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A Facile Approach to the Synthesis of Allylic Spiro Ethers and Lactones

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Dedicated to Marty Semmelhack on the occasion of his 65th birthday

Abstract: Treatment of 3-[(alkoxycarbonyl)alkyl]-substituted conjugated cycloalkenones with diisobutylaluminum hydride at –78 °C followed by acid quenching furnishes spiro ethers, whereas the corresponding 3-(carboxyalkyl)-substituted cycloalkenones generate spiro lactones upon reaction with sodium borohydride at 30 °C followed by acid quenching.

Key words: enones, heterocycles, lactones, spiro compounds

Oxygen heterocycles constitute an important class of molecules owing to their frequent occurrence in many natural products.¹ A number of synthetic methods have been developed for the construction of oxaspirocycles.² For spiro ethers, 1-(hydroxyalkyl)cycloalka-1,3-dienes have been used as starting materials,³ and for spiro lactones, cyclic tertiary alcohols substituted at C-1 with a carboxyalkyl side chain⁴ or cyclic carboxylic acids bearing a hydroxyalkyl side chain at the α-carbon⁵ have often been used as building blocks. In most cases, these substrates require lengthy preparations and transition metals need to be employed for the intramolecular cyclization reactions. For example, palladium acetate has been used to catalyze the intramolecular oxaspirocyclization of 1-(hydroxyalkyl)cycloalka-1,3-dienes to produce allylic spiro ethers.⁶ Similarly, tricarbonyliron was needed for the intramolecular coupling of cyclohexa-1,3-dienes with a pendant (alkoxycarbonyl)alkenyl group to afford heterospirocycles.⁷ Therefore, inexpensive reagents and mild reaction conditions are still needed for the preparation of spiro ethers and spiro lactones.

We now report a facile approach to the synthesis of allylic spiro ethers by treatment of 3-[(alkoxycarbonyl)alkyl]cycloalka-2-ones with diisobutylaluminum hydride followed by quenching of the reaction mixture with hydrochloric acid. In addition, spiro lactones can be obtained by reaction of cyclic 3-(carboxyalkyl)cycloalka-2-ones with sodium borohydride followed by acid quenching. It was expected that the allylic cation, e.g. 9, generated in situ upon reduction of a 3-[(alkoxycarbonyl)alkyl]cycloalka-2-ene, e.g. 1, with diisobutylaluminum hydride followed by acid quenching, would be attacked by the tethered hydroxy group to generate the allylic spiro ether 11 (Scheme 1).

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Oxaspiro[5.5]undec-7-ene (12) in 75% yield under the same reaction conditions. Five-membered-ring analogues 3 and 4 (Table 1, entries 3 and 4) also underwent intramolecular cyclization to produce 1-oxaspiro[4.4]non-6-ene (13) and 6-oxaspiro[4.5]dec-1-ene (14), in 66% and 72% yields, respectively. Under the same reaction conditions, the cyclohex-2-enone derivative 5 afforded hexahydrochromene derivative 15 in 60% yield (Table 1, entry 5). Unlike oxaspirocycles 11–14, larger oxaspirocycles, e.g. 20, cannot form under these conditions (Scheme 3). Thus, ethyl 5-(3-oxocyclohex-1-enyl)pentanoate (19) gave unidentified mixtures after being treated with diisobutylaluminum hydride at −78 °C followed by acid quenching (Scheme 3). The difficulty in forming 7-oxaspiro[5.6]dodec-1-ene (20) might be attributed to unfavorable formation of the seven-membered ring.

In conclusion, conjugated cyclic enones containing an (alkoxycarbonyl)alkyl- or carboxyalkyl side chain were found to readily react with hydrides to give allylic spiro ethers and lactones after acid quenching. This method can also be applied to the synthesis of fused oxabicycles. This synthesis of oxaspirocycles by reduction/dehydration of conjugated cyclic enones is more efficient than the previously reported methods.3

### Table 1  Synthesis of OXASPIROCycles and Fused Oxabicycles from 3-(Ethoxyalkyl)- and 3-(Carboxyalkyl)-Substituted Cycloalk-2-enones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>1</td>
<td>11</td>
<td>82</td>
</tr>
<tr>
<td>2b</td>
<td>2</td>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>3b</td>
<td>3</td>
<td>13</td>
<td>66</td>
</tr>
<tr>
<td>4b</td>
<td>4</td>
<td>14</td>
<td>72</td>
</tr>
<tr>
<td>5b</td>
<td>5</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>6b</td>
<td>6</td>
<td>16</td>
<td>67</td>
</tr>
<tr>
<td>7c</td>
<td>7</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>8c</td>
<td>8</td>
<td>18</td>
<td>44</td>
</tr>
</tbody>
</table>

a Isolated yields. Satisfactory spectral data were obtained for all compounds.  
b DIBAL-H was used for the cyclization.  
c Cyclization in the presence of NaBH₄ and CeCl₃·7H₂O.
1H (400 MHz) and 13C (100.4 MHz) NMR spectra were recorded on a Bruker-AC 400 spectrometer. IR spectra were recorded on a JASCO IR-700 spectrometer. Mass spectra were recorded on a JEOL JMS-HX 110 spectrometer. High-resolution mass spectra were obtained on an AEI MS-9 double-focusing mass spectrometer and a JEOL JMS-HX 110 spectrometer using the EI method.

