Synthesis of oxygen-containing heterocyclic compounds based on the intramolecular O–H insertion and Wolff rearrangement of α-diazocarbonyl compounds

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Received 1 March 2006; revised 1 May 2006; accepted 3 May 2006

Abstract—The addition products of Ti(IV)-enolate derived from β-keto α-diazo carbonyl compound to ketones or α,β-unsaturated compounds were subjected to Rh 2(OAc)4-catalyzed and photo-induced diazo decomposition. The Rh 2(OAc)4-catalyzed reaction afforded intramolecular O–H insertion products, while the photo-induced reaction gave Wolff rearrangement/intramolecular nucleophilic addition products. The transformations represent new approaches to tetrahydrofuran and γ-butyrolactone derivatives.

Oxygen-containing heterocycles, especially tetrahydrofuran and γ-butyrolactone derivatives, are important synthetic targets due to their occurrence in numerous natural products, their wide range of biological activities, and their utility as versatile intermediates in organic synthesis. In addition to the traditional methods, many new synthetic methodologies have been developed in recent years for this important class of heterocyclic compounds. In particular, transition metal catalyzed transformations have been successful and offer great potential. For example, platinum-catalyzed intramolecular hydroalkoxylation of γ-hydroxy olefins led to the formation of tetrahydrofuran derivatives. Palladium-catalyzed cyclization of allylic 2-alkynoates has been utilized to build γ-butyrolactone derivatives. In this paper, we report a new approach to both tetrahydrofuran and γ-butyrolactone derivatives based on the reaction of α-diazocarbonyl compounds.

We have recently studied the nucleophilic addition of Ti(IV) enolate 2, derived from β-keto α-diazo carbonyl compound 1, to various electrophiles (Scheme 1). Although the efficient addition of Ti(IV) enolate 2 to aldehydes has already been reported by Calter and co-workers, we have found that the corresponding reaction with less reactive ketones only occurs when they are activated by second equivalent of Ti(OiPr)4. We have also reported the reaction of Ti(IV) enolate 2 with α,β-unsaturated compounds. In this case, an interesting observation is that the 1,2- and 1,4-addition selectivity can be efficiently controlled by Lewis acids. Through the nucleophilic addition of Ti(IV) enolates with various carbonyl compounds, a series of δ-hydroxy β-keto α-diazoesters have been prepared—product structures are summarized in Scheme 1.

Since the addition products 3a–j bear two reactive functional groups (hydroxy and diazo) in appropriate positions, they are expected to undergo some useful intramolecular transformations upon diazo decomposition. First, we investigated the diazo decomposition of the addition products in the presence of rhodium (II) acetate, with the expectation that Rh(II)-carbene intramolecular O–H insertion should occur to afford tetrahydrofuran derivative. The reaction only took 10 min to complete after the addition of the diazo compounds to the refluxing toluene in the presence of a catalytic amount of Rh2(OAc)4. 1H NMR spectra of the crude products showed that only intramolecular O–H insertion products were formed in all cases (Table 1).

Next, photo-induced reaction of the diazo compounds 3a–j was examined, with the expectation that Wolff rearrangement should occur to generate the ketene...
intermediate 5, which may be followed by a intramolecular nucleophilic attack by the hydroxy group. The reaction was carried out in the anhydrous ether solution under UV irradiation (150 W high-pressure Hg lamp, \( \lambda > 200 \text{ nm} \)) at room temperature. The starting diazo compound was completely consumed after 14–17 h, and separation with silica gel chromatography afforded the major product in moderate yield for each case. \(^1\text{H} \) and \(^{13}\text{C} \) NMR spectra indicated that the major product was the expected \( \gamma \)-butyrolactone derivative 6a–j (Table 2).\(^{10}\) As showed by the data collected in Table 2, the yields were generally moderate. Products 6c–d were isolated each as a isomeric mixture with ratio near 1:1, while 6e was obtained as a single diastereomer (Table 2, entries 3–5). For the diazo compounds 3h–j, the irradiation was carried out with a 500 W high-pressure Hg lamp (Table 2, entries 8–10). The reaction time was significantly shortened, while the yield was comparable.

When diazo compound 3f was irradiated under the same condition, the expected 6f was not isolated. Instead, a \( \alpha, \beta \)-unsaturated product 7 was isolated in moderate yield. The product 7 was obviously formed through the elimination of MeOH from 6f. This result may be due to the instability of 6f which eliminates methanol quickly to give the more stable product 7 after 6f was first formed (Scheme 2).

