Electrocatalytic Dehydrogenative Esterification of Aliphatic Carboxylic Acids: Access to Bioactive Lactones

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Supporting Information

ABSTRACT: A scalable and efficient electrocatalytic dehydrogenative esterification is reported. With an indirect electrolysis strategy, both intra- and intermolecular-type reactions were amenable to this practical method. With n-Bu4NI as the catalyst, undesired decarboxylation and Baeyer–Villiger oxidation were suppressed. More importantly, this novel method provided reliable and direct access to the natural product cytosporanone A on a gram scale.

α-Acyloxy ketones and their alcohol derivatives represent core scaffolds that exhibit potent antifungal and antibacterial activities and are widely distributed in natural products (Figure 1a).1 Consequently, increasing attention has been devoted to the synthetic approach toward these structures since the pioneering work of Ochiai.2,3 For instance, some impressive works on iodine- and hypervalent iodine-catalyzed lactonization were achieved by Ishihara (Figure 1b).2b,c In 2011, Zhang and co-workers reported an alternative method using DDQ as the promoter (Figure 1b).2d Recently, with the explosive development of photoredox catalysis, the photooxidative approach has also been successfully applied to the synthesis of γ-keto lactones starting from different substrates (Figure 1c).3 However, the excessive use of oxidants and the relatively low efficiencies of these methods impose restrictions on large-scale application.

Since the classical works of Faraday and Kolbe on the electrolysis of aliphatic carboxylic acids, electrochemistry has emerged as a practical tool for organic synthesis.4 In particular, synthetic electrochemistry has been demonstrated as a powerful tool in cross-dehydrogenative coupling (CDC) reactions.5 For instance, Waldvogel has reported some impressive works on the cross-coupling reaction of phenols and anilines (Scheme 1a).5 Recently, Xu and co-workers unveiled some prominent research on intramolecular C–H/N–H and C–H/C–H coupling reactions (Scheme 1b).5,7 The intermolecular oxidative coupling reaction of electron-rich aromatic rings and thiophenols has been elegantly resolved by Lei’s group.

Scheme 1. Electrochemical Cross-Dehydrogenative Coupling

<table>
<thead>
<tr>
<th>Work</th>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waldvogel’s work</td>
<td>XH + R</td>
<td>R'XH</td>
</tr>
<tr>
<td>Xu’s work</td>
<td>R’</td>
<td>R’XH</td>
</tr>
<tr>
<td>Lei’s work</td>
<td>Arʻ⁻H⁻⁻⁻⁻⁺</td>
<td>Ar⁻⁻⁻⁻⁻⁺</td>
</tr>
<tr>
<td>Wang, Zeng’s work</td>
<td>Rx</td>
<td>Nu</td>
</tr>
</tbody>
</table>

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Figure 1. γ-Keto butyrolactone in natural products and its synthetic approach.
Moreover, extensive exploration of the dehydrogenative coupling reactions of ketones has also been unveiled by Wang, Zeng and other groups (Scheme 1d).8 Despite this significant progress, dehydrogenative esterification of carboxylic acids with ketones has receive far less attention, partly because of the undesired decarboxylation of the carboxylic acid.10,11 Encouraged by some remarkable work in electrochemical halide catalysis,6 we envisioned that an indirect electrochemical halide catalysis,9 we envisioned that an indirect dehydrogenative coupling reactions of ketones has also been described. We commenced the model reaction in an undivided cell using n-Bu4NI as the mediator under constant-current (10 mA) electrolysis (Table 1, entry 1). Promisingly, a current (10 mA) electrolysis (Table 1, entry 1). Promisingly, a parameter of current density (16% yield of the product was detected. Further screening of the parameter of current density (J) showed that 13.3 mA/cm² was the optimal value (Table 1, entry 2; for details, see the Supporting Information). To demonstrate the catalytic role of n-Bu4NI, the loading of the mediator was lowered to 20 mol %. Varying the supporting electrolyte had little effect on the reaction efficiency, and n-Bu4NOAc gave the highest yield (81%; Table 1, entries 3–6). To our delight, lowering the catalyst loading to 15% still maintained a good yield (Table 1, entry 7). Changing the Pt anode to a graphite or reticulated vitreous carbon (RVC) anode caused slight erosion in the yield (Table 1, entries 8 and 9).

To test the generality of this electrocatalytic dehydrogenative lactonization under the identified optimal conditions, various substituted γ-keto butanoic acids were synthesized and employed in the reaction. As shown in Scheme 2, the reaction performance is largely independent of the electronic properties of substitutions on the aryl ring (2b–j). Changing the substitution pattern to the meta or ortho position has little effect on the reaction performance. Specifically, the sterically congested substrate 1o reacted smoothly in this efficient transformation, thereby giving the product in 79% yield (2o). Additionally, this electrochemical protocol was also compatible with substrates bearing fused rings or a heterocycle (2p and 2q). It is particularly noteworthy that the lactone containing alkene functionality (2r), allowing for various derivatizations, was readily furnished in 73% yield. Because of their volatility in the presence of oxidant, alkyl-substituted γ-keto butanoic acids still remain notoriously challenging substrates in oxidative lactonization with traditional methods. Notably, benzyl γ-keto butanoic acid 1s containing two comparable reaction sites afforded the product 2s with excellent regioselectivity at a higher reaction temperature. Other γ-keto butanoic acids with complex skeletons were amenable substrates, and the diastereoselective product 2u, six-membered-ring product 2v, and even spiro lactones 2w and 2x were obtained in moderate to excellent yields.

