ORGANIC SYNTHESIS UTILIZING BECKMANN FRAGMENTATION: ASYMMETRIC CARBON-CARBON BOND FORMATION VIA CHIRAL ACETAL INTERMEDIATES

Hiromichi FUJIOKA,* Hidetoshi KITAGAWA, Takeshi YAMANAKA, and Yasuyuki KITA*
Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565, Japan

Treatment of racemic α-methoxycycloalkane oxime acetates 1 with (2R,4R)-2,4-bistrimethylsilyloxypentane in the presence of a catalytic amount of trimethylsilyl triflate (TMSOTf) afforded the chiral acetal intermediates 3, which were reacted with silicon-containing nucleophiles to give the chiral ω-cyano compounds 4, in a one-pot operation.

KEYWORDS asymmetric synthesis; Beckmann fragmentation; chiral acetal; ω-cyano alcohol; one-pot operation

Although Beckmann fragmentation is one of the long-known reactions, few studies on high-order use of its intermediates have been done so far. As an extension of our effort to develop the organic synthesis utilizing the intermediates of Beckmann fragmentation, we have succeeded in a novel asymmetric carbon-carbon bond formation by combination of Beckmann fragmentation reaction and asymmetric synthesis using a chiral acetal.

The overall transformation is shown in Chart 1. Reaction of racemic α-methoxycycloalkane oxime acetates 1 with (2R,4R)-2,4-bistrimethylsilyloxypentane in the presence of a catalytic amount of trimethylsilyl triflate (TMSOTf) gave the chiral acetals 3 quantitatively via oxonium ion intermediates 2. Reaction of 3 with silicon-containing nucleophiles afforded the ω-cyano compounds 4 in both high diastereomeric excess (de) and chemical yields. These transformations were carried out in a one-pot operation without isolation of 3.
Reaction of 3 (n=1) with allyltrimethylsilane in the absence of Lewis acid gave no 4 (n=1) (Table, entry 1). However, the addition of Lewis acid promoted the conversion of 3 (n=1) to 4 (n=1) (entries 2-4), and slow addition of the mixed Ti-catalyst $[\text{6TiCl}_4\cdot\text{5Ti(O-i-Pr)}_4]$ gave the best result (entry 4). The reaction also worked well for medium and large ring systems (entries 5 and 6). Other silicon-containing nucleophiles similarly reacted with 3 (n=1) in a highly diastereoselective manner. In these cases the mixed Ti-catalyst was ineffective and the use of TiCl$_4$ gave good results (entries 7 and 8). The stereochemistries of the products were determined as follows. The absolute configurations of the products in entries 1-4 were determined by converting the product in entry 4 to the key intermediate 7 for the synthesis of $\alpha$-$(R)$-lipoic acid (Chart 2). Thus, pyridinium chlorochromate (PCC) oxidation of 4 (94% de) in entry 4 followed by aqueous alkaline treatment under reflux conditions and methylation of the resulting acid afforded the hydroxy methylester 6. Ozonolysis of 6 followed by NaBH$_4$ treatment gave the dihydroxy methylester 7. The value of the specific rotation ($[(\alpha)_D +3.6^\circ]$) of 7 showed good agreement with the reported value ($[(\alpha)_D -3.9^\circ]$) except for the sign. The stereochemistries of the products in entries 5-8 were tentatively assigned by assuming the same sense of diastereoselection as observed for the products in entries 3 and 4 and also by referring to the results in the usual asymmetric synthesis using this chiral acetal. The method of converting 4 to the chiral $\omega$-cyano alcohols 5, oxidation/β-elimination procedure, has already been established. In fact, conversion of the product in entry 5 to 5 (n=3, Nu=allyl, $[(\alpha)_D +9.4^\circ]$) by the usual procedure [PCC, CH$_2$Cl$_2$/40%aq.KOH-MeOH (1/1), r.t.] proceeded in 92% overall yield without any

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>Nu-Y</th>
<th>Lewis acid(eq)</th>
<th>Product 4</th>
<th>Yield(%)</th>
<th>de (%) of 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n=1</td>
<td>$\rightarrow$SiMe$_3$</td>
<td>None</td>
<td>No reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>n=1</td>
<td>TMSOTi (2)</td>
<td>TiCl$_4$ (2)</td>
<td>Nu= $\rightarrow$</td>
<td>32</td>
<td>29$^a$($^b$)</td>
</tr>
<tr>
<td>3</td>
<td>n=3</td>
<td>TiCl$_4$ (2)</td>
<td>TiCl$_4$ (2)</td>
<td>88</td>
<td>68$^b$</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>n=3</td>
<td>TiCl$_4$*5Ti(O-i-Pr)$_4$ (30)</td>
<td>92</td>
<td>94$^b$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>n=7</td>
<td>TiCl$_4$*5Ti(O-i-Pr)$_4$ (30)</td>
<td>79</td>
<td>94$^b$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>n=7</td>
<td>TiCl$_4$*5Ti(O-i-Pr)$_4$ (30)</td>
<td>94</td>
<td>92$^b$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>n=1</td>
<td>TMS-TMS</td>
<td>TiCl$_4$ (4)</td>
<td>Nu= $\rightarrow$TMS</td>
<td>77</td>
<td>$\geq 95^c$</td>
</tr>
<tr>
<td>8</td>
<td>n=1</td>
<td>O$^{13}$Bu</td>
<td>TiCl$_4$ (4)</td>
<td>Nu=CH$_2$CO$_2$Bu $^{13}$Bu</td>
<td>66</td>
<td>$\geq 95^c$</td>
</tr>
</tbody>
</table>

a) Obtained with S configuration, predominantly. b) Determined by GC on a 25m HiCap-CBP 1 capillary column. c) Determined by 500MHz $^1$H-NMR.

![Chart 2](https://example.com/chart2.png)

1) PCC, CH$_2$Cl$_2$  
2) 40%aq.KOH-MeOH (1/1), reflux  
3) CH$_2$N$_2$  

4 (entry 4) → 57%  

(4) O$_3$, MeOH, -78°C then NaBH$_4$ treatment  

6 (57%)  

(57%)  

7 (60%)
In conclusion, we opened a novel way to get optically active \( \omega \)-cyano alcohols 5 from the readily available racemic cyclic \( \alpha \)-methoxy cycloalkanone oxime acetates 1.

REFERENCES AND NOTES


4) Compound 3 (n=1) was isolated and its structure was determined by spectroscopic data.


6) These phenomena observed in entries 2-6 were explained as follows: the reactions proceed through three different ion pairs ii-iv formed from Lewis acid-acetal complex i; and (1) the reaction with weak Lewis acid involves the intimate ion pair ii and shows extremely high stereoselectivity by inversive substitution (entries 4-6), (2) the reaction with stronger Lewis acid proceeds with modest selectivity through transition state iii (entry 3), and (3) the reaction with very powerful Lewis acid involves separated ion pair iv and affords the product with no selectivity. [cf. S. E. Denmark and N. G. Almstead, *J. Am. Chem. Soc.*, **113**, 8089 (1991); idem, *J. Org. Chem.*, **56**, 6485 (1991)].


(Received September 8, 1992)