A Novel Synthesis of 4-Acetoxyl 5(4H)-Oxazolones by Direct α-Oxidation of N-Benzoyl Amino-Acid Using Hypervalent Iodine

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Abstract: We have developed a new method to prepare 4-acetoxyl substituted 5(4H)-oxazolones by direct oxidation of N-benzoyl amino-acids using hypervalent iodine. The method is efficient, economical and easy to perform for the synthesis of quaternary substituted amino acid derivatives. We used online FTIR monitoring techniques to analyze the reaction, and gave a plausible reaction mechanism.

Keywords: oxidation; hypervalent iodine; 4-acetoxyl 5(4H)-oxazolones; N-benzoyl amino-acid; online FTIR

1. Introduction
2-Substituted amino acids and their derivatives are known as structural elements with important physiology [1–3]. As an important synthetic intermediate of 2-substituted amino acids, 2-acetoxy-2-amino acids have attracted tremendous interest in organic synthesis [4]. However, to date, chemists have only reported a few methods to synthesize these amino acids, such as oxidating the protected cystinylserine with Pb(OAc)₄ to the 2-acetoxy compound [5–7], using 2-benzamidotrifluorolactic acid as starting materials to yield 4-acetoxy-4-trifluoromethyl-2-phenyloxazol-5(4H)-one [8], treating oxazolone with mercuric acetate to form the diacetyl compound [9], transforming 2-acylaminoacrylate with N-chlorosuccinimide/HCl/LiOAc in acetic acid to the 2-acetoxy-2-amine acid derivatives [2], converting β-lactams with ruthenium trichloride in the presence of acetaldehyde and acetic acid with molecular oxygen into the corresponding 4-acyloxy β-lactams [10], and using anodic oxidation of 2-ethoxycarbonyl-2-acetamidoacetic acid derivatives, followed by saponification of the one ester groups to 2-alkoxy-2-amino acids and 2-acetoxy-2-amino acids [11]. There are some problems in these methods: 1. It is difficult to prepare the raw materials; 2. The use of metal reagents is expensive and not environmentally-friendly.

Metal-free reagents such as hypervalent iodine compounds have received much attention for low toxicity, mild reaction condition, easy handling and special reactivity compared with heavy metal reagents in organic synthesis reactions. Furthermore, hypervalent iodine reagents have been widely used in various oxidations, such as oxidative deaminated reactions [12,13], oxidative coupling reactions [14,15], oxidative halogenation reactions [16–18], oxidative cyclization reactions [19], oxidative addition [20,21], oxidative amination reaction [22], and so on.

Boto synthesized 2-acetoxy glycine through an unstable α-iodoglycine intermediate, which was then substituted by acetate ions from the reagent PhI(OAc)₂ (Scheme 1a) [23]. Recently, Xu’s group developed a cobalt-catalyzed decarboxylative C–O bond-forming reaction using hypervalent iodine as oxidizing agent (Scheme 1a). However, these methods involve deiodination or decarboxylative
process, which can only give tertiary substituted carbon atoms. Herein, we wish to report a direct oxidation of \( \alpha \)-C–H bond of \( N \)-benzoyl amino-acid using hypervalent iodine (Scheme 1b). With this method, a new synthesis of 4-acyetoxy substituted 5(4\( H \))-oxazolones was carried out. There are three advantages in our method: 1. Only hypervalent iodine oxidizing agent was used, which was cheap and easy to get; 2. Our method can directly oxidize the \( \alpha \)-C–H bond of amino acid derivatives, which does not involve deiodination or decarboxylative process; 3. With this method, quaternary substituted amino acid derivatives could be prepared.


