable nature of this newly developed electrochemical process was demonstrated on a 40 g scale following an operationally simple protocol. The remote lactonization of  $C(sp^3)$ -H bonds would constitute an important synthetic advance toward electrochemical C-O bond formation.

L actones represent privileged structural subunits in molecules of pharmaceutical, biological, and medicinal interest (Figure 1a).<sup>1</sup> Consequently, extensive synthetic efforts have been devoted to this notable structure.<sup>2,3</sup> Among developed approaches, the direct C–H/O–H oxidative coupling reaction has gained special attention for its high atom economy (Figure



Figure 1. Lactones in bioactive molecules and evaluation of accessible methods.



1b).<sup>3</sup> For instance, Martin<sup>3a</sup> and Gevorgyan<sup>3b</sup> independently reported the pioneering work of copper-catalyzed intramolecular oxidative coupling of  $C(sp^2)$ -H with aromatic carboxylic acids in 2013. Palladium-catalyzed C-H activation/C-O coupling has also been developed by Wang's group.<sup>3c</sup> Recently, Gonzalez-Gomez and co-workers disclosed an efficient photocatalytic version of  $C(sp^2)$ -H lactonization.<sup>3f</sup> However, most of these works involve the use of transition-metal catalysts, photocatalysts or organocatalysts together with strong oxidants, which are of high cost for large-scale industrial application. Moreover, the existing intramolecular C-H/O-H oxidative couplings are limited to reactions between aromatic carboxylic acids and  $C(sp^2)$ -H bonds. The direct lactonization of  $C(sp^3)$ -H bonds with carboxylic acids, especially with aliphatic carboxylic acids, remains less explored.<sup>4</sup>

Organic electrosynthesis obviates the use of dangerous and toxic reagents, and the past decades have witnessed extensive exploration in this aspect, given its environmental benignity and operational simplicity.<sup>5,6</sup> As carboxylic acids are normally inexpensive and benchtop stable, the electrochemical transformation of carboxylic acids into other useful motifs is of great significance. Treatment of carboxylic acids with (external or electrogenerated) base generates carboxylate anion, which undergoes anodic oxidation to generate carboxylate radical. This reactive intermediate usually proceeds via a radical decarboxylative homocouplings, which is known as the Kolbe reaction.<sup>7</sup> Electrogenerated carboxylate radical could also undergo intramolecular addition to electron-rich alkenes to produce lactones.<sup>8</sup> We envisioned that direct lactonization of

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 $C(sp^2)$ -H bonds could occur if C-O coupling proceeds fast enough to outcompete the Kolbe decarboxylation. In addition, if 1,5-hydrogen-atom-transfer (HAT) makes remote C-H homolytic cleavage possible, lactonization of  $C(sp^3)$ -H bonds would be achieved, though it is elusive for electrosynthesis. Herein, we describe an electrochemical dehydrogenative lactonization of aromatic and aliphatic carboxylic acids with  $C(sp^2/sp^3)$ -H bonds (Figure 1c). This strategy exhibits broad substrate scope, operational simplicity and high regioselectivity under additive-, metal-, and external oxidant-free conditions. The scalability of this method was demonstrated on a 40 g scale following an operationally simple protocol.

The optimized reaction conditions are demonstrated in Figure 2 (see Table S1 for details). The cyclization of 2-



Figure 2. Optimized conditions.

biphenylcarboxylic acid **1a** proceeded smoothly in an undivided cell equipped with a Pt anode and a Pt cathode using n-Bu<sub>4</sub>NBF<sub>4</sub> in CH<sub>3</sub>CN/MeOH (7:1 v/v) as the supporting electrolyte under constant current conditions, giving lactone **2a** in 99% yield. Pleasingly, the yield of **2a** could still be obtained in 93% yield using cheap graphite plates as the anode and cathode.

After the optimal reaction conditions were identified, the substrate generality was investigated (Scheme 1). First, the electronic variation in the para substitution of Ar<sup>2</sup> ring was investigated. The results showed that halogen (2b-d), trifluoromethyl (2e), ester (2f), methyl (2g) and tert-butyl (2h) groups were all well tolerated, giving lactones 2b-h in 71-80% yields. However, when a strong electron-donating group (OMe) was attached to the *para* position of  $Ar^2$  ring, the yield decreased to 42% (2i). For substrates with two possible reactive sites, the preferable formation of *para*-substituted lactones were observed (2i-l). 2-Thienvl-substituted benzoic acid proved to be an amenable substrate giving lactone 2m with a low yield, which may due to the partial oxidation of electron-rich thiophene moiety. Additionally, multisubstituted substrate was also welltolerated to give the corresponding product 2n in 62% yield. The generality of this methodology was further demonstrated by preparing substituted lactones 20-2w in moderate to excellent yields. To demonstrate the practicability of this method, we also tested some substrates for lactonization using graphite as the anode and cathode. The results showed that the lactonizations could be carried out smoothly by employing graphite as the electrodes, giving lactones 2a, 2g-h, 2j, 2o, 2p, 2r, and 2v in 67-93% yields.