Table 2. Photo-induced diazo decomposition of 3a–j.\(^{10}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>3a–j</th>
<th>Reaction time (h)</th>
<th>Product 6a–j</th>
<th>Yield (%)(^a)</th>
<th>dr(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>14</td>
<td>6a</td>
<td>69</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>16</td>
<td>6b</td>
<td>78</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>17</td>
<td>6c</td>
<td>67</td>
<td>50:50</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>14.5</td>
<td>6d</td>
<td>58</td>
<td>47:53</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>14</td>
<td>6e</td>
<td>71</td>
<td>100:0</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>17</td>
<td>7(^i)</td>
<td>54</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>3g(^f)</td>
<td>6</td>
<td>6g</td>
<td>33</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>5</td>
<td>6h</td>
<td>67</td>
<td>50:50</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>5</td>
<td>6i</td>
<td>77</td>
<td>65:35</td>
</tr>
<tr>
<td>10</td>
<td>3j</td>
<td>5</td>
<td>6j</td>
<td>57</td>
<td>56:44</td>
</tr>
</tbody>
</table>

\(^a\) The reaction mixture in a quartz tube was irradiated with a 150 W high-pressure Hg lamp if not specially noted.
\(^b\) Refer to the yields after separation with silica gel column.
\(^c\) Determined by \(^1\text{H} \) NMR (300 MHz) of the crude product.
\(^d\) The product was 7, as shown in Scheme 2.
\(^e\) The reaction gave a complex mixture when irradiated with 150 W high-pressure Hg lamp.
\(^f\) Irradiation was carried out in a Pyrex tube with a 500 W high-pressure Hg lamp.
It was also noticed that photo-induced decomposition of 3g resulted in a complex mixture when irradiated with 150 W high-pressure Hg lamp for long time. When irradiated with 500 W high-pressure Hg lamp, γ-butyrolactone 6g was isolated in 33% yield (Table 2, entry 7). Considering the mechanism of this rearrangement reaction, it could be expected that both alkyl and phenyl group could transfer to form ketene intermediates 9 and 10 (Scheme 3). The phenyl shift has been known to have higher 1,2-shift preference in Wolff rearrangement. Consequently, 1,2-phenyl shift may predominate in this case, thus giving 9 as the main Wolff rearrangement product. The intramolecular nucleophilic addition may not be efficient for ketene 9, because of the steric bulkiness of the phenyl group as well as the unfavorable 1,6 addition. Side reactions may occur from 9. As a result, the reaction gave a complex mixture or low yield of γ-butyrolactone 6g.

Finally, when substrate 3i and 3j were irradiated, in addition to 6i and 6j, 11 and 12 were separated as minor products (Scheme 4). The double bond cis/trans isomerization occurred under the photochemical conditions.

In summary, we have developed a concise and efficient protocol to synthesize tetrahydrofuran or γ-butyrolactone derivatives via intramolecular O–H insertion, and γ-butyrolactone derivatives via Wolff rearrangement from simple substrates in two steps, respectively. These oxygen-containing cyclic derivatives are highly substituted and some of them have spiro structures. The two-step transformations provide an alternative approach to access these types of heterocycles.

Acknowledgements

The project is generously supported by Natural Science Foundation of China (Grant No. 20572002, 20521202, 20225205, 20390050) and the Ministry of Education of China (Cheung Kong Scholars Program).

References and notes


7. General Procedure for Rh2(OAc)4-catalyzed reaction of 3a–j. To a suspension of a catalytic amount of Rh2(OAc)4 (approximately 0.5 mol%) in toluene (6 mL) at reflux was added dropwise diazo compound 4a–j (0.30 mmol) in toluene (2 mL). After addition, the reaction mixture was refluxed for 10 min and then allowed to cool to room temperature. The solvent was removed in vacuo to obtain 4a–j. 4b: 97%; IR (neat) 2927, 1768, 1744, 1145, 1115 cm−1; 1H NMR (300 MHz, CDCl3) δ 1.30 (t, J = 7.2 Hz, 3H), 1.24–1.28 (m, 12H), 2.52 (s, 2H), 4.17–4.30 (m, 2H), 4.54 (s, 1H); 13C NMR (75 MHz, CDCl3) δ 14.0, 21.9, 28.6, 39.6, 40.9, 61.9, 79.3, 85.3, 1115, 166.4, 208.4; EI-MS (m/z, relative intensity): 240 (M+), 183 (31), 167 (14), 137 (86), 95 (100). HRMS caled for C13H20O4: 240.1361; found: 240.1360.


A quartz tube or a Pyrex tube was charged with a solution of 3a–j (0.30 mmol) in dry ethyl ether (6 mL) under nitrogen atmosphere. The resulting solution was irradiated with a high-pressure mercury lamp (150 W or 500 W) at room temperature until complete disappearance of the diazo substrate. The reaction mixture was then concentrated under vacuum, and the residue was purified by silica gel column chromatography (petroleum ether–EtOAc, 5:1) to afford the γ-butyrolactone derivatives 6a–j. 6a: 69%; colorless oil; IR (neat) 2937, 2862, 1772, 1734 cm⁻¹; H NMR (300 MHz, CDCl₃) δ 1.33 (t, J = 7.2 Hz, 3H), 1.37–1.88 (m, 10H), 2.31 (dd, J = 13.2, 9.9 Hz, 1H), 2.42 (dd, J = 13.2, 9.6 Hz, 1H), 3.70 (dd, J = 9.9, 9.6 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H); C NMR (75 MHz, CDCl₃) δ 13.8, 22.3, 24.5, 36.4, 36.5, 37.2, 46.7, 61.9, 85.3, 167.9, 171.1; EI-MS (m/z, relative intensity): 226 (M⁺, 6), 208 (8), 183 (32), 153 (63), 137 (84), 98 (100), 55 (85). HRMS calcd for C₁₂H₁₈O₄ 226.1205; found: 226.1201.