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Acylation of 2,4-Disubstituted Thiazolidines and Oxazolidines. Concomitant Epimerization at C-2

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Acylation of diastereomers of 2,4-disubstituted 4(R)-alkoxycarbonyl thiazolidines and oxazolidines with acyl chlorides affords (2R,4R)-3-acyl isomer as only product without any racemization. The reaction proceeds via concomitant epimeriaztion at C-2 of (2S,4R) diastereomer of the substrates.

The bisfunctional carbons, which signify the carbons linking two heterofunctional groups in some heterocycles such as thiazolidine and oxazolidine, have proved to furnish characteristic reactivities.[1] Szilagyi et al. observed that (2R,4R)-2-alkyl-3-acyl-4-thiazolidine carboxylic acid esters (cis-2, X=S) are obtained exclusively by virtue of epimerization at C-2, a bisfunctional carbon of (2S,4R) diastereomer of substrate (trans-1)[2] when diastereomers of 2-alkyl-4-(R)-thiazolidine carboxlylic acid esters are acylated with acyl chlorides or acid anhydrides. It was suggested that the reason for the preferential production of cis-2 (X=S) is the faster reaction rate of the cis-1 and trans-1 via ring-opened intermediate 3 (X=S, cis-1 $\rightleftharpoons$ 3 $\rightleftharpoons$ trans-1 in Scheme 1). However, the driving force of the reaction, that is, what makes cis-1 have the preference, still remains problems. In this paper we describe that the reaction occurs not only in thiazolidines but also in oxazolidines. Furthermore, we found that the driving force is the difference in the rates of acylation between cis-1 and trans-1 due to their different steric factors, and that the Schiff base type open chain intermediate 3, through which the equilibrium has been anticipated,[3,4] is generally stable in the case of oxazolidine.

The cis and trans diastereomers of thiazolidine and oxazolidine 1, which are obtained by condensation of cysteine and serine esters with corresponding aldehydes,[4] exist in a ratio of ca. 1 : 1 when they reach thermodynamic equilibrium. Figure 1 is the ^{1}H-NMR spectrum of 2-phenyl-4-(R)-ethoxycarbonyl oxazolidine 1, where the protons at 2-positions of trans and cis diastereomers appeared at 5.67 and 5.23 ppm, respectively.[5] The peak at 8.36 ppm evidently suggests the existence of a proton attached on C=N bond of imine. In addition, there are two absorptions at 3500-3100 and 1640 cm^{-1} in IR spectrum, indicating the -OH and C=N vibration, and a peak at 166 ppm in ^{13}C-NMR spectrum suggesting the carbon of C=N bond. All the spectroscopic data demonstrate that there is an

equilibrium between cis-1 and trans-1 (X=O; R^1=Ph; R^2=Et) through ring-opend intermediate 3.

