단신

치환된 Silylpropargylic Alcohol의 Ortho Ester Claisen 재배열반응의 입체 선택성에 관한 연구

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Stereoselectivity of the Ortho Ester Claisen Rearrangement of Substituted Silylpropargylic Alcohols

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The ortho ester Claisen rearrangement has been very useful synthetic methodology in organic synthesis.1 The ortho ester Claisen rearrangement of the propargylic alcohols has been very effective method for producing the corresponding allene esters of biologically significant.2 Particularly the rearrangement involving a β-substituted vinyl participant is a potentially powerful reaction because a diastereomeric allene product may be generated. However, only one example yielding 1,3-disubstituted allenes by ortho ester Claisen rearrangement3 has been examined using substituted secondary propynyl alcohols by Heathcocks group.4 His group was able to obtain high stereoselectivity (80-90% of the syn selectivity) of the rearrangement of the propynyl alcohol bearing a bulky alkyl group at C-1 position. The results are noteworthy due to the fact that the diastereoselectivity of the ortho ester Claisen rearrangement is generally moderate or poor because the mixture of E and Z of the vinyl moiety of the intermediate ketone acetel may be generated.1,2,4

The ortho ester Claisen rearrangement of substituted silylpropargylic alcohols might be an efficient route to obtain the stereo-defined substituted silylallenes which has been very useful intermediates in organic synthesis.5 Therefore, the study on the rearrangement of the 1-alkyl-3-silylpropynol 2 leading to the 1,3-disubstituted silylallenes 3 is reported in this paper.

To investigate the substitution effect of the rearrangement series of silylpropargylic alcohols with various R groups at C-1 position were prepared in good yields by the addition of the corresponding aldehydes to a solution of lithium silylacetylide in THF at -78 °C followed by warming to room tem-
The result shows an interesting contrast against Heathcoks finding with the 1-alkyl substituted propynols. He showed the increasing trend of the diastereoselectivity of the rearrangement as increasing the steric bulkiness at C-1. However, our result implicates that the steric bulkiness does not seem to affect the stereoselectivity with an exception of the cyclohexyl group case in the entry 6. Increasing temperature generally lowers the ratio of the selectivity.

Our results are contrasted with Heathcoks findings; When R¹ is replaced with H, the steric interaction between the two reacting centers of the rearrangement may be small favoring the stable E geometry and the RS isomer is produced predominantly as R¹ is more bulky. Comparing with his results, the poor selectivity in the entry 1-4 may be assumed to that the transition state of the ketene acetal intermediates disfavors the E isomer (E-Req), that results in the mixture of E and Z geometry of the ketene acetals affecting the poor selectivity of the silylallenyl esters.

\[
\text{TMS} \overset{\text{n-BuLi, } H^\text{-R}}{\longrightarrow} \text{TMS} \overset{\text{CH}_2\text{CH}_2\text{C(OEt)}_3}{\longrightarrow} \text{TMS} \overset{\text{CH}_2\text{CH}_2\text{CO}_2\text{H (cat) heat}}{\longrightarrow} \text{TMS} \overset{\text{3SR(a-f)}}{\longrightarrow} \text{TMS} \overset{\text{3SS(a-f)}}{\longrightarrow}
\]

Table 1. Preparation of the silylpropargylic alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>R group</th>
<th>Product</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>methyl</td>
<td>2a</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>isopropyl</td>
<td>2b</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>t-butyl</td>
<td>2c</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>phenyl</td>
<td>2d</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>p-methoxyphenyl</td>
<td>2e</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>cyclohexyl</td>
<td>2f</td>
<td>91</td>
</tr>
</tbody>
</table>

Table 2. The orthoester claisen rearrangement of the silylpropargylic alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant</th>
<th>R group</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ds SR:SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>methyl</td>
<td>80</td>
<td>12</td>
<td>3a</td>
<td>60</td>
<td>51:39</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>isopropyl</td>
<td>120</td>
<td>4</td>
<td>3b</td>
<td>72</td>
<td>53:47</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>t-butyl</td>
<td>80</td>
<td>4</td>
<td>3c</td>
<td>60</td>
<td>60:40</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>phenyl</td>
<td>120</td>
<td>12</td>
<td>3d</td>
<td>56</td>
<td>55:45</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>p-methoxyphenyl</td>
<td>80</td>
<td>12</td>
<td>3e</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>cyclohexyl</td>
<td>80</td>
<td>5</td>
<td>3f</td>
<td>67</td>
<td>93:7</td>
</tr>
</tbody>
</table>
In the case of cyclohexyl substituent the major 3f(SR) was obtained in the 93:7 ratio after 5 hours at 80 °C. Further reaction only resulted in decreasing selectivity. It was found that the selectivity was highly temperature dependent. Reaction at 150 °C for 12 hrs ended up with roughly 1:1 mixture of the diastereomers. The trend was observed in the entry 1-4, but only with a small degree. We are now not sure the origin of the high selectivity in the case of cyclohexyl substituent. We assume that E isomer of ketene acetal (C_E) is probably favored due to the analogy that Z isomer (C_Z) might face the steric interaction between the vinyl methyl and cyclohexyl moiety more severely than the cases of other bulky substituents in the entry 1-4.

