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## Stereoselective 1,5-rearrangement of vinylketene-*N*,*O*-acetals: novel vinylogous Ferrier reaction

Masaharu Inui, Seijiro Hosokawa,<sup>†</sup> Atsuo Nakazaki and Susumu Kobayashi\*

Faculty of Pharmaceutical Sciences, Tokyo University of Science (RIKADAI), 2641 Yamazaki, Noda, Chiba 278-8510, Japan

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Abstract—Vinylketene-*N*,*O*-acetals underwent Lewis acid-induced 1,3- or 1,5-rearrangement to afford the corresponding *C*-alkylated products. 1,5-Rearrangement proceeded predominantly in dichloromethane, and it is quite interesting to achieve an unprecedented high degree of asymmetric induction in such a remote position. Crossover experiments indicated that the reaction proceeded through an ion pair intermediate.

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We recently reported an unusual MeAlCl<sub>2</sub>-induced 1,3rearrangement of vinylketene-*N*,*O*-acetal to *C*-alkylated  $\beta$ , $\gamma$ -unsaturated imide.<sup>1</sup> For example, when vinylketene-*N*,*O*-acetal **2**, prepared from  $\alpha$ , $\beta$ -unsaturated chiral imide **1**, was treated with 2 equiv of MeAlCl<sub>2</sub> in toluene at -78 °C,  $\alpha$ -migration product **3** was isolated in 36% yield with high (20:1) stereoselectivity. A by-product in this reaction was the 1,5-rearranged product **4** which was isolated in 25% yield (Scheme 1).

The reaction might proceed through an initial cleavage of the acetal moiety by the action of MeAlCl<sub>2</sub>, followed by recombination of the ion pairs at either the  $\alpha$ - or  $\gamma$ -position. We were particularly interested in the 1,5rearrangement because (1) such a rearrangement of vinylketene acetal is regarded as an unprecedented vinylogous Ferrier reaction,<sup>2</sup> and (2) 1,5-rearrangement product could not be easily obtained by the conventional  $\gamma$ -alkylation of the corresponding  $\alpha$ , $\beta$ -unsaturated imide 1<sup>3</sup> (Scheme 2). These considerations led us to investigate this rearrangement in detail.

Since the intermediate of the reaction is an ion pair, it seemed that the ratio of 1,3- and 1,5-product might be



Scheme 1. 1,3-and 1,5-rearrangement of ketene-N,O-acetal.

Keywords: 1,5-Rearrangement; Vinylketene-N,O-acetal; Vinylogous Ferrier reaction; Lewis acid.

<sup>\*</sup> Corresponding author. Tel./fax: +81 4 7121 3671; e-mail: kobayash@rs.noda.tus.ac.jp

<sup>&</sup>lt;sup>†</sup>Present address: Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan.

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Scheme 2. The mechanism of the rearrangement.

strongly affected by the solvent used.<sup>4</sup> We then carried out the reaction of **2** in dichloromethane, and indeed, the 1,5-rearranged product **4** was isolated as a major product in 78% yield along with **3** in 15% yield when 10 equiv of MeAlCl<sub>2</sub> was used. Among several representative Lewis acids, aluminum-based Lewis acids afforded **4** in higher yield.<sup>5</sup> As shown in Table 1, use of a large excess of Lewis acid resulted in a slight increase of the yield of **4**.

We next prepared  $\gamma$ -substituted vinylketene-*N*,*O*-acetal **5** from the corresponding unsaturated chiral imide, and **5** was then subjected to MeAlCl<sub>2</sub>-induced rearrangement (Table 2). Although the ratio of 1,5- and 1,3-rearranged products was not high compared to the  $\gamma$ -unsubstituted substrate **2**, the reaction in slightly more

**Table 1.** Rearrangement of ketene-*N*,*O*-acetal in toluene or CH<sub>2</sub>Cl<sub>2</sub>

polar  $CH_2Cl_2$  resulted in an increase of 1,5-rearranged product 7. Surprisingly, the 1,5-rearrangement proceeded in highly stereoselective manner affording 7 in 20:1 ratio.

The stereochemistry of the newly formed chiral center at the  $\gamma$ -position was determined as shown by correlating to the known monobenzyl ether of 2-methyl-1,3-propanediol **8**.<sup>6</sup> (Scheme 3) Thus, **7** was treated with ozone in CH<sub>2</sub>Cl<sub>2</sub>–MeOH, followed by reduction with NaBH<sub>4</sub> to obtain **8**. Measurement of the specific rotation established the stereochemistry of **8** and eventually the stereochemistry of **7**.