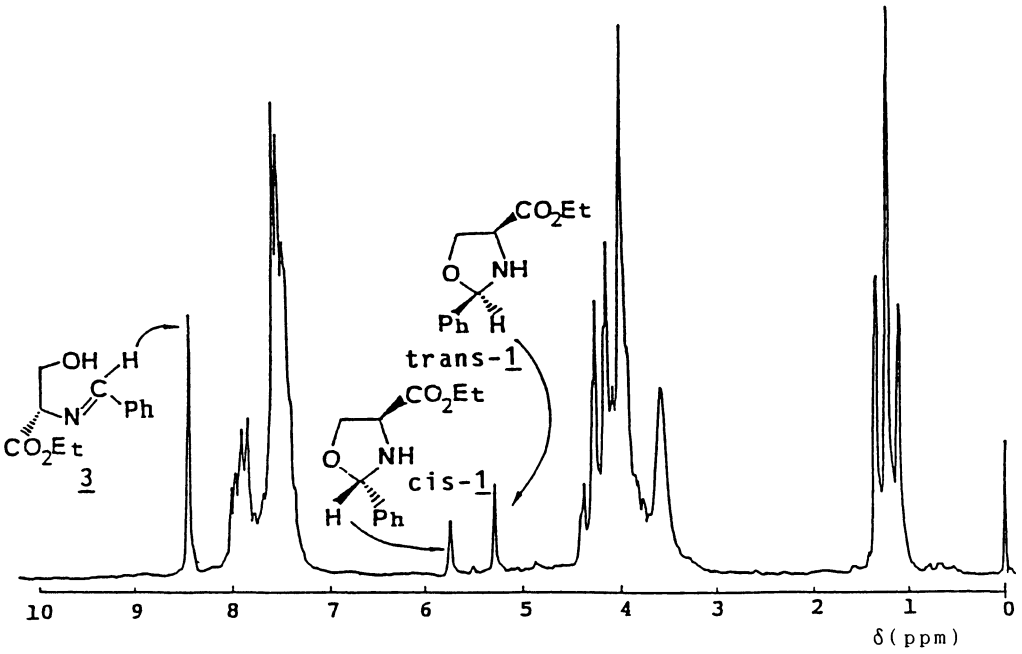
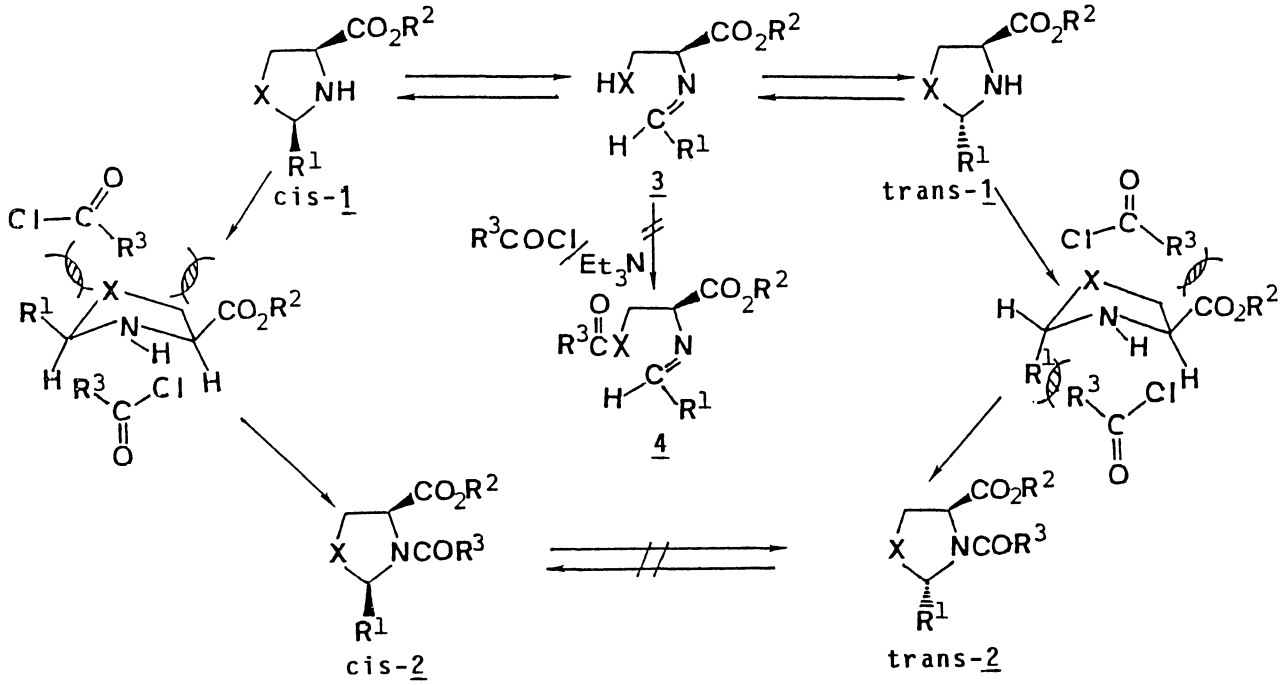


Fig. 1. ^{1}H-NMR spectrum of 2-phenyl-4-(R)-carbonylethoxy oxazolidine. The integration indicates that ratio of 3 :cis-1 : trans-1 is 2 : 1 : 1.