As shown in Scheme 1, the electrochemical cyclization of biaryl carboxylic acids has been demonstrated as a powerful method for lactones synthesis. It would be more valuable if the protocol could be applied to diaryl acrylic acids, since the resulting coumarin derivatives are important in the fragrance and flavor industry (Scheme 2). With a minor modification of the standard conditions, diaryl acrylic acids 3 could undergo lactonization with  $C(sp^2)$ -H bonds to give coumarins 4 in moderate yields.

Having investigated the lactonization of  $C(sp^2)$ -H bonds, we next turned our attention to the regioselective lactonization of

Scheme 1. Substrate Scope with Respect to Biaryl Carboxylic  $\operatorname{Acids}^a$ 



<sup>*a*</sup>Reaction conditions: undivided cell, Pt anode, and cathode  $(1.5 \times 1.5 \text{ cm}^2, J = 13.3 \text{ mA/cm}^2)$ , 1 (0.5 mmol), CH<sub>3</sub>CN (7 mL), MeOH (1 mL), *n*-Bu<sub>4</sub>NBF<sub>4</sub> (2 mmol) at room temperature for 1.5–2.5 h. <sup>*b*</sup>*n*-Bu<sub>4</sub>NClO<sub>4</sub> was employed as the electrolyte. <sup>*c*</sup>J = 9 mA/cm<sup>2</sup>. <sup>*d*</sup>The ratio of regiomers (rr) was determined by the <sup>1</sup>H NMR spectrum. <sup>*e*</sup>Changed reaction conditions for the yields in parentheses: graphite anode and cathode (1.5 × 1.5 cm<sup>2</sup>), 3 h.

Scheme 2. Electrochemical Lactonization of Diaryl Acrylic Acids



C(sp<sup>3</sup>)–H bonds (Scheme 3). It is well-known that the regioselective lactonization of a substrate with multiple reactive sites would be more challenging.<sup>4b,c</sup> To our delight, as shown in Scheme 3, when 2-benzylbenzoic acids 5a-e were subjected to anodic oxidation under the standard conditions, phenyl phthalides 6a-e were exclusively generated without observing of the C(sp<sup>2</sup>)–H coupling products. This remarkable selectivity might attribute to the higher stability of five-membered ring products compared with that of seven-membered ones. For 2-phenethyl benzoic acid **5f** with two reactive benzylic C(sp<sup>3</sup>)–H bonds, isochroman-1-one **6f** was obtained as the single product. Subsequently, a series of alkylated benzoic acids containing tertiary carbon were examined. As expected, all of the cyclized



<sup>*a*</sup>Reaction conditions: undivided cell, Pt anode and cathode ( $1.5 \times 1.5$  cm<sup>2</sup>, J = 13.3 mA/cm<sup>2</sup>), **5** (0.5 mmol), CH<sub>3</sub>CN/MeOH (7/1 v/v), *n*-Bu<sub>4</sub>NBF<sub>4</sub> (2 mmol) at rt for 2–3 h. <sup>*b*</sup>J = 20 mA/cm<sup>2</sup>. <sup>*c*</sup>J = 15.6 mA/cm<sup>2</sup>

products **6g–k** with a new quaternary carbon center were regioselectively accessed in moderate to excellent yields. In order to make the protocol more general and appealing, we also tested the lactonization of aliphatic carboxylic acid (**5l**). The challenge of using aliphatic carboxylic acid is that its lower oxidative potential facilitate the decaboxylative homocoupling process. We were delighted to find that 4-phenylbutyric acid underwent lactonization of  $C(sp^3)$ —H bond smoothly to afford fivemembered lactone **6l** in 62% isolated yield under our electrolysis conditions. The recovery of substrate **5m** illustrates that benzylic radical is formed by 1,5-HAT instead of direct benzylic oxidation. The failure of substrates **5n** and **5o** indicates that a stabilized benzylic radical intermediate is essential for this transformation.

