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Stereorecognition Enhancement by the Sulfur Functional Group in the Lipase Hydrolysis. An Efficient Synthesis of the Optically Active β-Hydroxy Nitriles

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β-phenylthio and β-methylthioacetoxy nitriles have been found to be good substrates for the kinetic resolution by lipase to give optically active β-hydroxy nitriles with high enantioselectivity.

Optically active β-hydroxy nitriles are expected to be useful chiral building blocks for asymmetric synthesis, because cyano groups are precursors of amino and carbonyl groups. It is, therefore, desired to establish a simple method to supply chiral β-hydroxy nitrile derivatives that have certain elementary skeletons. However, there are very few reports on the preparation of chiral β-hydroxy nitriles.[1,2]

We studied a convenient preparation of those compounds in optically pure state on the lipase catalyzed resolution. Since lipases have been successfully used for the kinetic resolution of various functionalized alcohols,[3] several kinds of commercially available lipases have been screened using 3-valeroyloxybutyronitrile as a substrate. However, it has been found that all of the tested lipases have no capability to resolve the nitrile with high enantioselectivity.[4] The highest E value of the resolution [5] was about 6 and the optical purity of 3-hydroxybutyronitrile produced by lipase hydrolysis at about 40 % conversion was only 35% ee using the lipase P (Pseudomonas fluorescence). The fact that the enantioselectivity depends on the structure of the acid component of the ester [6] envisioned us to survey the ester which has a good specificity to the lipase.

We now wish to report here that phenylthioacetoxy and methylthioacetoxy groups are just desired acid components to enhance the enantioselectivity of lipase P. In contrast to the above mentioned results of the resolution of 3-valeroyloxynitrile as a substrate, the enantioselectivity of the lipase hydrolysis improved dramatically when 3-methylthioacetoxy- and 3-phenylthioacetoxy nitriles 1 were subjected to the resolution. As shown in Table 1, all of the E value of the resolution suffice for the use of this reaction in organic synthesis practically.

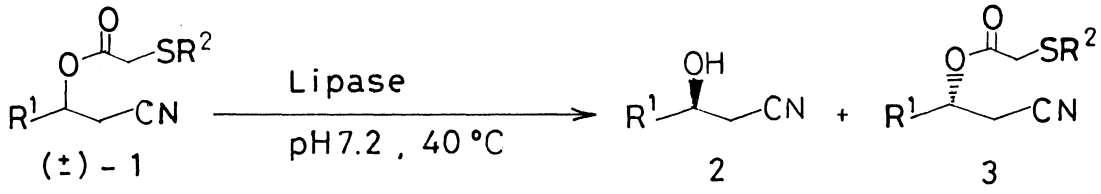

Table 1. Kinetic Resolution of Ester 1 by Lipase Hydrolysis

Entry	R^1	R^2	Alcohol 2 ee(conv.%)	MeO of MTPA ester L : H (Config.)[a]	$[\alpha]_D$ [b]	Ester 3 ee(conv.%)	E [5]
1	CH_3	CH_3	84%ee(44)	92.0 : 8.0 (R)[c]	+4.1°	>98%ee(64)	29<6>[d]
2	CH_3	n-C_4H_9	66%ee(56)	83.0 : 17.0(R)[c]	+3.7°	------	16
3	Ph	CH_3	81%ee(35)	9.6 : 90.4(R)	+53.5°	>98%ee(75)	18<8>[d]
4	Ph	Ph	94%ee(41)	3.0 : 97.0(R)	+68.2°	>98%ee(63)	74
5	$PhCH_2CH_2$-	Ph	88%ee(46)	6.0 : 94.0(S)	-23.4°	>98%ee(68)	36<1>[d],<5>[e]
6	PhCH=CH-	Ph	91%ee(40)	4.3 : 95.7(R)	+10.8°	>98%ee(60)	55<6>[d],<12>[e]

a) The absolute configuration assignment is tentative. Based on the result of ^{1}H-NMR analysis of 84% ee of (3R)-3-hydroxybutyronitrile, the configuration was presumed from the diastereomeric differences in chemical shifts made by the methoxy group in (+)-MTPA esters.[7] "L" means low field peak, "H" means high field peak. b) All specific rotations were measured in EtOH (c ca. 1.) at 23 °C. c) Determined by the specific rotation. The alcohol 2 (Entry 1, 84%ee),$[\alpha]^{25}_D$-89.3° (c 2.30,H_2O), Lit., -10.08° (R).[1] d) Results from valeroyloxynitriles. e) Results from methylthioacetoxynitriles.

With aromatic substrates (entries 3-6), the reaction of phenylthioacetoxyester afforded alcohols produced with higher optical purity than that of alcohols converted from the methylthioacetoxy nitriles. It may presumed us to the idea that phenylthioacetoxy group is suitable for nitriles which involve aromatic substituent in the molecule. A typical procedure of the present resolution is described as follows: A solution of nitrile 1 (R^1= CH_3, R^2= CH_3, 100 mg, 0.577 mmol) in 0.1 M phosphate buffer (pH 7.2, 3.0 ml) and acetone (0.1 ml) was incubated with lipase P (50 mg) at 40 °C for 3 h. The mixture was extracted with ethyl acetate and separated by silica-gel TLC after determination of the hydrolysis ratio (44% conv.) by ^{1}H-NMR. The optical purities of the alcohol 2 produced (39% yield) and the residual ester 3 (50% yield), the latter of which was converted into the alcohol by lithium aluminum reduction in quantitative yield, were determined as 84% ee and 81% ee by the 200 MHz ^{1}H-NMR analysis of the (+)-MTPA esters respectively.

Considering the broad substrate specificity of the lipase, the present method to improve the enantioselectivity by changing the ester group is expected to provide a versatile and efficient method for the preparation of optically active alcohol derivatives under mild condition. Further experiments to determine the scope and limitation of this useful method are now in progress.

References

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