CHEMISTRY LETTERS, pp. 661-664, 1983.

CONVERSION OF RACEMIC CYANOHYDRIN INTO ONE OPTICALLY ACTIVE ISOMER IN THE PRESENCE OF BRUCINE

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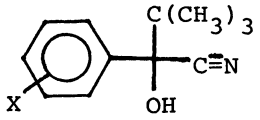
When a solution of a cyanohydrin and brucine in methanol was kept at room temperature, one optically active isomer of the cyanohydrin was obtained as brucine complex in a yield of more than 50%.

In a previous paper, we have reported a novel optical resolution method of tertiary acetylenic alcohols by complexation with brucine.[1] We have postulated by X-ray structural study of the 1:1 brucine complex of 1-(*o*-bromophenyl)-1-phenylpropynol that linearity of acetylenic group is important to form the complex in which the alcohol recognizes the chirality of brucine.[1] By adopting this idea, we succeeded in obtaining optically active cyanohydrins easily. Linear cyano group would play the similar role as acetylenic group in the formation of brucine complex of the cyanohydrin. Surprisingly, it was also disclosed that racemic cyanohydrins are converted into one optically active isomer in the yields of more than 50% in the presence of brucine. This is not a simple optical resolution method but a novel preparative method of optically active cyanohydrins.

When a solution of *dl*-1-cyano-2,2-dimethyl-1-phenylpropanol (1a, 1.0 g, 5.3 mmol) and brucine (2.1 g, 5.3 mmol) in MeOH (2 ml) was kept in a capped flask for 12 h, 1:1 brucine complex of *d*-1a (2.08 g, 67%, mp 112-114 °C) separated out as colorless prisms. Decomposition of the complex with dil HCl gave 97%ee[2] *d*-1a (0.67 g, 67%, $[\alpha]_D$ +15.5°[2]). From the filtrate, *dl*-1a (0.33 g, 33%) was obtained. Yield of *d*-1a of more than 50% shows a conversion of *l*-1a to *d*-1a through racemization during the complexation. If so, one can get 100%ee cyanohydrin in 100% yield by continuing the complexation until the conversion is completed. However, when the above complexation experiment was carried out for 24 h, 96%ee *d*-1a was



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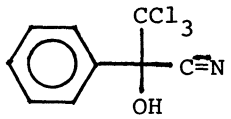
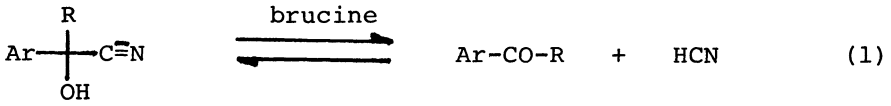


2

a : X=H d : X=*p*-OH

b : X=*p*-Cl e : X=*m*-OH

c : X=*p*-CH_3



(1)

obtained in 69% yield. Nonetheless, the yield increased up to 100% by leaving the MeOH solution to evaporate gradually during the complexation. For example, when a solution of *dl*-1a (1.0 g) and brucine (2.1 g) in MeOH (2 ml) was kept in an uncapped flask at room temperature for 1, 3, 6, 12, and 24 h, amount of solvent decreased to 1.9, 1.8, 1.6, 1.3, and 0.6 ml (weighing method), respectively, and the yield of *d*-1a increased up to 100%. The yield and %ee of *d*-1a obtained by these complexations are shown in Fig. 1. When the complexation of the 94%ee *d*-1a (1.0 g) obtained by the 24 h experiment in Fig. 1 with brucine (2.1 g) in MeOH (2 ml) was repeated one more time in an uncapped flask for 24 h, 100%ee *d*-1a (1.0 g, 100% $[\alpha]_D$ +15.9°) was obtained.

By the similar 24 h complexation experiment as shown in Fig. 1, 100%ee *d*-1b ($[\alpha]_D$ +5.5°) and 52%ee *l*-1c ($[\alpha]_D$ -2.6°) were obtained in 89 and 98% yield, respectively. When two more complexations were repeated for the 52%ee *l*-1c, 100%ee *l*-1c ($[\alpha]_D$ -5.0°) was obtained in 48% yield. Similarly, *l*-1d ($[\alpha]_D$ -7.3°, 66%) and *l*-1e ($[\alpha]_D$ -13.0°, 67%) were finally obtained by repeating the 24 h complexation two and three times, respectively. Optical purity of these two compounds was not determined because their acetates could not be prepared.[2] However, these are probably 100% optically pure, since $[\alpha]_D$ values did not change by further complexation. This resolution method, however, was not applicable to the cyanohydrin derived from alkyl aryl ketones of smaller alkyl than t-butyl. For example, the cyanohydrin prepared