Having surveyed the intramolecular dehydrogenative reaction, we were poised to apply this method to the intermolecular dehydrogenative esterification of acetophenone (3) with acids (Scheme 3). To overcome the lower reactivity of the intermolecular-type reaction, a higher catalyst loading (20 mol %) and temperature (60 °C) were employed. Pleasingly, a 41% yield was observed with the assistance of the supporting electrolyte n-Bu4NOAc. Interestingly, other supporting electrolytes failed to give any products. Subsequently, the esterification of propiophenone (5) with different acids was investigated. Both aliphatic and aromatic acids were well-tolerated, thereby giving products 6a and 6b in 36% and 38% yield, respectively.

### Table 1. Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>x</th>
<th>SE</th>
<th>anode</th>
<th>J (mA/cm²)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
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<td>16</td>
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<td>2</td>
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<td>-</td>
<td>Pt</td>
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<td>74</td>
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<tr>
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<td>20</td>
<td>n-Bu4NOAc</td>
<td>Pt</td>
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<td>81</td>
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<tr>
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<td>Pt</td>
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<td>78</td>
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<tr>
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<td>n-Bu4NPF6</td>
<td>Pt</td>
<td>6.7</td>
<td>76</td>
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<tr>
<td>6</td>
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<td>n-Bu4NCIO4</td>
<td>Pt</td>
<td>6.7</td>
<td>70</td>
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<tr>
<td>7</td>
<td>15</td>
<td>n-Bu4NOAc</td>
<td>Pt</td>
<td>6.7</td>
<td>81</td>
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<td>8</td>
<td>15</td>
<td>n-Bu4NOAc</td>
<td>C</td>
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<td>73</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>n-Bu4NOAc</td>
<td>RVC</td>
<td>6.7</td>
<td>69</td>
</tr>
</tbody>
</table>

“Reaction conditions: undivided cell, platinum anode and cathode (1.5 cm × 1.5 cm), J = 6.7 mA/cm², 1 (0.5 mmol), CH3CN (8 mL), TFE (0.5 mL), n-Bu4NI (0.075 mmol), and n-Bu4NOAc (1 mmol) at 40 °C for 3 h (3.4F). aIsolated yields.

16% yield of the product was detected. Further screening of the parameter of current density (J) showed that 13.3 mA/cm² was the optimal value (Table 1, entry 2; for details, see the Supporting Information). To demonstrate the catalytic role of n-Bu4NI, the loading of the mediator was lowered to 20 mol %. Varying the supporting electrolyte had little effect on the reaction efficiency, and n-Bu4NOAc gave the highest yield (81%; Table 1, entries 3–6). To our delight, lowering the catalyst loading to 15% still maintained a good yield (Table 1, entry 7). Changing the Pt anode to a graphite or reticulated vitreous carbon (RVC) anode caused slight erosion in the yield (Table 1, entries 8 and 9).

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### Scheme 2. Substrate Scope of γ-Keto Butanoic Acids

| Reaction conditions: undivided cell, platinum anode and cathode (1.5 cm × 1.5 cm), J = 6.7 mA/cm², 1 (0.5 mmol), CH3CN (8 mL), TFE (0.5 mL), n-Bu4NI (0.075 mmol), and n-Bu4NOAc (1 mmol) at 40 °C for 3 h (3.4F). aA higher reaction temperature (50 °C) was required.

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To probe the scalability of the electrocatalytic lactonization of γ-keto butanoic acids, a scaled-up reaction was performed as illustrated in Scheme 4. With graphite plates as the anode and cathode, 10 g of substrate 1a was treated with 15 mol % n-Bu4NI, and the lactone product 2a was obtained in 71% yield; 2a could then undergo diastereoselective reduction to afford the natural product 7 with >99/1 dr. This preparative experiment indicated that this electrochemical approach opened a practical route to bioactive cytosporanone A.1e

To gain insight into the reaction mechanism, some control experiments were carried out (Figure 2a). Initially, the commonly used radical scavenger TEMPO and 1,1-diphenylethylene were tested to elucidate the nature of the reaction. Treatment with 3 equiv of radical scavenger had no significant effect on the efficiency of the reaction (eq 1), which suggested that a radical process might not be the main pathway. Subsequently, the methyl-protected substrate 8 was employed in the reaction to identify the intermediate involved in the reaction (eq 2). Surprisingly, monohydroxylated product 9 was detected and isolated in 86% yield, even under an inert atmosphere, using 2 equiv of n-Bu4NI as the electrolyte. On the basis of a previous report,3d we speculated that α-hydroxylated ketone 9 might be generated from an iodinated counterpart via nucleophilic attack. Additionally, a cyclic voltammetric study was also performed (see the Supporting Information for details). An obvious catalytic current was observed, which further verified the catalytic role of n-Bu4NI.

On the basis of these results, a plausible catalytic cycle was proposed (Figure 2b). First, reduction at the cathode gives carboxylic ion intermediate 10, which can be directly iodinated via keto–enol tautomerism in the presence of in situ-generated iodine. However, there also remains another pathway that involves acyl hypoiodite species 11 according to related reports.10e,12 The homolytic dissociation of acyl hypoiodite 11 would induce an undesired decarboxylative process, while the hypervalent iodine could also be intercepted by the intramolecular keto moiety to give iodinated intermediate 12. Because of the higher reaction rate of the iodination, the side decarboxylation is avoided. Finally, nucleophilic cyclization of 12 affords the product 2a and regenerates iodide. In addition, the intermolecular product may be attributed to a similar nucleophilic attack process.

In summary, an electrocatalytic dehydrogenative esterification that provides a scalable and direct access to bioactive α-acyloxy lactones is disclosed. The metal-free, oxidant-free, highly efficient features endow it with potential practical applications. Additionally, an unexpected intermediate 9 was identified, and a plausible catalytic cycle was proposed. Further investigation of the enantioselective version of this reaction is currently in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03333.

Detailed experimental procedures and spectral data (PDF)

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Notes
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