REGIOSPECIFIC PREPARATION OF 2-OXAZOLINES PROMOTED BY SILICON TETRAFLUORIDE

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Abstract—Silicon tetrafluoride promotes reaction of oxiranes with nitriles to give 2-oxazolines in good yield.

2-Oxazolines have received considerable attentions as excellent synthetic intermediates, e.g., masked carboxylic acids, and possess diverse utilities for industrial applications. A variety of synthetic procedures have been reported until now, and among them the reaction of epoxides with nitriles constitutes the most straightforward and attractive approach. However, the only procedure reported for that employs sulfuric acid at 0 °C—room temp as a promoter, and the yields of 2-oxazolines were generally less than 20%. We report herein that SiF₄ promotes reaction of oxiranes with nitriles effectively to form 2-oxazolines in good yields with high regioselectivities.

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\hline \hline \\
\text{O} \\
\hline \hline \\
\text{R}^4 \\
\text{N} \\
\end{array}
\]

\[
\text{SiF}_4, \text{ R}^4\text{CN} \quad 0^\circ \text{C} \to \text{R}. \text{T.}
\]

Stirring a solution of styrene oxide (0.5 mmol) in acetonitrile (3 ml) under atmosphere of SiF₄ at room temp. for 1 h. gave 4-phenyl-2-oxazoline in 80% yield. A variety of 2-oxazolines was prepared under similar conditions, and Table 1 summarizes the results. As shown, 2-oxazolines were formed regiospecifically, i.e., the nitrogen atom was introduced into the more substituted carbons. The reaction proceeds generally in the nitrile as solvent under an excess of SiF₄. When a stoichiometric amount of nitrile was used, formation of a considerable amount of fluorohydrin was observed. Although an electron-withdrawing group on the oxirane ring decreased the reactivity (run 10), the 1-cyano-2-oxazoline was formed in good yield under the more forcing conditions (at 80 °C). Furthermore, the present reaction has an important chemoselectivity: mono-substituted aliphatic oxiranes did not undergo 2-oxazoline formation but the starting materials were...
recovered almost unaffected.

Table 1. Preparation of 2-Oxazolines

<table>
<thead>
<tr>
<th>Run</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Yield of 2 (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>C₅H₁₁</td>
<td>C₅H₁₁</td>
<td>H</td>
<td>CH₃</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>C₅H₁₁</td>
<td>C₅H₁₁</td>
<td>H</td>
<td>C₂H₅</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>C₆H₁₃</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>(CH₂)₁₁</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₂CH₂CHCH₂CH₂OBn</td>
<td>CH₃</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₂CH₂CHCH₂CH₂OBn</td>
<td>C₂H₅</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>CH₃</td>
<td>(CH₂)₄</td>
<td>CH₃</td>
<td>CH₃</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>(CH₂)₁₀</td>
<td>CH₃</td>
<td>CH₃</td>
<td>38</td>
</tr>
<tr>
<td>10</td>
<td>C₅H₁₁</td>
<td>C₅H₁₁</td>
<td>CN</td>
<td>CH₃</td>
<td>74</td>
</tr>
</tbody>
</table>

`The reaction was carried out at 0 °C--room temp. for 1--12 h under an atmosphere of SiF₄. All new compounds were fully characterized by nmr, ir, mass spectra, and/or combustion analyses, and in some cases by direct comparison with the authentic samples prepared by the reported method. Yields refer to isolated materials. The reaction was carried out at 80 °C.

The stereochmistry of the reaction was examines using 4-1-butylcyclohexane derivatives (3 and 4). The oxirane (3) gave 5 exclusively in 67 % yield, whereas 4 gave a mixture of isomers together with fluorohydrin (7), indicating that an SN₁ process was involved in the case of 4 probably due to a substantial torsional strain on an attack from the equatorial side.
The oxazoline formation exercised in the present study shows an extended utility of SiF₄ as selective Lewis acid.⁷

REFERENCES AND NOTES
4. Reactions were most conveniently run in an ordinary glassware apparatus fitted with a balloon filled with SiF₄. After the completion of the reaction, an aqueous KF solution was added to the mixture, and normal workup followed by separation on SiO₂ TLC gave 2-oxazolines.
6. The structures of 5, 6, and 7 were established based on their spectroscopic analysis. They afforded the following spectra: 5: ir(neat) 2950, 1670, 1475, 1440, 1385, 1235, 990, and 900 cm⁻¹; pmr(CDCl₃) δ 0.88(9H, s), 1.20-1.86(9H, m), 1.96(3H, s), and 3.80(2H, s). 6: ir(neat) 2950, 1680, 1450, 1380, 1360, 1225, 990, 805, and 750 cm⁻¹; pmr(CDCl₃) δ 0.86(9H, s), 1.16-1.88(9H, m), 1.96(3H, s), and 3.96(2H, s). 7: ir(neat) 3320, 2950, 1460, 1365, 1060, 880, and 735 cm⁻¹, pmr(CDCl₃) δ 0.88(9H, s), 1.00-2.12(10H, m, including an OH proton), 3.54(2H, d, J=19.7 Hz); ¹⁹Fmr (CDCl₃/CFCI₃) -172 ppm. Detailed explanation for the formation of fluorohydrin, see ref. 3.

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