A few new methods for asymmetric synthesis

Shō Itō and Tetsuto Tsunoda

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima, 770 Japan

Aza-Claisen rearrangement of N-2-(E)-butenyl-N-butylpropanamide was found to proceed smoothly at $\sim 135^\circ$C in the presence of LDA to furnish syn-N-butyl-2,3-dimethyl-4-pentenamide in $\sim 94\%$ yield and $>99\%$ de. The reaction with the corresponding N-(1S)-1-phenethyl derivative yielded (2R,3S)-N-[(1S)-1-phenethyl]-2,3-dimethyl-4-pentenamide in $83\%$ de. An efficient and generally-applicable two-step procedure for the hydrolysis of N-monosubstituted amides was also developed and the corresponding carboxylic acids were obtained in good yields without any epimerization at the $\alpha$-position of the acyl group. The amines used for the chiral induction can be recovered in $71\%$ yield.

INTRODUCTION

Stereoselectivity is one of the major concerns of chemists interested in modern organic synthesis. In this talk, we will discuss a few developments achieved by our group in this area.

AZA-CLAISEN REARRANGEMENT OF AMIDE ENOLATES

Claisen rearrangement of ester enolates initiated by Ireland (ref. 1) has widespread application in the homologation of acids and alcohols (ref. 2). From the present standard, however, the diastereoselectivity observed (syn:anti=8:92 (ref. 1)) is not entirely satisfactory. This is mainly due to the insufficient stereocontrol in the enolate formation (E:Z=95:5 in kinetic enolate (ref. 3)). On the other hand, aza-Claisen rearrangement of the enolates of N-2-alkenyl-N-alkylcarboxamides has not fully been investigated for the synthetic utility, probably because the resulted N-alkylamides have little synthetic value. However, since bulkier dialkylamino groups tend to produce more Z-enolates (often $>99:1$ (ref. 3)) than alkoxyl groups and a trivalent nitrogen atom could have an auxiliary for the chiral induction unlike a divalent oxygen atom, we have investigated the rearrangement in order to establish its stereochemical outcome and to develop a methodology in asymmetric synthesis.

Diastereoselectivity

N-2(E or Z)-butenyl-N-butylpropanamide (1E or 1Z) (ref. 4) was treated in THF at $-78^\circ$C with LDA to form the corresponding amide enolate 2. The solvent was removed at 0°C in vacuo and the residue was heated in a high-boiling nonpolar solvent to give N-butyl-2,3-dimethyl-4-pentenamide (4: a mixture of the syn and anti isomers, 4s and 4a) (Method A). The results are listed in TABLE 1 (ref. 5).
TABLE 1. Aza-Claisen rearrangement of N-butenyl-N-butylpropanamides (1)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd</th>
<th>Method</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Period (h)</th>
<th>Isolated yield of 4 (%)</th>
<th>Isolated yield of 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1E</td>
<td>A</td>
<td>xylene</td>
<td>135</td>
<td>4</td>
<td>92</td>
<td>99.5:0.5</td>
</tr>
<tr>
<td>2</td>
<td>1E</td>
<td>A</td>
<td>decane</td>
<td>135</td>
<td>4</td>
<td>94</td>
<td>99.4:0.6</td>
</tr>
<tr>
<td>3</td>
<td>1E</td>
<td>A</td>
<td>decane</td>
<td>148</td>
<td>14</td>
<td>90</td>
<td>37:63</td>
</tr>
<tr>
<td>4</td>
<td>1Z</td>
<td>A</td>
<td>decalin</td>
<td>180</td>
<td>1</td>
<td>46</td>
<td>22:78</td>
</tr>
<tr>
<td>5</td>
<td>1Z</td>
<td>A</td>
<td>decalin</td>
<td>180</td>
<td>5</td>
<td>39</td>
<td>31:69</td>
</tr>
</tbody>
</table>

The reaction of 1E proceeded smoothly at ~135°C, though it was too slow in boiling THF (14% yield after 14 h). Satisfactory yield (92%) and syn-anti ratio (99.5:0.5) was obtained after 4 h (entry 1). The excellent diastereoselectivity revealed both the exclusive formation of the Z-enolate 2E from 1E and the unique intervention of a chair-like conformation (A) in the transition state of the rearrangement. Choice of nonpolar solvent has little effect (entries 1, 3), but prolonged heating caused extensive epimerization at the α-position of the carbonyl group (entry 3) (ref. 6).