2. Results

Reaction of \( N \)-benzoyl isoleucine (1a) with 1.0 equiv \( \text{PhI(OCOCF}_3\text{)}_2 \) in acetic anhydride and toluene (\( v/v = 4:1 \)) at 60 °C for 1.5 h gave 4-acyetoxy substituted 5(4\( H \))-oxazolone (1b) as oxidative product in 40% yield (\( \text{dr} = 1:1 \), Table 1). We found that 1.5 equiv of \( \text{PhI(OCOCF}_3\text{)}_2 \) give much better yield, but the increase of \( \text{PhI(OCOCF}_3\text{)}_2 \) to 3.0 equivalent afford lower yield (entry 2–3). Replacement of \( \text{PhI(OCOCF}_3\text{)}_2 \) with \( \text{PhI(OAc)}_2 \) or \( \text{PhI(OPiv)}_2 \) led to the reducing of the yield, and the latter gave only 19% yield (entry 5–6). In the absence of \( \text{PhI(OCOCF}_3\text{)}_2 \), only oxazolones (1c) was afforded, which can give desired product 1b by the oxidative annulation with addition of \( \text{PhI(OCOCF}_3\text{)}_2 \) (see supporting Information). \( \text{AgF}_2 \) gave only coupling product without desired product. The temperature also has great influence on this oxidation reaction, which gave lower yields at 30 °C and 90 °C (entry 7–8). Further assessment of the solvent effect indicated that toluene was the best solvent for this reaction, providing higher yield than other commonly used solvents such as ACN, DCE, Acetone and THF (entry 10–13).

Table 1. Direct \( \alpha \)-oxidation of \( N \)-benzoyl amino-acid using hypervalent iodine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant (equiv)</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{PhI(OCOCF}_3\text{)}_2 ) (1)</td>
<td>60</td>
<td>toluene</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>( \text{PhI(OCOCF}_3\text{)}_2 ) (1.5)</td>
<td>60</td>
<td>toluene</td>
<td>68 (63 b)</td>
</tr>
<tr>
<td>3</td>
<td>( \text{PhI(OCOCF}_3\text{)}_2 ) (3)</td>
<td>60</td>
<td>toluene</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>( \text{PhI(OCOCF}_3\text{)}_2 ) (0)</td>
<td>60</td>
<td>toluene</td>
<td>no</td>
</tr>
<tr>
<td>5</td>
<td>( \text{PhI(OAc)}_2 ) (1.5)</td>
<td>60</td>
<td>toluene</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>( \text{PhI(OPiv)}_2 ) (1.5)</td>
<td>60</td>
<td>toluene</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>( \text{AgF}_2 ) (1.5)</td>
<td>60</td>
<td>toluene</td>
<td>no</td>
</tr>
</tbody>
</table>
With the optional conditions in hand, we then examined the substrate scope of N-benzoyl amino acid substrates (Table 2). Both α-alkyl and benzyl substituted N-benzoyl amino-acid (2a–10a) gave desired 4-acetoxyl 5(4H)-oxazolones (2b–10b) in moderated yields with some coupling products in 0–20% yields (except for 1a, see supporting information). Beside coupling products, α-alkyl substrates 3a and 5a also gave rearrangement product N-(1-oxo-alkyl)-benzamide in about 20% yields, while substituted N-benzoyl amino-acids (6a–10a) gave some elimination products in about 10–30% yields (see supporting information). In these conditions, ether and ester groups were very tolerant, as shown in entry 8–9.

Table 1. Cont.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant (equiv)</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>PhI(OCOCF₃)₂ (1.5)</td>
<td>30</td>
<td>toluene</td>
<td>38</td>
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<tr>
<td>9</td>
<td>PhI(OCOCF₃)₂ (1.5)</td>
<td>90</td>
<td>toluene</td>
<td>43</td>
</tr>
<tr>
<td>10</td>
<td>PhI(OCOCF₃)₂ (1.5)</td>
<td>60</td>
<td>ACN</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>PhI(OCOCF₃)₂ (1.5)</td>
<td>60</td>
<td>DCE</td>
<td>43</td>
</tr>
<tr>
<td>12</td>
<td>PhI(OCOCF₃)₂ (1.5)</td>
<td>60</td>
<td>Acetone</td>
<td>8</td>
</tr>
<tr>
<td>13</td>
<td>PhI(OCOCF₃)₂ (1.5)</td>
<td>60</td>
<td>THF</td>
<td>no</td>
</tr>
</tbody>
</table>

a Yields were based on 1H NMR analysis of reaction mixture after 1.5 h using (2E)-2-Butenedioic acid as standard; b Isolated yields.