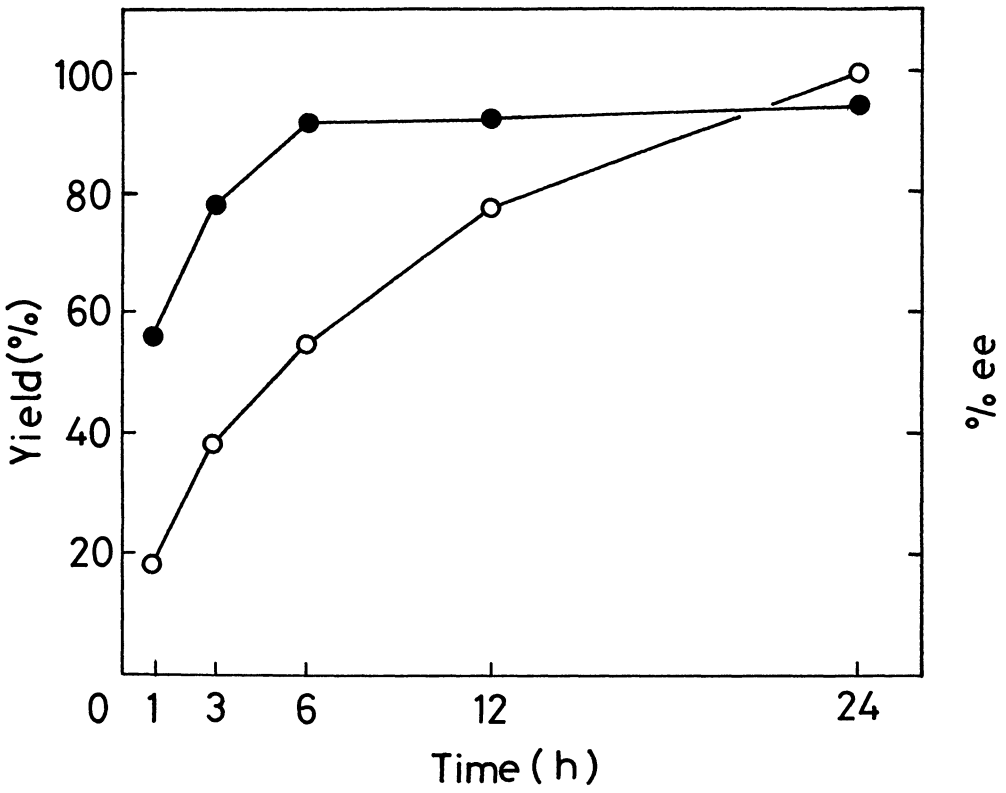


Fig. 1. Yield (%, O) and optical purity (%ee, ●) of the optically active cyanohydrin (*d*-1a) obtained by complexation with brucine in MeOH.

from acetophenone, propiophenone, and butyrophenone did not form the complex with brucine.

Optically active cyanohydrins are useful starting material to prepare various chiral compounds. As far as we know, only one successful example of optical resolution of a cyanohydrin, 1-cyano-1-(*m*-phenoxyphenyl)methanol, by a classical diastereomeric method has been reported.[3] Therefore, our simple preparative method of optically active cyanohydrins would be useful. The process of the complete conversion of racemic cyanohydrin to one optically active isomer consists of racemization of cycnohydrin through equilibrium (Eq. 1) and selective inclusion of one enantiomer in brucine. The enantiomer which is selectively included forms more stable brucine complex than that of the other enantiomer. The stable complex crystallizes out and the less stable complex is more soluble in solvent and dissociates to brucine and cyanohydrin, and the latter racemizes. By repeating the process, racemic cyanohydrin is completely converted to one enantiomer. Conversion of racemic 2-(*p*-carboxybenzyl)-2,3-dihydroindenone to its *d*-enantiomer by similar process in a yield of more than 90% has been reported.[4]

It is interesting that cyanohydrins are stabilized by including in brucine. Such a stabilization is well shown in the following result. Although a cyanohydrin having electron-withdrawing groups such as 2,2,2-trichloro-1-cyano-1-phenylethanol (2) is very sensitive to base, brucine can be used to resolve 2. When a solution of 2 (3.5 g, 14 mmol) and brucine (5.5 g, 14 mmol) in MeOH (30 ml) was kept in a capped flask at 5 °C for 12 h, 1:1 brucine complex of *d*-2 (3.78 g, 42%, mp 81-82 °C) was obtained as colorless needles. Decomposition of the complex with dil HCl gave 100%ee *d*-2 (1.46 g, 42%, $[\alpha]_D$ +8.1°). From the MeOH solution, however, decomposed product phenyl trichloromethyl ketone (1.8 g, 58%) was obtained. When the complexation was carried out at room temperature, 2 completely decomposed to the ketone.

Possibility of the production of optically active cyanohydrin by brucine-assisted stereoselective addition of HCN to the ketone which is formed by the equilibrium of Eq. 1, would be neglected by the following reason. Bubbling of HCN to a solution of t-butyl phenyl ketone (3.0 g) and brucine (7.3 g) in MeOH (30 ml) for 1 min at room temperature gave *dl*-1a (3.5 g, 100%). There may be little possibility of racemization during such a short period even if the optically active 1a is initially formed by stereoselective reaction. For instance, 94%ee *d*-1a (1.0 g) was recovered unchanged after treating with brucine (2.1 g) in MeOH (30 ml) for 5 min at room temperature.

References

1) F. Toda, K. Tanaka, and H. Ueda, Tetrahedron Lett., 22, 4669 (1981).

2) All the $[\alpha]_D$ values were measured in MeOH (*c* 0.01) with a 1-dm cell at 25 °C. Enantiomeric excess (ee) of 1 and 2 was determined by NMR analysis of their acetates in $CDCl_3$ with using the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III), $Eu(hfc)_3$ (Aldrich, 99+%)

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4) H. Leuchs, Ber., 54, 830 (1921).

(Received February 17, 1983)