

ASYMMETRIC TRANSFORMATION OF 2-CHLOROALKANOIC ACIDS VIA OXAZOLINE
DERIVATIVES

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Abstract --- Asymmetric transformation of 2-chloroalkanoic acids via oxazoline derivatives were examined using (S)-phenylalaninol as a chiral auxiliary. After the transformation optical purities of the acids were appreciably improved compared with those of the acids obtained before the transformation.

In a previous paper, the asymmetric transformation of 2-phenylalkanoic acids via oxazoline derivatives was reported.¹⁾ Although the optical yields were not very high (29-53%), the transformation appeared to be a unique method for syntheses of chiral acids. Oxazoline derivatives were originally used by Meyers et al. for asymmetric syntheses of various chiral acids, but in the case of 2-chloroalkanoic acids the optical yields were rather low compared with other successful examples.²⁾ Therefore, we examined the asymmetric transformation of 2-chloroalkanoic acids via oxazoline derivatives.

Oxazoline derivatives (1a-e) were synthesized from (S)-phenylalaninol³⁾ and the ethyl imidate hydrochlorides, which were prepared from 2-chloroalkyl cyanides⁴⁾ (Scheme 1). A typical example of the syntheses was described bellow. Ethyl 2-chloropropioimidate hydrochloride (8.6 g, 0.05 mol) and 8.3 g (0.055 mol) of (S)-phenylalaninol were suspended in 100 ml of dry CH₂Cl₂, and the suspension was stirred for 10 h at room temperature. The products were applied on a silica-gel chromatography, and then distilled under reduced pressure. The oxazoline derivative (1a) was obtained as the mixture of two epimers at C-2 exo methine of

Table 1. Hydrolysis of 1 before and after the asymmetric transformation and diastereomeric composition of 1 after the asymmetric transformation.

Hydrolysis	Before the asym. trans.				After the asym. trans.					
	τ	Yield	$[\alpha]_D^{25^a)}$	O.p. ^{b)}	Conf.	Yield	$[\alpha]_D^{25^a)}$	O.p. ^{b)}	Conf.	Diaster. comp.
	h	%	(°)	%		%	(°)	%		
<u>1a</u>	1.5	94	+0.13	0.8 ^{c)}	(R)	73	+7.77	44.9 ^{c)}	(R)	71:29 ^{g)}
<u>1b</u>	1.5	82	+0.33	2.6 ^{c)}	(R)	72	+6.56	51.7 ^{c)}	(R)	75:25 ^{g)}
<u>1c</u>	1.5	86	+0.43	3.2 ^{d, f)}	(R)	71	+9.85	74.1 ^{d, f)}	(R)	77:23 ^{h)}
<u>1d</u>	1.5	61	0	0 ^{d)}	(RS)	52	+8.88	75.9 ^{d, f)}	(R)	76:24 ^{h)}
	4.5	88	0	0 ^{d)}	(RS)	74	+8.48	72.5 ^{d, f)}	(R)	
<u>1e</u>	1.5	45	+5.73	23.5 ^{e, f)}	(R)	62	+16.2	66.4 ^{e, f)}	(R)	76:24 ^{h)}
	6	91	+0.51	2.1 ^{e, f)}	(R)	79	+15.0	61.5 ^{e, f)}	(R)	

a) These rotations in methanol, concentration approximately 5 g/100 ml.

b) Optical purities were based upon the highest rotation values available.

c) 2a: $[\alpha]_D^{23} +17.3^\circ$ (MeOH), 2b: $[\alpha]_D^{23} +12.7^\circ$ (MeOH), H. Hashimoto and H. Simon, *Angew. Chem.*, 87, 111 (1975).

d) 2c: $[\alpha]_D^{27} -13.3^\circ$ (MeOH), 2d: $[\alpha]_D^{27} -11.7^\circ$ (MeOH), W. Gaffield and W. G. Galetto, *Tetrahedron*, 27, 915 (1971).

e) 2e: $[\alpha]_D^{27} -24.4^\circ$ (c 5, MeOH), T. Polonski, *Tetrahedron*, 31, 347 (1975).

f) The diastereomeric composition of 1c-e suggested that the optical purities of the obtained acids 2c-e were lower than the calculated values.

g) The diastereomeric composition was measured by ¹H NMR.

h) The diastereomeric composition was measured by GLC.

and 2e in the optical yields of 3.2%, 0%, and 2.1% respectively. These results indicated that under these conditions, the contribution of kinetic resolution was small to the disagreement between the calculated optical purities and the diastereomeric composition. The disagreement, therefore, considered to be mainly due to the insufficient optical purities of the compared data.