We speculate that the plane of the oxazolidin-2-one moiety might be almost perpendicular to that of the



Table 2. Rearrangement of  $\gamma$ -substituted ketene-N,O-acetal

	Me BnO 5	N O MeAICl <sub>2</sub> N O solvent Me		H He			
Entry	Solvent	MeAlCl <sub>2</sub> (equiv)	6		7		
			Yield (%)	d.s.	Yield (%)	d.s.	
1	Toluene	5	57	42:1	24	20:1	
2	$CH_2Cl_2$	4	39	23:1	52	20:1	



Scheme 3. Determination of the stereochemistry at the  $\gamma$ -position.

dienolate anion, and that the conformation shown in Figure 1 might be more stable.<sup>7</sup> An alternative rotational isomer seems to suffer from steric interaction between the aluminum group and the *sec*-butyl group of the chiral auxiliary. Then, the oxocarbenium ion might approach from the less hindered upper face to produce 7. The sense of the stereochemical course of the  $\alpha$ -alkylation leading to **3** and **6** could also be explained by considering the same transition state.<sup>1</sup>



Figure 1. Proposed transition state.

Table 3. Crossover experiment using 2 and 9

For the solvent, we think that the intermediary ion pair exists as a solvent separated ion pair rather than as a contact ion pair in dichloromethane, and, therefore, the ion pair might undergo recombination at the more reactive  $\gamma$ -position predominantly.<sup>8</sup> In toluene, on the other hand, initially formed contact ion pair might readily react at the near  $\alpha$ -position.

In order to confirm the reaction mechanism, we conducted a crossover experiment. Thus, a mixture of two vinylketene-N,O-acetal 2 and 9 was treated with MeAlCl<sub>2</sub> in toluene or dichloromethane at -78 °C. Crossover products are 11 and 12 for 1,3-rearrangement, and 14 and 15 for 1,5-rearrangement, respectively. Authentic samples of these compounds were prepared by a rearrangement of the corresponding vinylketene-N,O-acetals. Results are shown in Table 3. Yields are based on the <sup>1</sup>H NMR analysis of the mixture of rearranged products. In toluene (entry 1), the formation of crossover products was not detected by careful analysis of the <sup>1</sup>H NMR spectra.<sup>9</sup> On the other hand, in the case of dichloromethane (entry 2), a small amount of 1,5-rearranged products, 14 and 15 (5% of each), was formed in addition to noncrossover products. These results clearly demonstrate the solvent effect we have speculated above. In dichloromethane, the solvent separated ion pair might undergo an intermolecular recombination. In this case, the alkylation occurs at the more reactive  $\gamma$ -position.

In summary, we have observed a novel 1,5-rearrangement of vinylketene-N,O-acetals, which could be regarded as a formal vinylogous Ferrier reaction. Although synthetic applicability of the present rearrangement is not significant due to the limitation of substrates, the excellent stereoselectivity is noteworthy considering that the reaction takes place at a rather remote site from the chiral center. Therefore, this rearrangement would be a unique method for the formal stereoselective  $\gamma$ -alkylation of  $\alpha$ , $\beta$ -unsaturated carbonyl derivative. Improvements in yield, regioselectivity, and reaction conditions are now in progress.

ROCH <sub>2</sub> O MeAICl <sub>2</sub>	•	RO V V V V V V V V V V V V V V	R	
2 R = PhCH <sub>2</sub> X <sub>N</sub> = X <sub>N</sub> <sup>1</sup> (1 equiv.) 9 R = p-ToICH <sub>2</sub> X <sub>N</sub> = X <sub>N</sub> <sup>2</sup> (1 equiv.) $X_N^1: -N_N^0$ $X_N^2: -N_N^0$	3 10 11 12	$R = PhCH_2 \qquad X_N = X_N^1$ $R = p\text{-TolCH}_2 \qquad X_N = X_N^2$ $R = PhCH_2 \qquad X_N = X_N^2$ $R = p\text{-TolCH}_2 \qquad X_N = X_N^1$	4 13 14 15	$R = PhCH_2 \qquad X_N = X_N^1$ $R = p\text{-TolCH}_2 \qquad X_N = X_N^2$ $R = PhCH_2 \qquad X_N = X_N^2$ $R = p\text{-TolCH}_2 \qquad X_N = X_N^1$

Entry	Solvent	MeAlCl <sub>2</sub> (equiv)		Yield (%)							
				a-Alkylation				γ-Alkylation			
			3	10	11	12	4	13	14	15	
1	Toluene	4	14	10	_		23	15		_	
2	$CH_2Cl_2$	8	9	19			29	24	5	5	

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- 5. The use of SnCl<sub>4</sub> or TiCl<sub>4</sub> gave a complex mixture of products, no reaction occurred with BF<sub>3</sub>·OEt<sub>2</sub>. EtAlCl<sub>2</sub> and AlCl<sub>3</sub> were not effective in terms of yield and selectivity.
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- <sup>1</sup>H NMR spectra (600 MHz) were recorded on a Bruker AVANCE 600 spectrometer. Each product is distinguishable by the proton either at the 4-position of oxazolidin-2one or the vinylproton at the β-position.