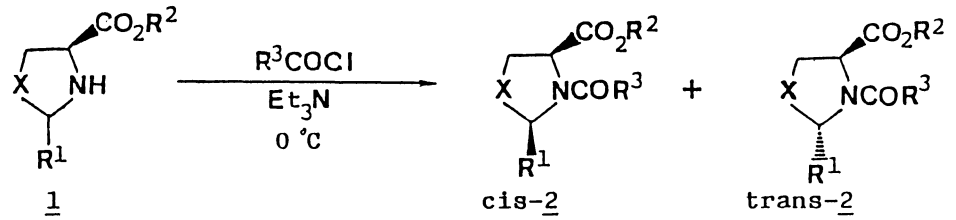
Surprisingly, when the equilibrated system was acylated with various acylating reagents in the presence of triethylamine in dichloromethane at 0 °C 3-acyl-oxazolidines 2 (X=O) were obtained in high yields without any open chain products such as 4 (X=O).



Scheme 1.

The results for acylation of oxazolidines and also thiazolidines, are summarized in Table 1.

Table 1. Acylation of thiazolidines and oxazolidines



1 cis-2 trans-2

Run	X	R^1	R^2	R^3	Yield/%	2 [b] cis(%)	2 [b] trans(%)
a	O	Ph	Et	H[a]	85	75	25
b	O	Ph	Et	Me	96	67	33
c	O	Ph	Et	Ph	95	100	0
d	S	Styryl	Me	H[a]	82	80	20
e	S	Styryl	Me	Me	84	100	0
f	S	Styryl	Me	Ph	85	100	0
g	S	t-Bu	Me	H[a]	85	67	33
h	S	t-Bu	Me	Me	90	90	10
i	S	t-Bu	Me	Ph	94	100	0
j	S	n-Pr	Me	H[a]	82	75	25
k	S	n-Pr	Me	Ph	75	100	0

a) CH_3CO_2CHO was used as an acylating reagent. b) Ratios of cis-2 : trans-2 were determined by ^{1}H-NMR integral ratio of H-2 of the diastereomers.[5]

Looking into the table, we could find that ratio of cis-2 : trans-2 is strongly related to the bulkiness of acylating reagents (see run a, b, c, or g, h, i) as well as that of groups substituted on C-2 (see run d, g, j, or e, h). This fact implies that the preferential acylation of cis-1 results from the steric difference between cis and trnas diastereomers of 1. It is easy to reveal the difference by configuration analysis. In cis-1, the carbonyl group of acylating reagents is difficult to approach to amino group from the side where $-CO_2R^2$ or $-R^1$ orient, but easy from the opposite site of the ring, while in trans-1 both sides are sterically crowded by either $-CO_2R^2$ or $-R^1$ group.

The possible mechanism has been suggested in Scheme 1 on the basis of sterical configuration. The lack of ring-opened product 4 can be explained by the lower nucleophilicity of hydroxyl group of 1 relative to amino group of 2. The interchange of cis-2 and trans-2 has been experimentally proved impossible under above mentioned conditions. Because of higher nucleophilicity of -SH than that of -OH, the Schiff base type intermediate (3, X=S) in thiazolidine system is unstable and tends to form ring.

The reaction described in this article is of great interest in both synthetic and mechanistic aspects. By this methodology, we can perform a 1,3-asymmetric induction in high chemical yields and get a good diastereomeric excess without racemization. We are expecting the utilities of resulting chiral heterocycles in asymmetric synthesis, especially those bearing functional groups in $-R^1$ such as cis-2d, 2e,and 2f.

References

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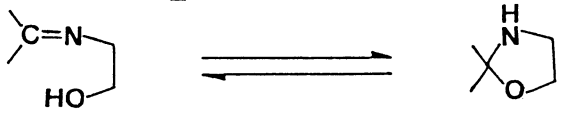
6) It has been reported that oxazolidines 2 exist in equilibrium with Schiff base type ring-opened isomer 1.



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