Stereospecific Piperidine Synthesis via Regiospecific Baeyer-Villiger Oxidation

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As part of an effort to synthesize functionalized piperidine alkaloid natural products\textsuperscript{1,2} we desired the lactone 2, congener of the cis-2-carboxymethyl-5-hydroxypiperidine 4. Lactone 2 should be readily available via Baeyer-Villiger oxidation of the readily available 2-azabicyclo[2.2.2]octan-5-one (1) if oxidation were to proceed via methine migration as does the carbocyclic analog\textsuperscript{3}. Unfortunately, azabicyclic analogs of 1 have been reported to undergo methylene migration during Baeyer-Villiger oxidations\textsuperscript{4}.

Initial oxidation attempts with 1 and \textit{m}-chloroperbenzoic acid (MCPBA) resulted in formation of mixtures of lactones 2 and 3 derived from both methine and methylene migration during rearrangement. It has now been found that sodium acetate buffered 28% peracetic acid (PAA) in acetic acid cleanly converts 1 to the desired lactone 2. A summary of oxidation attempts is shown in the Table.

2-Benzylxoxycarbonyl-5-oxo-2-azabicyclo[2.2.2]octane (1):
Hydrolysis of 2-ethoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene (2.0 g, 11.2 mmol) according to the procedure of Cava\textsuperscript{3} gives a crude amine which is dissolved in dichloromethane (30 ml) and added to a solution of potassium hydroxide (628 mg) in water (20 ml). Benzyl chloroformate (2.0 g) is added to the stirred mixture and after 2 h the mixture is heated for 1 h on a steam bath. The organic layer is separated, dried over magnesium sulfate, the solvent is evaporated, and the residue distilled to give 2-benzylxoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene; yield: 2.2 g (81%); b.p. 122-128°/0.25 torr.
The azabicyclic olefin (6.66 g, 27.4 mmol) is added to a solution of mercuric(II) nitrate (13.93 g, 42.9 mmol) in 50% aqueous tetrahydrofuran (33 ml) and the mixture is stirred at room temperature for 24h. Addition of 3 molar sodium hydroxide (33 ml) followed by sodium borohydride (6.24 g in 3 molar sodium hydroxide (66 ml) affords two layers. The aqueous layer is washed with ether and the combined organic layers are dried over magnesium sulfate. Removal of solvent affords a crude alcohol (7.03 g) which is stirred for 2 h with pyridinium chlorochromate (8.7 g, 40.4 mmol) in dichloromethane (50 ml). The solution is diluted with ether (375 ml), filtered through Florisil, and the solvent is evaporated to give crude ketone [cyclopentyl (5.72 g). Dry column chromatography (Woelm Silica Gel for Dry Column, Act. III, 2:1 hexane:ethyl acetate, Rf 0.3) gives pure ketone 3; yield: 4.41 g (63%); Kugelrohr distillation: b.p. 155-170/0.05 torr.

**Table.** Experimental Conditions and Results of the Baeyer-Villiger Oxidation of 1

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Buffer</th>
<th>Yield [%]</th>
<th>Isomeric Purity [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAA</td>
<td>NaOAc</td>
<td>80%</td>
<td>2 (100)</td>
</tr>
<tr>
<td>PAA</td>
<td>33%</td>
<td>2 (100)</td>
<td></td>
</tr>
<tr>
<td>MCPBA</td>
<td>NaHCO₃</td>
<td>80%</td>
<td>2 (69), 3 (31)</td>
</tr>
<tr>
<td>MCPBA</td>
<td></td>
<td>85%</td>
<td>2 (65), 3 (35)</td>
</tr>
</tbody>
</table>

⁴ Product isolated by Kugelrohr distillation.
⁵ Product isolated by T.L.C.
⁶ Ratios of isolated products are consistent with those determined by integration of the N.M.R. spectra of the crude reaction mixtures.

1H-N.M.R. (CDCl₃): δ = 7.40 (s, 5H); 5.20 (s, 2H); 4.65 (broad m, 1H); 3.75 (dd, 1H, J = 11 Hz, 2 Hz); 3.60 (dd, 1H, J = 11 Hz, 2 Hz); 2.65 (dd, 1H, J = 20 Hz, 2 Hz); 2.30 (dd, 1H, J = 11 Hz, 2 Hz); 2.17-1.77 ppm (broad, 4H).

**6-Benzoxycarbonyl-3-oxo-6-aza-2-oxacyclo[3.2.2]nonane (2):**
Buffered MCPBA: A dichloromethane (10 ml) solution of ketone 1 (190 mg, 0.73 mmol) sodium hydrogen carbonate (105 mg, 1.28 mmol), and m-chloroperbenzoic acid (187 mg, 1.08 mmol) is stirred in the dark for 42 h. Excess peracid is decomposed by adding 10% aqueous sodium sulfite and then the solution is extracted with dichloromethane to afford, after the workup described above, a mixture (200 mg). T.L.C. purification as described for lactone 2 above gives lactone 2; yield: 110 mg (55%), and lactone 3; yield: 50 mg (25%), Rf 0.4.

C₁₃H₁₃NO₄ calc. C 65.44 H 6.62 N 5.09 (2753) found 65.62 6.12 4.87

1H-N.M.R. (CDCl₃): δ = 7.30 (s, 5H); 5.15 (s, 2H); 4.65 (broad s, 1H); 4.35 (t, 2H, J = 15 Hz); 2.85 (dd, 1H, J = 14 Hz); 3.55 (dd, 1H, J = 14 Hz, 5Hz); 3.10 (broad, 1H); 2.3-1.8 ppm (broad, 4H).

MCPBA: A dichloromethane (20 ml) solution of ketone 1 (500 mg, 1.99 mmol) and m-chloroperbenzoic acid (580 mg, 3.35 mmol) is stirred in the dark for 42 h. The usual workup affords 480 mg of a mixture which upon T.L.C. separation as above gives lactone 2; yield: 253 mg (49%), and lactone 3; yield: 138 mg (27%).

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