In summary, these studies demonstrated the synthetic utility of the ortho ester Claisen rearrangement of 1-alkylsubstituted-3-trimethylsilylpropynol providing the corresponding diastereomeric silylallenyl ethers, albeit in a limited scope of selectivity. We observed that TMS group at C-3 generally led to decreasing selectivity of the rearrangement as compared with the results of the corresponding ketene acetals (R'=H) by Heathcock group.26

The cyclohexyl group is the most effective in the rearrangement, affording 93:7 ratio of the selectivity. The selectivity of the ortho ester Claisen rearrangement is observed to be highly temperature dependent; lowering temperature causes slightly increasing selectivity in general. The temperature dependence in selectivity is mostly observed in the case of cyclohexyl substituent.

**EXPERIMENTAL SECTION**

The typical procedure of the preparation of the ynoles and the ortho ester Claisen rearrangement

1-Cyclohexyl-3-trimethylsilyl-prop-2-yn-1-ol (2f). To a solution of 1.00 g (0.01 mmol) of trimethylsilylacetylene in 30 mL of THF was added 4.3 mL (0.011 mol) of 2.5 M n-BuLi in hexanes at -78 °C dropwise. The solution was stirred for 1 hr and 1.3 mL (0.011 mol) of freshly distilled cyclohexencarboxaldehyde was added in one portion. The mixture was stirred for 1 hr and then allowed to warm to room temperature. Water was added. The organic layer was separated and extracted with ether three times. The extracts were dried over MgSO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with 5% ether in hexanes. Concentration gave 1.95 g (91%) of 2f: IR (neat) 3341, 2926, 2853, 2667, 2171, 1450, 1407, 1379, 1250, 1084, 1032 cm⁻¹; ¹H NMR (500MHz, CDCl₃) 3.95 (4H, d, J=6.0 Hz, methylene H), 2.80-1.80 (12H, m, hexyl Hs and OMe), 0.12 (9H, s, Si(CH₃)₃) ppm; ¹³C NMR (200MHz, CDCl₃) 105.8, 90.1, 67.5, 50.0, 43.9, 28.4, 28.0, 26.4, 25.9, 0.01(3).

rel-(2S,4R)-5-Cyclohexyl-2-methyl-3-trimethylsilanyl-penta-3,4-dienoic acid ethyl ester(3f). To 500 mg (2.38 mmol) of the propargylic alcohol 2f was added 3.40 mL (16.7 mmol) of triethyl ortho-propionate and 11 mg (0.14 mmol) of propionic acid. The solution was stirred for 5 hrs at 80 °C. The ratio of the diastereomeric allenic esters was determined by GC analysis (93:7). Ethanol and the excess ortho propionate were removed under reduced pressure. The residue was chromatographed on silica gel with 1% and 2% ether in hexanes to give 470 mg (67%) of allenic ester 3f: IR (neat) 2926, 2853, 2178, 1937, 1736, 1449, 1248, 1177, 1100, 841 cm⁻¹; ¹H NMR (200MHz, CDCl₃) δ 5.00 (1H, brt, vinyl H), 4.11 (2H, q, J=7.1 Hz, -OCH₂CH₃), 3.0 (1H, m, methine H, 1.00-2.00 (14H, CH₂CH- and hexyl Hs), 1.27 (3H, t, J=7.1 Hz, -OCH₂CH₃), 0.11 (9H, s, -Si(CH₃)₃) ppm; ¹³C NMR. (80MHz, CDCl₃) δ 205.4, 172.0, 128.4, 98.4, 94.7, 60.3, 40.0, 36.8, 33.4, 33.3, 26.2, 17.4, 14.1, 1.1(3); FAB+: mass m/z 294.1.

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REFERENCES


6. The major diastereomer of 3f (91:9 from an attempt) was identified by conversion of 3f to the alcohol 6 and compared with the alcohol from the Heathcock allene 5. The direct desilylation of 3f to 5 only resulted in a diene adduct.