3. Discussion

In order to study the reaction kinetics, we used online FTIR techniques (fourier-transform infrared spectra, React IR 15) to monitor the reaction [24–26]. At first, we collected the FTIR data of raw material 1a, the intermediate 1c, PhI(OCOCF₃)₂, acetic acid, trifluoroacetic acid and product 1b
in the solvent (anhydrous toluene:acetic anhydride = 4:1) respectively. To prove the formation of intermediate 1c before the oxidative annulation, we added the Phl(OCOCF₃)₂ in the reaction system 10 min after raw material 1a and acetic anhydride were heated at 60 °C. In the experiments, ReactIR was continuously used to acquire online IR spectra. The ConcIRT analysis and 3D surface plot tracked changes in absorbance profiles that occur over time of the intermediate 1c, Phl(OCOCF₃)₂, acetic acid, trifluoroacetic acid, and product 1b, which were shown in Figures 1 and 2.

![Figure 1. ConcIRT component profiles of oxidative reaction. 1. Added the material; 2. Added the oxidation Phl(OCOCF₃)₂; 3, 4. Got sample.](image1)

![Figure 2. In situ reaction of IR, 3D surface plot of oxidative reaction.](image2)

At first, the peak height at 1822 cm⁻¹ (C=O bond, pale red line) increased due to the producing of the intermediate 1c, and it decreased when we add the oxidant Phl(OCOCF₃)₂ to the reaction system. The peak at 1719 cm⁻¹ (C=O bond, green line) increased due to the formation of acetic acid, and it reduced because of the ligand exchange with Phl(OCOCF₃)₂. The peak at 1792 cm⁻¹ (C=O bond, wathet blue line) increased, showing the formation of trifluoroacetic acid. At the same time, the peak at 1078 cm⁻¹ (C=O bond, brown line) and 1862 cm⁻¹ (C=O bond) began to increase, indicating the formation of the product 1b. Moreover, the variation trend of ConcIRT showed that the complete reaction needed about 1.5 h (As shown in the Figure 1).
On the basis of the above experiments, a plausible reaction mechanism was proposed as shown in Scheme 2 [27]. At first, the raw material 1a was converted to intermediate 1c [28], which was then transformed to the enolized intermediate 1d. After the ligand exchange of Phl(OCOCF$_3$)$_2$ with AcOH, the I–O bond of 1e was formed accompanied by the leave of CF$_3$COOH. Then the AcO$^-$ added to the double bond accompanied by the elimination of Phl, the final product 1b was afforded.

\[
\begin{align*}
1a & \xrightarrow{\Delta, AcO} 1c \\
1c & \xrightarrow{\text{Phl(OCOCF}_3\text{O)}_2 (1.5 \text{ equiv)} \text{ toluene/AcO, 60°C, 2h}} 1d \\
1d & \xrightarrow{\text{Phl(OCOCF}_3\text{O)}_2 \text{ HOAc}} 1e \\
\end{align*}
\]

**Scheme 2.** A plausible reaction mechanism of the oxidative annulation reaction.

### 4. Conclusions

In summary, we have developed a new method to prepare 4-acetoxy substituted 5(4H)-oxazolones by direct oxidation of N-benzoyl amino-acids using hypervalent iodine. These 4-acetoxy substituted 5(4H)-oxazolones can be used as synthetic intermediates for different bioactive compounds or peptidomimetic constituents. The method is efficient, economical and easy to perform for the synthesis of quaternary substituted amino acid derivatives. We used online FTIR monitoring techniques (React IR 15) to monitor the reaction, and gave a plausible reaction mechanism. The synthetic applications of this process are currently underway in our laboratory.

**Supplementary Materials:** Supplementary materials are available online.

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**Author Contributions:** W.-X.Z. and S.W. conceived and designed the experiments; G.W. performed the experiments; W.-X.Z. and G.W. analyzed the data; S.W. contributed reagents/materials/analysis tools; G.W. wrote the paper. All authors have read the final version of the manuscript.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**


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