A soln of 1 (0.50 g, 2.55 mmol) in THF (10 mL) was added slowly by syringe to 1.0 M DIBAL-H in cyclohexane (10 mL) at –78 °C. The mixture was stirred at –78 °C for 1 h. A homogeneous soln was obtained after slow addition of 6 M aq HCl (ca. 5.0 mL) to the mixture and subsequent removal of the cooling bath. The mixture was stirred for 10 min and was concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 10:1).

Yield: 0.12 g (82%).

IR (CH3Cl2): 3049, 2983, 1726, 1605, 1445 cm–1.

1H NMR (400 MHz, CDCl3): δ = 5.77 (dt, J = 10.0, 3.7 Hz, 1 H), 5.38 (d, J = 10.0 Hz, 1 H), 3.81–3.88 (m, 2 H), 1.93–1.97 (m, 4 H), 1.61–1.78 (m, 4 H), 1.58–1.68 (m, 2 H, 6 H).

13C NMR (100 MHz, CDCl3): δ = 36.60, 36.38, 30.80, 26.19.

1-Oxaspiro[5.5]undec-7-ene (12)12 was prepared by the same method as that described above for 11.

Yield: 0.13 g (44%).

IR (CH3Cl2): 3431, 3407, 3387, 1767, 1663 cm–1.

1H NMR (400 MHz, CDCl3): δ = 3.24 mmol) in MeOH (100 mL) at 0 °C. The mixture was stirred at 30 °C for 30 min, and the addition of 6 M aq HCl (5.0 mL) followed. The mixture was stirred for 10 min and was concentrated in vacuo. The residue was diluted with H2O (3 × 200 mL) and brine (3 × 200 mL), dried (MsO4; 10 g), filtered through a bed of Celite, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 5:1).

Yield: 0.15 g (67%).

IR (CH3Cl2): 3493, 3407, 3387, 1870, 1659, 1459 cm–1.

1H NMR (400 MHz, CDCl3): δ = 5.46 (s, 1 H), 3.96–4.01 (m, 1 H), 3.85–3.88 (m, 1 H), 3.53 (td, J = 11.52, 2.68 Hz, 1 H), 1.64–2.17 (m, 10 H).

13C NMR (100 MHz, CDCl3): δ = 136.09, 122.22, 74.75, 67.95, 31.92, 30.02, 28.14, 25.30, 20.54.

MS (EI): m/z (%) = 138 (20) [M+], 137 (100), 119 (63), 107 (51), 95 (55), 93 (89), 79 (51), 71 (100), 57 (83), 55 (63).


1-Oxaspiro[4.5]dec-6-en-2-one (16);14 Typical Procedure
CeCl3·7H2O (3.62 g, 9.72 mmol) and NaBH4 (1.23 g, 32.4 mmol) were added separately in five portions to a stirring soln of 6 (0.50 g, 3.24 mmol) in MeOH (100 mL) at 0 °C. The mixture was stirred at 30 °C for 30 min, and the addition of 6 M aq HCl (5.0 mL) followed. The mixture was stirred for 10 min and was concentrated in vacuo. The residue was diluted with H2O (100 mL). The aqueous solution was extracted with EtOAc (3 × 50 mL). The combined organic soln was washed with H2O (3 × 200 mL) and brine (3 × 200 mL), dried (MsO4; 10 g), filtered through a bed of Celite, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 1:1).

Yield: 0.16 g (43%).

IR (CH3Cl2): 3049, 2983, 1726, 1605, 1445 cm–1.

1H NMR (400 MHz, CDCl3): δ = 5.38 (d, J = 10.0 Hz, 1 H), 5.64 (d, J = 10.0 Hz, 1 H), 2.10–2.17 (m, 3 H, 2 H), 1.96–2.01 (m, 2 H, 2 H), 1.81–1.85 (m, 1 H, 1 H), 1.65–1.77 (m, 2 H).

13C NMR (100 MHz, CDCl3): δ = 176.67, 132.56, 128.45, 83.56, 34.53, 34.03, 28.72, 24.56, 19.30.

1-Oxaspiro[4.4]non-6-en-2-one (17)14,15 Bicyclic lactone 17 was prepared by the same method as that described above for 16.

Yield: 0.18 g (40%).

IR (CH3Cl2): 3493, 3407, 3387, 2666, 1664 cm–1.

1H NMR (400 MHz, CDCl3): δ = 6.08–6.10 (m, 1 H, 2 H), 2.39–2.42 (m, 2 H, 2 H), 2.21–2.30 (m, 3 H, 2 H), 2.04–2.06 (m, 1 H).

13C NMR (100 MHz, CDCl3): δ = 176.54, 137.44, 131.74, 97.74, 36.26, 33.44, 31.11, 29.68.

3,4,6,7,8,8a-Hexahydro-2H-chromene (15)
Chromene 15 was prepared by the same method as that described above for 11.

Yield: 0.17 g (60%).

IR (CH3Cl2): 3431, 3407, 3387, 1870, 1659, 1459 cm–1.

1H NMR (400 MHz, CDCl3): δ = 2.72 (s, 1 H), 4.82 (s, 1 H), 2.43–2.74 (m, 4 H), 2.04–2.15 (m, 3 H), 1.72–1.81 (m, 2 H), 1.55–1.60 (m, 1 H).

13C NMR (100 MHz, CDCl3): δ = 172.48, 130.56, 126.15, 76.03, 30.47, 29.10, 25.84, 24.90, 19.55.

MS (EI): m/z (%) = 152 (83) [M+], 124 (55), 110 (23), 97 (45), 96 (58), 91 (36), 82 (61), 79 (72), 67 (100), 55 (92).

HRMS (EI) m/z calcld for C9H14O: 152.0837; found: 152.0840.
References

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