The rearrangement of 1Z (ref. 4) required much higher temperature than for 1E, and yet the yield and the ratio were poor after 1 h (entry 4), the reason presumably being steric in nature (cf. B). Prolonged heating not only changed the ratio but also decomposed the product 4.

Although somewhat higher temperatures are required, the aza-Claisen rearrangement of amide enolates is superior to the Claisen rearrangement of ester enolates because of better yield and higher stereoselection.

Chiral induction

A trivalent nitrogen atom can have an extra alkyl group which can be used as a chiral auxiliary, in addition to the two groups participating in the rearrangement. Thus the aza-Claisen rearrangement of amide enolates can be utilized for the enantioselective synthesis of chiral acid derivatives unlike that of ester enolates.

In principle, the rearrangement of N-2(E)-butenyl-N-[(1S)-1-phenethyl]-propanamide (6) would give a diastereomeric mixture (7) of N-[(1S)-1-phenethyl]-2,3-dimethyl-4-pentenamides (designated as 7sS, 7sR, 7aS, and 7aR as shown). While the diastereoselectivity (syn:anti) is determined by the factors described above, the diastereofacial selectivity, which results in the enantiomeric ratio (S:R) of the acids, the ultimate products, would be controlled by the chirality of the auxiliary. We have investigated the reaction of 6.

In addition to the Method A described above, Method B was introduced, in which amide enolate was prepared in toluene (or hexane) at -78°C in the presence of lithium hexamethyldisilazide (or LDA) (1.2-1.5 equiv.), and then heated in a sealed tube. The results are listed in TABLE 2 (ref. 7).

TABLE 2. Aza-Claisen rearrangement of N-2(E)-butenyl-N-[(1S)-1-phenethyl]-propanamide (6)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Temp. (°C)</th>
<th>Period (h)</th>
<th>Isolated yield of 7 (%)</th>
<th>Diastereomeric ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>150</td>
<td>6</td>
<td>48</td>
<td>42.0:5.9:47.1:4.9</td>
</tr>
<tr>
<td>2</td>
<td>B (LDA)</td>
<td>120</td>
<td>6</td>
<td>68</td>
<td>91.8:8.2</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>120</td>
<td>6</td>
<td>85</td>
<td>91.5:8.5</td>
</tr>
<tr>
<td>4</td>
<td>B (hex)</td>
<td>120</td>
<td>71</td>
<td>71</td>
<td>91.6:8.4</td>
</tr>
</tbody>
</table>

As is seen in TABLE 2, no anti isomer was detected in Method B. The diastereoselectivity (S:R), however, remained at 11:1 (83% de).
HYDROLYSIS OF N-MONOSUBSTITUTED AMIDES VIA ACETOXYPIVALIMIDES

The classical procedures for the hydrolysis of amide linkage require severe conditions (strong bases or acids, and elevated temperature) incompatible with substrates having acid- or base-sensitive groups. Although many excellent methods have been developed for nonsubstituted and N,N-disubstituted amides (ref. 9), the available methods for the hydrolysis of N-monosubstituted amides seem to suffer from serious limitations. Since they were quite unsatisfactory in our hand to hydrolyze the N-substituted amides obtained above (ref. 10), we have developed another mild and efficient method of our own.

The present method consists of two steps: N-alkylcarboxamides 8 were converted to N-acyl-N-alkylacetoxypivalamides 9, and then, taking advantage of much faster hydrolysis of imides than that of amides, and utilizing the intramolecular nucleophilic attack (N-O acyl migration), the desired amides bonds were selectively cleaved under mild conditions to give the corresponding carboxylic acids 10 and N-alkylhydroxypivalamides 11 via acyloxy-pivalamides 12.

The results are listed in TABLE 3. As a typical example (entry 2), N-butylcyclohexanecarboxamide (8a) was converted to the corresponding acetoxypivalimide 9a in 89% yield with acetoxypivaloyl chloride (2 equiv.) in CH2Cl2 (room temp., 2.5 h) in the presence of Et3N (2 equiv.) and 4-N,N-dimethylaminopyridine (0.1 equiv.). The imide 9a was then hydrolyzed in THF (room temp., 19 h) with 1M LiOH (2.2 equiv.) to give cyclohexanecarboxylic acid 10a in 87% yield along with 8a, the product of the alternative cleavage, in 10% yield.