Since an excellent yield of lactonization could be obatined by using inexpensive graphite electrodes, undivided cell, and constant current electrolysis (Figure 2, condition 2), which are essential for large-scale electrosynthesis. To make this protocol more practical, 40 g of **1a** in a container was pumped to an undivided glass cell equipped with cheap graphite anode and cathode for lactonization. After a simple workup of the resulting mixture, product **2a** was obtained in 84% yield (33 g) with high purity (>97%) without column chromatography (Figure 3, see the **SI** for details), which indicates that the present protocol has a potential industrial applications.

Lactone is an important class of synthon in organic synthesis. Taking **2a** and **6l** as examples, their hydrolysis easily gave benzoic acid derivatives 7 and 8 (Figure 4a).<sup>9</sup> The present method provides an efficient route for the remote hydroxylation of  $C(sp^2/sp^3)$ —H bonds. By using product **2u** as the starting material, natural product cannabinol could be obtained in five steps according to previous report (Figure 4b).<sup>3c</sup> Previous report for the construction of compound **2u** needed palladium catalysis with excess amount of PhI(OAc)<sub>2</sub> as the oxidant and excess amount of KOAc as the base.<sup>3c</sup>



Figure 3. Large-scale synthesis.



(b) Natural products synthesis



Figure 4. Synthetic applications.

Some control experiments were conducted in order to gain an understanding of the reaction mechanism. At the outset, radical scavenger TEMPO was tested to identify the reaction pathway. As shown in Scheme 4, adding 3 equiv of TEMPO to the reaction

#### **Scheme 4. Control Experiments**



mixture led to the formation of radical trapping adducts **9a,b** in 91–99% yields. Further kinetic isotope effect studies verified that the aromatic C–H cleavage might not be the turnoverdetermining step, suggesting a carboxylate radical initiative mechanism.<sup>3f</sup> To determine which moiety (carboxylate or aromatic moiety) is oxidized preferentially, the cyclic voltammetric study was also carried out (see Figure S10 for details). The results showed that the carboxylate moiety has an oxidation potential of 1.4 V vs Ag/AgCl, while the aromatic moiety has an oxidation potential over 2.0 V vs Ag/AgCl, which indicate carboxylate moiety is oxidized preferentially under the optimized conditions. These results are consistence with the radical trapping experiments. The mechanism is different from the well-known anodic acetoxylation of aromatic coumounds developed by Eberson and co-workers.<sup>10,11</sup> In Eberson's work, anodic oxidaiton of aromatic moiety was the first step, followed

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by the nucleophilic attack of acetoxyl anion to lead to the acetoxylated products.

On the basis of these results and previously related reports, <sup>3f,4b</sup> a plausible mechanism was proposed as shown in Figure 5. First,



Figure 5. Plausible mechanism.

the cathodic dehydrogenation of carboxylic acid or deprotonation via electrogenerated MeO<sup>-</sup> affords carboxylate anion, which after further electrooxidation generating carboxylate radical **10**. Then, the carboxylate radical **10** undergoes two different pathways depending on the substrate structure. For the lactonization of the  $C(sp^2)$ -H bond, a *6-endo-trig* cyclization gives intermediate **11**. In the case of lactonization of the  $C(sp^3)$ -H bond, a 1,5-HAT process occurs to form a stabilized benzyl radical **12**. Finally, radicals **11** and **12** convert to products **2a** and **6a**, respectively, by losing an electron and a proton.

In conclusion, a scalable and practical electrochemical process was developed for direct dehydrogenative lactonization of  $C(sp^2/sp^3)$ —H under external oxidant-, additive-, and metalfree conditions. The electrochemical reaction proceeds with high regioselectivity, delivering a variety of lactones, including coumarin derivatives which are important in the fragrance and flavor industry. The reaction is clean, low cost, and easy to scale up, as demonstrated by a 40 g scale reaction, which is of potential industrial application.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03617.

Detailed experimental procedures and spectral data (PDF)

## AUTHOR INFORMATION

# **Corresponding Authors**

- \*E-mail: shengzhang@nynu.edu.cn.
- \*E-mail: xukun@nynu.edu.cn.
- \*E-mail: zengcc@bjut.edu.cn.

#### ORCID <sup>©</sup>

Sheng Zhang: 0000-0002-9686-3921 Kun Xu: 0000-0002-0419-8822 Chengchu Zeng: 0000-0002-5659-291X

## Notes

The authors declare no competing financial interest.

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