ASYMMETRIC TRANSFORMATION OF 2-CHLOROALKANOIC ACIDS *via* OXAZOLINE DERIVATIVES

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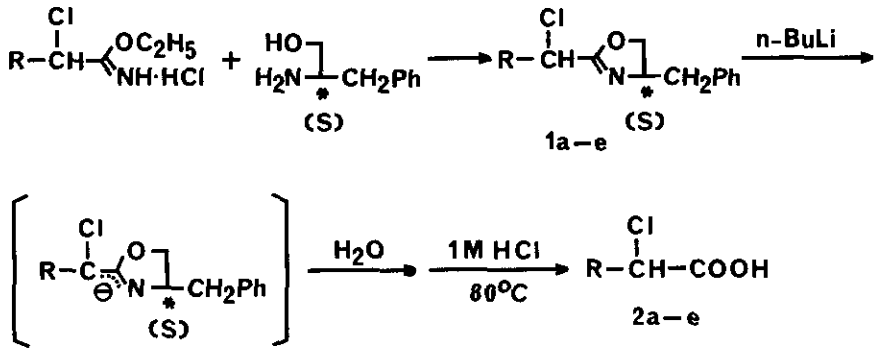
Abstract --- Asymmetric transformation of 2-chloroalkanoic acids *via* oxazoline derivatives were examined using (S)-phenylalaninol as a chiral auxiliary. After the transformation optical purities of the acids were appreciably improved compared with those of the acids obtained before the transformation.

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)-phenylalaninol[3] and the ethyl imidate hydrochlorides, which were prepared from 2-chloroalkyl cyanides[4] (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 CH_2Cl_2, 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

Scheme 1



R= a:CH_3–, b:C_2H_5–, c:n-C_3H_7–, d:n-C_4H_9–, e:i-C_4H_9–

the ring (8.35 g, 74.8%): bp 124-126°C/1.5 mmHg; $[\alpha]_D^{25}$ -70.7° (c 1.04, MeOH); IR (neat) 1665 cm^{-1} (C=N); Found: m/e 223.0771. Calcd for $C_{12}H_{14}NOCl$: M, 223.0765.

1a-e were prepared as described above and used for the following asymmetric transformation (Scheme 1). For example, 671 mg (3 mmol) of 1a was dissolved in 3 ml of dry THF and the solution was cooled to -78°C under Ar. To the solution 3.6 mmol of 1 M n-BuLi was added dropwise, and the mixture was stirred at -78°C. After 45 min, 3 ml of 25% aq.THF was added to the mixture and the oxazoline derivative was extracted with ether. The derivative was hydrolyzed (1 M HCl, 80°C, 1.5 h), and the product was distilled (bulb to bulb) to give 237 mg (72.7%) of 2-chloropropionic acid (2a): $[\alpha]_D^{25}$ +7.77° (c 5.12, MeOH). This acid was identified by it's IR, MS, and NMR spectra. The results of the hydrolysis of 1a-e before and after the asymmetric transformation are summarized in Table 1.

The diastereomeric composition of 1a-e after the transformation was measured by ^1H NMR or GLC (OV-101 0.27ϕ×50 m), and the results were listed in Table 1. Although the optical purities of 2a and 2b corresponded to the diastereomeric composition, the calculated optical purities of 2c-e disagreed with the composition of 1c-e. From the diastereomeric composition of 1c-e, the optical purities of 2c-e were expected to be about 50%, but the calculated optical purities of 2c-e were higher than those expected. In the hydrolysis of 1e, there seemed to be a possibility that some kinetic resolution was occurring. However, before the transformation, hydrolyses of 1c (1.5 h), 1d (4.5 h), and 1e (6 h) gave 2c, 2d,

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.				
	T / h	Yield / %	$[\alpha]_D^{25}$[a] / (°)	O.p.[b] / %	Conf.	Yield / %	$[\alpha]_D^{25}$[a] / (°)	O.p.[b] / %	Conf.	Diaster. comp.
1a	1.5	94	+0.13	0.8[c]	(R)	73	+7.77	44.9[c]	(R)	71:29[g]
1b	1.5	82	+0.33	2.6[c]	(R)	72	+6.56	51.7[c]	(R)	75:25[g]
1c	1.5	86	+0.43	3.2[d,f]	(R)	71	+9.85	74.1[d,f]	(R)	77:23[h]
1d	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)	
1e	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° (MeOH), 2b: $[\alpha]_D^{23}$ +12.7° (MeOH), H. Hashimoto and H. Simon, Angew. Chem., 87, 111 (1975).

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

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

f) The diastereomeric conposition 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 ^{1}H 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 obatained before the transformation.

Fig. 1. Mutarotation of 1d (0.1 M) in 2 M KOH-MeOH at 25°C.

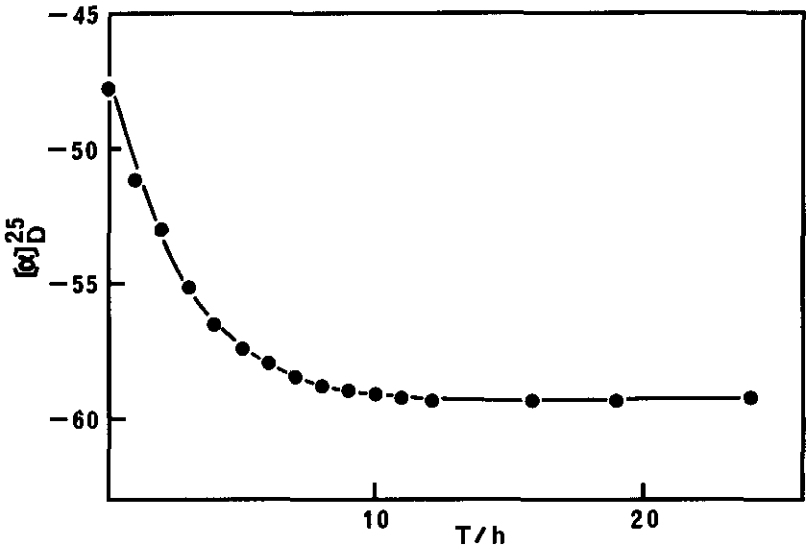


Table 2. Hydrolysis of 1d before and after the equilibrium

Mutarotation 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 1d was measured. The lithio carbanion of 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 1d (0.1 M) was prepared and kept at 25°C. An aliqot 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 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 2d. Specific optical rotations of 2d at 0 and 24 h were shown in Table 2. Under this epierization 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 carboxilic acids. Elucidation of the detailed mechanism of this transformation is now in progress.

References and note

1) S. Shibata, H. Matsushita, H. Kaneko, M. Noguchi, M. Saburi, and S. Yoshikawa, Chem. Lett., 1981, 217.

2) A. I. Meyers, Acc. Chem. Res., 11, 375 (1978); A. I. Meyers, G. Knaus, and P. M. Kendall, Tetrahedron Lett., 1974, 3495; They reported asymmetric syntheses of 2a: $[\alpha]_D^{25}$ -0.4° (c 10.5, MeOH), 2b: $[\alpha]_D^{25}$ -1.04° (c 10.6, MeOH), and 2d: $[\alpha]_D^{25}$ -3.30° (c 10.9, MeOH).

3) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, Chem. Pharm. Bull., 13, 995 (1965).

4) S. M. McElvain and J. W. Nelson, J. Am. Chem. Soc., 64, 1825 (1942).

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