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Lipase-catalyzed hydrolysis of methyl-3-phenylglycidate

Guo Jun ZHENG, Jian Jun WANG, Tian Rui REN[1], Liu YANG
Wan Ru SUN*

State Key Laboratory of Microbial Resources, Institute of Microbiology, CAS, Beijing, 100080
[1]Laboratory of Chemistry Computer, Institute of Chemical Metallurgy, CAS, Beijing, 100080

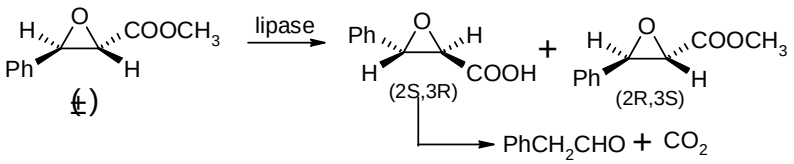
Abstract: The enzymatic resolution of racemic methyl 3-phenylglycidate was investigated. It was found that the hydrolysis rate of (2S, 3R)-enantiomer was faster than that of (2R, 3S)-enantiomer by a new lipase. At optimal condition 96% of (2R, 3S)-methyl phenylglycidate with ee of 100% was recovered from the racemic mixture.

Keywords: Lipase, methyl 3-phenylglycidate, resolution, chirality.

Large amount of facts indicated that enantiomers were different from each other in biological activity, physiological activity and toxicity in clinical applications[1]. It resulted in the increase of interest on preparation of chiral drugs. Optical active 3-phenylglycidic ester, especially (2R,3S)-methyl 3-phenylglycidate is an important starting material for production of many chiral drugs, such as taxol, (2R,3S)-diltiazem *etc*[2,3].

For the above purpose, a series of lipases were screened. Finally we have isolated a new lipase from a soil example. It enantioselectively catalyzes the hydrolysis of methyl 3-phenylglycidate to (2S,3R)-3-phenylglycidic acid which is unstable and decomposes to phenylacetaldehyde. (2R,3S)-3-Methyl phenylglycidate is left behind and can be recovered easily. Here we wish to described the optimal condition of this enzymatic resolution for preparing (2R,3S)-3-methyl phenylglycidate from racemic mixture (**Figure 1**).

Figure 1 Enzymatic resolution of methyl-3-phenylglycidate



The resolution reaction in 0.2 mol/L phosphate buffer at various pH was studied to find the optimal pH. At pH 6.0, 96% of (2R,3S)-3-methylphenylglycidate in the

mixture can be obtained with ee of 100%. Both the ee value and the recovery rate decreased with increase of reaction pH in the range of 6.0~7.5. While pH above 7.5, ee value and yield fell down to 0. But when the phosphate buffer was replaced by borate buffer, ee value (95%) and recovery rate (84%) remained in high level at pH 7.5. It showed that enantioselectivity and conversion of enzymatic reaction is not only affected by pH of reaction system and also by the kind of buffer. Since the substrate and product are insoluble in water, addition of organic solvent was tested. Diisopropyl ether was the only one which can decrease the reaction time with no effect on the yield and ee value at pH 6.0.

Table 1 Effect of pH value and buffer on ee and yield

PH	Ee (%)*	Yield (%)**
6.0	100	48
6.5	95.4	47
7.0	94.9	44
7.5(phosphate buffer)	0	0
7.5(borate buffer)	95	42
8.0	0	0

*determined by chiral GC (G-TA type)
**wt of 2R3Sisomer obtained/wt of the racemic mixture

Procedure: To 5 mL of phosphate buffer (pH = 6.0), 5 mg lipase and 50 mg ester were added. The reaction system was shacked for 24 hrs. Then the aqueous phase was extracted 3 times with ethyl acetate. The organic extract were combined and dried over anhydrous sodium sulfate. After taking off the solvent , the product was obtained as a colorless oil.

The Products obtained were analized by GC. The optical purity was determined by GC (G-TA type) chiral column using methyl cinnamate as internal standard; column length 10 m; nitrogen as carrier gas; fluid rate 2.5 ml/min; sample conc.2μ g/ml; oven temperature 105°C; temperature of the injection chamber 160°C and detector temperature 200°C. The retention time for the standard (2R3S) methyl glycidate is 8.722 min, and 9.461 min for its enantiomer 2R3S. All the samples were analyzed according to above specific condition.

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