Pergamon

Tetrahedron Letters, Vol. 35, No. 25, pp. 4375-4376, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0786-W

Enantioselective Microbial Oxidation of 1-Arylethanol in an Organic Solvent

Kaoru Nakamura,* Yuko Inoue, and Atsuyoshi Ohno,

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

Abstract: Reactivity in enantioselective oxidation of 1-arylethanol by *Geotrichum candidum* is improved when the microbe is entrapped with a water-adsorbent polymer and the reaction is conducted in hexane. Cyclohexanone as an additive improves the rate of oxidation as well as ee of the remained alcohol.

Application of enzymatic systems to asymmetric syntheses has widely been developed in the last decade. However, the use of biological systems has been limited to two systems; microbial reductions and lipase-catalyzed transesterifications. Microbial reduction represented by that with bakers' yeast has widely been used for the syntheses of chiral alcohols.[1,2] On the other hand, microbial oxidations have not been considered to be an useful tool for organic synthesis mainly because of difficulty in microbial oxidation in comparison to reduction; bakers' yeast has long been believed to have little activity for oxidation of alcohol.[2] Recently, Fantin *et al.* reported that 1-phenylethanol is oxidized by bakers' yeast, although the oxidation requires long time. Efficiency of enantioselective oxidation was unsatisfacatory[3] and they had to look for microbes in order to obtain satisfactory results.[4] Since a dehydrogenase usually catalyzes both reduction of a ketone and oxidation of an alcohol, certain methodology to enhance the activity for oxidation relative to reduction may change the direction of microbial reaction toward oxidation. In the present paper, we would like to report a novel method for microbial enantioselective oxidation of racemic alcohols. The reaction affords satisfactory result when hexane is used as a solvent with a partnership of cyclohexanone.

When racemic 1-phenylethanol (rac-**1a**) was reacted with *Geotrichum candidum* IFO 4597 in water for 24 h, the alcohol was oxidized to give a mixture of the alcohol (88 %) and the corresponding ketone (**2a**, 12 %). Absolute configuration and ee of the remaining **1a** were determined to be *R* and 17 %, respectively. The result reveals that kinetic resolution proceeds and the microbe oxidizes (*S*)-**1a** selectively. The value of ee, however, was not satisfactory and was hardly improved by prolonged reaction times. On the contrary, when the microbe was immobilized with a water-adsorbent polymer and the reaction was conducted in hexane,[5,6] the oxidation proceeded more rapidly than that in an aqueous system and (*R*)-**1a** of 86 % ee was obtained after 24 h. The use of immobilized microbe in an organic solvent, thus, enhances the rate of oxidation as well as ee of the remained alcohol. However, since stereoselectivity in this system is still unsatisfactory, we have looked for an efficient additive to couple with oxidation of the substrate alcohol and found that cyclohexanone is an excellent reagent for the purpose. Thus, as shown in Table 1, (*R*)-**1a** of 99 % ee was obtained in 50 % chemical yield. Another substrate, racemic 1-(2-furyl)ethanol (rac-**1b**), was also oxidized

smoothly by the aid of the same method to give (*R*)-**1b** of 96 % ee in 49 % chemical yield.

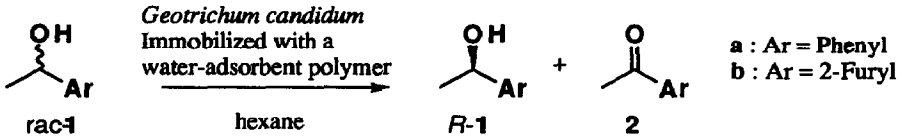

Table 1. Oxidation of 1-Arylethanol by *Geotrichum candidum*

Entry	Substrate[a]	Solvent[b]	Immobilization[c]	Cyclohexanone[d]	2 : 1	% Ee of 1	(Config.)
1	rac-**1a**	water	-	-	12 : 88	17	(*R*)
2	rac-**1a**	hexane	-	-	29 : 71	43	(*R*)
3	rac-**1a**	hexane	+	-	48 : 52	86	(*R*)
4	rac-**1a**	water	-	+	44 : 56	89	(*R*)
5	rac-**1a**	hexane	-	+	48 : 52	95	(*R*)
6	rac-**1a**	hexane	+	+	50[e] : 50[e]	99	(*R*)
7	rac-**1b**	water	-	-	11 : 89	23	(*R*)
8	rac-**1b**	hexane	+	+	50 : 50[f]	96	(*R*)

[a] 0.08 mmol. [b] [water] = 3 ml, [hexane] = 6 ml. [c] 0.5 g of BL-100 (Osaka Yuki Kagaku Kogyo Co., Ltd.). [d] 0.2 mmol. [e] Yield of **1a** = 50 %, Yield of **2a** = 50 %. [f] Yield of **1b** = 49 % (Undecane was used as GC standard).

In a typical experiment, a solution of **1** (0.08 mmol) and cyclohexanone (0.2 mmol) in 6 ml of hexane was added to the immobilized microbe (0.5 g of the water-adsorbent polymer (BL-100)[5,6] to 3 ml of microbial suspension) and the resulting suspension was shaken (100 stroke /min) at 30 °C for 24 h. Dodecane (internal standard for GC) was added and the reaction mixture was filtered. The biocatalyst was washed with ether and the filtrates were combined. Chemical yields (**1a** = 50 %, **2a** = 50 %) and ee of (*R*)-**1a** were measured using a chiral GC-column (G-TA, 0.25 mm x 30 m, 100 °C, He, 2 ml/min).

Although mechanism for the rate enhancement accompanying the improvement of ee of the remaining alcohol by an immobilized system in an organic solvent is not clear at present, it is plausible that reduction of the corresponding ketone to the (*S*)-alcohol is retarded in organic media. Further studies including isolation of enzymes are under investigation in our laboratory.

References

1 Servi, S., *Synthesis*, **1990**, 1-25.

2 Csuk, R.; Glänzer, B. I., *Chem. Rev.*, **1991**, *91*, 49-97.

3. Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Poli, S., Sinigaglia, M. *Tetrahedron Lett.*, **1993**, *34*, 883-884.

4. Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Poli, S., Gardini, F. *Tetrahedron : Asymm.*, **1993**, *4*, 1607-1612.

5. Nakamura, K.; Takano, S.; Terada, K.; Ohno, A. *Chemistry Lett.*, **1992**, 951-954.

6. Nakamura, K.; Takano, S.; Ohno, A. *Tetrahedron Lett.*, **1993**, *34*, 6087-6090.

(*Received in Japan* 9 *February* 1994; *accepted* 11 *April* 1994)