ENZYMATIC SYNTHESIS OF OPTICALLY ACTIVE α-HYDROXYBENZYLPYRIDINES

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Abstract —— Synthesis of optically active α-hydroxybenzylpyridines by asymmetric reduction of benzoylpyridines and benzoylpyridine *N*-oxides with baker's yeast, and enantioselective esterification of racemic α-hydroxybenzylpyridines by use of lipase PS have been described.

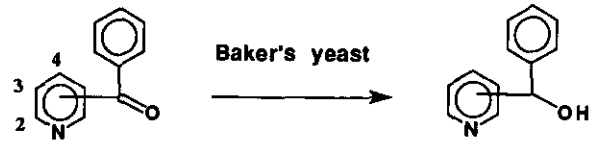
In the previous papers, we have reported the synthesis of chiral pyridylethanols by asymmetric reduction of acetylpyridines[1] and chemoselective asymmetric reduction of acetylpyridine *N*-oxides with baker's yeast.[2] In these reactions, the enzyme activity to acetylpyridines and acetylpyridine *N*-oxides was different, especially as for stereoselectivity.

As the further extention of these works, we investigated the preparation of optically active α-hydroxybenzylpyridines[3] by asymmetric reduction of benzoylpyridines, benzoylpyridine *N*-oxides with baker's yeast.

At first, as shown in Table I, 2-, 3- and 4-benzoylpyridines (**1a-c**) were incubated with baker's yeast at 30°C for 96-106 h to give α-hydroxybenzylpyridines (+)-(**2a**), (-)-(**2b**) and (-)-(**2c**) [3] in high chemical yields (86-89%). In these reactions, 4-benzoylpyridine (**1c**) was reduced enantioselectively to afford alcohol (-)-(**2c**) (86%ee), however, 2- and 3-benzoylpyridines (**1a** and **1b**) were reduced in low optical yields (26 and 36%, respectively).

Dedicated to Professor E. C. Taylor on the occasion of his 70th birthday.

Table I. Asymmetric Reduction of Benzoylpyridines (1a-c) with Baker's Yeast



1 2

a) 2, b) 3, c) 4

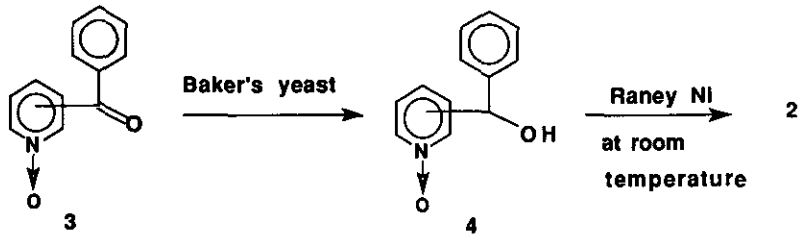
1	2	h	Temp. (°C)	Yield of 2(%)	$[\alpha]_D$ in $CHCl_3$	%ee [a]	Config.
1a	(+)-2a	106	30	86	+26.5° (c 6.3)	26	
1b	(-)-2b	96	30	89	-4.3° (c 5.1)	36	
1c	(-)-2c	106	30	86	-63.6° (c 3.8)	86	(S) [b]

a) By hplc analysis (Chiralcel OD (DAICEL), hexane:2-propanol =95:5). b) See ref. 4.

Next, we tried the asymmetric reduction of benzoylpyridine *N*-oxides (**3a-c**)[1b,5] with baker's yeast. When 2- and 4-benzoylpyridine *N*-oxides (**3a** and **3c**) were incubated with baker's yeast at 30 and 33° C for 72 and 73 h, chemoselective reductions[2] proceeded to give α-hydroxybenzylpyridine *N*-oxides (**4a** and **4c**)[6] in 42 and 79% chemical yields, which were converted by reduction with Raney Ni to the corresponding α-hydroxybenzylpyridines (**2a** and **2c**) of 66 and 90%ee , respectively. On the other hand, in the same reaction of 3-benzoylpyridine *N*-oxide (**3b**), reduction showed no enantioselectivity (Table II).

