ONE-STEP SYNTHESIS OF 4H-3,1-BENZOXAZIN-4-ONES FROM WEINREB AMIDES AND 1,4,2-DIOXAZOL-5-ONES VIA COBALT-CATALYZED C–H BOND ACTIVATION

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Dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday

Abstract – A one-step synthesis of 4H-3,1-benzoxazin-4-ones from readily available Weinreb amides and 1,4,2-dioxazol-5-ones under Cp*Co(III) catalysis is described. The reactions proceeded in moderate to good yields with high functional group compatibility.

4H-3,1-Benzoxazin-4-ones (benzoxazinones, 1)1 inhibit a variety of proteases, such as chymotrypsin,2a HL elastase,xb HSV-1 protease,2d cathepsin G,2e C1r,2f and human chymase.2g Cetilistat, a lipase inhibitor containing a benzoxazinone core, was reported as an anti-obesity agent.1 In addition, benzoxazinones 1 can be converted to quinazolin-4(3H)-ones.1 The importance of 1 in medicinal chemistry and drug-discovery prompted organic chemists to investigate their synthetic methods (Figure 1).1,4–7 2-Aminobenzoic acids and related derivatives are classical and frequently used starting materials for the synthesis of benzoxazinones.1 Transition metal-catalyzed carbonylation4 or amination5 reactions of orto-functionalized aryl halides, oxidation of indoles,1,6 and oxidation of other appropriate precursors2 provide 1. Preparation of these synthetic precursors, however, often requires multiple steps to access functionalized derivatives for investigation of the biological activities (Figure 1a).

On the other hand, transition metal-catalyzed directing group-assisted C–H bond activation8 enables the synthesis of benzoxazinones 1 from simpler compounds. Pd(II)-catalyzed C–H carbonylation reactions of aniline derivatives using CO gas were reported by Lloyd-Jones, Booker-Milburn, and co-workers,9a and Yu and co-workers9b (Figure 1b). A major drawback of these methods, however, is the requirement of highly toxic gaseous CO. Cp*Rh/Ir(III)-catalyzed orto-C–H amidation reactions of aromatic aldehydes10 or their equivalents11 afforded 2-aminobenzaldehyde derivatives, which were converted to 1 (Figure 1c).
In these cases, an additional oxidation step was necessary as the oxidation state of the directing group differs from that of I.

Here we report a one-step synthesis of benzoxazinones \(1\) from Weinreb amides \(2\) by directed C–H amidation using 1,4,2-dioxazol-5-ones (dioxazolones, \(3\)) under Cp*Co(III) catalysis and subsequent cyclization.\(^{12,13}\) Our protocol conveniently provided \(1\) using readily available starting materials and catalyst\(^4\) without any additional redox or cyclization step (Figure 1d).

![Figure 1. Synthetic methods of benzoxazinones 1](image)