Although the true optical purities of 2c-e obtained after the transformation must be lower than the calculated values, the optical purities of 2a-e were appreciably improved compared with those of 2a-e obtained before the transformation.

Fig. 1.

Mutarotation of $\underline{1d}$ (0.1 M) in 2 M KOH-MeOH at 25°C.

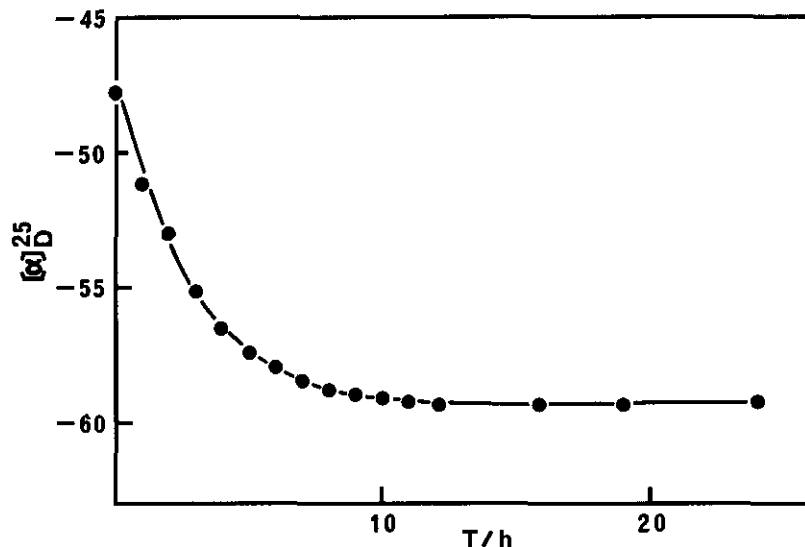


Table 2. Hydrolysis of $\underline{1d}$ before and after the equilibrium

Mutarotation $\frac{T}{h}$	$[\alpha]_D^{25}$ (MeOH) (°)	O.p. a) %	Conf.
0	+7.63 (c 5.14)	65.2	(R)
24	-0.87 (c 5.07)	7.4	(S)

a) Optical purities were based upon the highest rotation values available (see Table 1).

To examine whether this asymmetric transformation was governed by thermodynamic or kinetic control, the mutarotation of $\underline{1d}$ was measured. The lithio carbanion of $\underline{1d}$ was prepared and quenched with water as described above. The product was purified with silica-gel chromatography to give an epimerized oxazoline derivative.

An alkaline solution (2 M KOH-MeOH)

of the epimerized $\underline{1d}$ (0.1 M) was prepared and kept at 25°C. An aliquot of the solution was used for the measurement of the mutarotation (Fig. 1). The optical rotation did not change after 12 h indicating that the epimerization attained equilibrium under the conditions. Two samples of $\underline{1d}$, which were taken from the alkaline solution at 0 and 24 h, were hydrolyzed (1 M HCl, 80°C, 1.5 h) to give $\underline{2d}$. Specific optical rotations of $\underline{2d}$ at 0 and 24 h were shown in Table 2. Under this epimerization condition, asymmetric induction governed by thermodynamic control was small. These facts indicate that the transformation was governed by

kinetic control.

In this asymmetric transformation, using a simple chiral auxiliary (S)-phenylalaninol, 2-chloroalkanoic acids were obtained in fairly high optical purities compared with the asymmetric syntheses.²⁾ These facts showed the versatility of the asymmetric transformation for the syntheses of chiral 2-substituted carboxylic acids. Elucidation of the detailed mechanism of this transformation is now in progress.

References and note

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