TABLE 3. Two-step hydrolysis of N-monosubstituted carboxamides 8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amides 8 R</th>
<th>Acylation Period (h)</th>
<th>Yield of 9 (%)</th>
<th>Hydrolysis Period (h)</th>
<th>Yield of 10 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c-Hex PhCH2</td>
<td>6</td>
<td>90</td>
<td>24</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>c-Hex Bu</td>
<td>2.5</td>
<td>89</td>
<td>19</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>Pent Bu</td>
<td>0.75</td>
<td>91</td>
<td>19</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>Ph Bu</td>
<td>9.75</td>
<td>99</td>
<td>19</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>c-Hex 1-Phenetyl</td>
<td>8b</td>
<td>92</td>
<td>24</td>
<td>89</td>
</tr>
</tbody>
</table>

a Three equiv. of acyl chloride and Et3N were used.
b Five equiv. of acyl chloride and Et3N were used.

The method can satisfactorily be applied to the straight chain (entry 3), branched chain (entries 1, 2, 5) and aromatic (entry 4) carboxamides. The sterically hindered amides such as N-1-phenethylcyclohexanecarboxamide, can also be hydrolyzed smoothly (entry 5)(ref. 11).

In order to test the mildness of the hydrolytic conditions, the amide 4 (syn:anti=99.5:0.5, entry 1, TABLE 1) was subjected to the reaction sequence. 2,3-Dimethyl-4-pentenoic acid 10c obtained in 78% overall yield showed practically no indication of epimerization (syn:anti=99.2:0.8).

The recovery of amines is often desirable, especially when chiral amines are used in asymmetric synthesis. This can also be realized in two steps: For example, N-1-phenthlyhydroxypivalamide 11d, the by-product of the hydrolysis (entry 5, TABLE 3), was converted to the carbamate 13 (diethyl carbamate (1.4 equiv.), NaH (2.8 equiv.) in DMF, room temp., 21 h) in 89% yield, through the cyclic carbamate 14 (ref. 12). The carbamate was smoothly hydrolyzed by 48% NaOH (large excess) at 120° to give 1-phenthylamine in 80% yield.
Thus, the present reaction sequence was shown to have wide applicability to the hydrolysis of N-monosubstituted amides.

REFERENCES AND NOTES

4. The compounds 1B and 1Z were prepared from N-butylpropanamide by the sequential reactions with NaH in DMF and E-crotyl bromide (77% yield) or Z-crotyl tosylate (90% yield). The minor isomers present in the products were separated by SiO2 impregnated with AgNO3. The compound 6 was prepared from N-1-(5)-1-phenethyl propanamide and E-crotyl bromide (60% yield). The purity was ~100% in all cases.
5. While the syn:anti ratio of the product was determined by GLC after the conversion of 4 to the pivalimide 5 (pivaloyl chloride, Et3N, 4-N, N-dimethylaminopyridine), their stereochemistry was established by the comparison of 5 with those obtained by the Claisen rearrangement of the corresponding ester enolates (ref. 1).
6. The reaction in polar solvents proceeded with poor selectivity (e.g. Compound 6 in THF at 120°C for 2 h gave the ratio 7sS:7sR =79:21) and greater tendency of epimerization.
7. The diastereomeric ratio in 7 was determined by LC. The configuration of each diastereomer was established by 1) the conversion of 4s to the mixture of 7sS and 7sR, and 2) the hydrolysis of 7sS and subsequent ozonolysis of the product to (+)-2,3-dimethylsuccinic acid (ref. 8).
11. The participation of the neighboring hydroxyl group in the hydrolysis was verified by the following experiments: The hydrolysis of N-butyl-N-hexanoylpivalamide with no site of possible participation gave N-butylhexanamide in 79% yield under the same conditions as in entry 3. TABLE 3, revealing the preferencial nucleophilic attack on the "wrong" carbonyl group.

Furthermore, N-benzyl-N-cyclohexanecarbonyloxyypivalamide was isolated (33% yield) along with hydrolysis products, when the reaction of N-benzyl-N-(cyclohexanecarbonyl)-acetoxyypivalamide was quenched after 10 h.

12. When the reaction was quenched after 0.5 h, the carbamate 15 was isolated in 27% yield along with 13 (18% yield) and the starting 11d (42% yield).