We recently reported Cp*Co(III)-catalyzed C–H amidation of Weinreb amides \(2\) using dioxazolones \(3\)\(^{15a,16,17}\) as a part of our studies on Cp*Co(III) catalysis.\(^\text{15}\) While investigating this reaction, we found that benzoxazinone \(1\text{aa}\) was obtained as a major product along with a smaller amount of amidation product \(4\text{aa}\) when \(2\text{a}\) and \(3\text{a}\) were heated at 100 °C for 24 h in DCE with catalytic amounts of Cp*Co(CO)\(_2\), AgSbF\(_6\), and AgOAc (Table 1, entry 1). Benzoxazinone \(1\text{aa}\) would be formed from amidation product \(4\text{aa}\) through nucleophilic attack of the introduced amide to the relatively electrophilic Weinreb amide moiety, releasing \(N,O\)-dimethylhydroxylamine. We next investigated the reaction conditions to maximize the yield of \(4\text{aa}\). After several investigations, we speculated that the released \(N,O\)-dimethylhydroxylamine would be problematic because it can reversibly react with \(1\text{aa}\) to give \(4\text{aa}\), and/or coordinate to the cobalt center to inhibit the catalysis. Therefore, we added acetic anhydride to scavenge \(N,O\)-dimethylhydroxylamine, and the yield was improved to 73% (entry 2). In this case, \(4\text{aa}\) was not observed in the crude mixture. Almost the same result was observed when the concentration was increased to 0.3 M (entry 3). A shorter reaction time and lower temperature (entry 4, 80 °C for 18 h) slightly improved the yield, possibly due to the decreased decomposition of \(1\text{aa}\). Finally, the reaction proceeded smoothly in the absence of AgOAc to provide \(1\text{aa}\) in 84% isolated yield (entry 5). We also
examined \(O\)-methyl hydroxamate 5 and morpholine amide 6 as the substrate (Scheme 1). The reaction using 5 afforded a large amount of unidentified byproducts, and 1aa was obtained only in 5% yield. Substrate 6 afforded 1aa as a major product, but the starting material remained in 50% after 18 h, indicating the low reactivity of 6 in the C–H amidation step.

Table 1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>additives</th>
<th>conc. (X M)</th>
<th>temp. (°C)</th>
<th>time (h)</th>
<th>% yield&lt;sup&gt;b&lt;/sup&gt; 1aa</th>
<th>4aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOAc (10 mol%)</td>
<td>0.1</td>
<td>100</td>
<td>24</td>
<td>44</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>AgOAc (10 mol%) Ac_2O (1.0 equiv)</td>
<td>0.1</td>
<td>100</td>
<td>24</td>
<td>73</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>AgOAc (10 mol%) Ac_2O (1.0 equiv)</td>
<td>0.3</td>
<td>100</td>
<td>24</td>
<td>73</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>AgOAc (10 mol%) Ac_2O (1.0 equiv)</td>
<td>0.3</td>
<td>80</td>
<td>18</td>
<td>81</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>Ac_2O (1.0 equiv)</td>
<td>0.3</td>
<td>80</td>
<td>18</td>
<td>86 (84°)</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions were performed using 2a (0.10 mmol), 3a (0.20 mmol), Cp*Co(CO)_2 (0.01 mmol), AgSbF_6 (0.02 mmol), and additives in DCE unless otherwise noted. <sup>b</sup>Determined by \(^1\)H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. <sup>c</sup>Isolated yield.

Scheme 1. Reactions using other amides as substrate

The substrate scope of our optimized conditions to give benzoxazinones 1 is summarized in Table 2. Aromatic Weinreb amides bearing various functional groups at the para-position afforded 1aa–1fa in 56%–84% yields. While meta-Me-substituted Weinreb amide 2g reacted exclusively at the less hindered
C–H bond to give 1ga, Weinreb amides with a meta-F- and meta-OMe-substituent afforded regioisomeric mixtures (1ha/1ha' and 1ia/1ia') with moderate selectivities. 2-Naphthyl- and 3-benzothienyl Weinreb amides 2j and 2k successfully underwent the reaction to give tricyclic products 1ja and 1ka. It is noteworthy that α,β-unsaturated Weinreb amide 2l provided monocyclic product 1la, although the yield was diminished. The major product of this reaction is a C–H amidation product 4la (ca. 50% yield). On the other hand, Weinreb amides derived from acrylic acid and crotonic acid afforded no desired products, and unidentified byproducts were observed in both cases. The presented protocol demonstrated the wide scope of dioxazolones; aromatic, heteroaromatic, and aliphatic dioxazolones were well tolerated and afforded moderate to good yields (1ab–1aj). Benzoxazinone 1aj was slightly sensitive to hydrolysis.

Table 2. Substrate scope

<table>
<thead>
<tr>
<th>R</th>
<th>1aa, 84%</th>
<th>1ba, 83%</th>
<th>1ca, 81%</th>
<th>1da, 56%</th>
<th>1ea, 56%</th>
<th>1fa, 66%</th>
<th>1ga, 81%</th>
<th>1ha/1ha', 74% (3.9/1)</th>
<th>1ia/1ia', 79% (1/2.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = OMe, 1ha/1ha', 74% (3.9/1)</td>
<td>R = F, 1ia/1ia', 79% (1/2.3)</td>
</tr>
<tr>
<td>H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = H, 1aa, 84%</td>
<td>R = H, 1aa, 84%</td>
</tr>
<tr>
<td>OMe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = OMe, 1ba, 83%</td>
<td>R = OMe, 1ba, 83%</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = F, 1ca, 81%</td>
<td>R = F, 1ca, 81%</td>
</tr>
<tr>
<td>Ac</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = Ac, 1ea, 56%</td>
<td>R = Ac, 1ea, 56%</td>
</tr>
<tr>
<td>CO₂Me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = CO₂Me, 1fa, 66%</td>
<td>R = CO₂Me, 1fa, 66%</td>
</tr>
<tr>
<td>Me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = Me, 1ag, 81%</td>
<td>R = Me, 1ag, 81%</td>
</tr>
<tr>
<td>Cl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = Cl, 1ah, 66%</td>
<td>R = Cl, 1ah, 66%</td>
</tr>
<tr>
<td>CF₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = CF₃, 1ad, 49%</td>
<td>R = CF₃, 1ad, 49%</td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = Ph, 1aj, 72%</td>
<td>R = Ph, 1aj, 72%</td>
</tr>
</tbody>
</table>

*Reactions were performed using 2 (0.30 mmol), 3 (0.60 mmol), Cp*Co(CO)₂ (0.03 mmol), AgSbF₆ (0.06 mmol), and Ac₂O (0.30 mmol) in DCE (1 mL). Isolated yields were shown.*
A proposed catalytic cycle and reaction mechanism for 1aa based on previous reports\(^\text{16}\) of Cp*Co(III)-catalyzed C–H amidation reactions is shown in Figure 2. Iodide abstraction from [Cp*Co(CO)I\(_2\)] with AgSbF\(_6\) generates cationic species I, which undergoes coordination of 2a (II) and C–H bond activation to give metallacycle III. After coordination of dioxazolone 3a to form IV, CO\(_2\) extrusion and insertion of the nitrogen to the C–Co bond generate V. Proto-demetallation of V regenerates the catalyst with the release of intermediate 4aa. Cyclization of 4aa provides benzoxazinone 1aa and N,O-dimethylhydroxylamine. The final cyclization step would be reversible, and 1aa and 4aa would be in equilibrium. When we treated 1aa with N,O-dimethylhydroxylamine hydrochloride and K\(_2\)CO\(_3\) in DCE at 80 °C for 3 h, the 53:47 mixture of 1aa and 4aa was obtained (Scheme 2). This result proved the reversibility of the cyclization, and indicated that the equilibrium constant is not sufficient. Therefore, benzoxazinone 1aa was obtained as a sole product by trapping N,O-dimethylhydroxylamine with Ac\(_2\)O. We detected 7 by \(^1\)H NMR analysis of the crude reaction mixture.

![Figure 2. Proposed catalytic cycle and reaction mechanism](image-url)
In summary, we demonstrated that benzoxazinones 1 were obtained in only one step from Weinreb amides 2 and dioxazolones 3 with high functional group compatibility under Cp*Co(III) catalysis. The presented method may enable fast and easy access to functionalized benzoxazinones 1 for the discovery of new biologically active derivatives.

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SUPPORTING INFORMATION
Supplementary (synthesis of the starting azides, HPLC chromatograms, IR, 1H and 13C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/25790/99/1.

REFERENCES AND NOTES


14. A cobalt complex Cp*Co(CO)I₂ is commercially available from Kanto Chemical Co., Inc; Catalog No. 07129-12.