Finally, we examined the asymmetric esterification of racemic α-hydroxybenzylpyridines ((±)-**2**) by use of lipase PS (Amano).[7] When compounds ((±)-**2**) were treated with vinyl acetate in *t*-butyl methyl

Table II. Asymmetric Reduction of Benzoylpyridine N-Oxides (3a-c) with Baker's Yeast



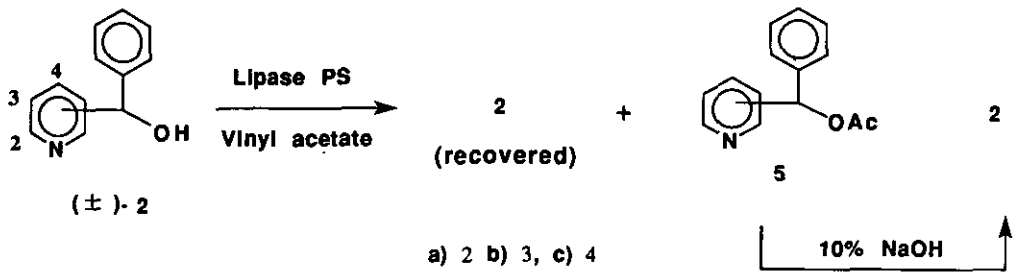
a) 2, b) 3, c) 4

3 → 4						4 → 2					
3	h	Temp. (°C)	4	Yield of 4(%)	$[\alpha]_D$ in MeOH	h	2	Yield of 2(%)	$[\alpha]_D$ in $CHCl_3$	%ee [a]	Config.
3a	73	30	(-)-4a	42	-2.0° (c 1.5)	84	(+)-2a	93	+81.6° (c 6.1)	66	
3b	86	30	4b	89	0.0°	86	(-)-2b	87	0.0	0	
3c	72	33	(-)-4c	79	-76.7° (c 2.0)	48	(-)-2c	68	-66.5° (c 1.0)	90	(S) [b]

a) By hplc analysis (Chiralcel OD (DAICEL), hexane:2-propanol=95:5) b) See ref. 4.

ether in the presence of lipase PS for 4-9 days (esterification % : < 50%), the optically active acetates (5) were isolated, and hydrolysis of the acetates (**5**) with 10% NaOH gave the corresponding chiral α-hydroxybenzylpyridines (**(-)-2a**, **(+)-2b** and **(+)-2c**). In this enantioselective esterifications, the optical yield of 2-isomer (**(-)-2a**) was 57% ee, however, those of the other two isomers (**(+)-2b** and **(+)-2c**) were low (24 and 12% ee). On the contrary, when the above reaction mixtures were treated with for 6-7days (esterification % : > 50 %), 4-isomer (**(-)-2c**) was obtained in 67% ee, but 3-isomer (**(-)-2b**) was low (25% ee) (Table III).

Table III. Enantioselective Esterification of α-Hydroxybenzylpyridines((±)- 2) with Lipase PS



(±)- 2	Time (Temp.) (° C)	a) Esterification(%)	2 (recovered)	Yield of 2 (%)	$[\alpha]_D$ of 2 in $CHCl_3$	5	Yield of 5 (%)	$[\alpha]_D$ of 5 in $CHCl_3$	2 from 5	$[\alpha]_D$ of 2 in $CHCl_3$	b) %ee (config.)
2a	9days at 30°	36				(-)-5a	31	-24.0° (c 1.9)	(-)-2a	-78.0° (c 1.2)	57
2b	6days at 30°	32				(+)-5b	39	+1.2° (c 2.4)	(+)-2b	+4.5° (c 1.2)	24
	8days at 33°	54	(-)-2b	37	-3.8° (c 2.3)						25
2c	90h at 30°	41				(+)-5c	38	+21.8° (c 2.0)	(+)-2c	+16.3° (c 1.6)	12
	6days at 30°	60	(-)-2c	31	-39.3° (c 1.1)						c) 67 (s)

a) Monitored by nmr spectra (60 MHz). b) By hplc analysis (Chiralcel OD (DAICEL), hexane : 2-propanol= 95 : 5). c) See Table I, II and ref. 4.

Thus, it was found that the reduction of 4-benzoylpyridine (**1c**) and 4-benzoylpyridine *N*-oxide (**3c**) with baker's yeast proceeded enantioselectively to give 4-(α-hydroxybenzyl)pyridine (**(+)-2c**) and its oxide (**(-)-4c**), respectively in high optical yields.

EXPERIMENTAL

Typical experiments are as follows:

Reduction of 4-benzoylpyridine (1c) with baker's yeast.

A mixture of 4-benzoylpyridine (**1c**) (1 g) and baker's yeast (500 g)(purchased from Oriental Yeast Co.) in water (250 ml) was fermented for 106 h at 30° C. The mixuture was extracted continuously with

$CHCl_3$ using a Soxlet apparatus and the extract was dried over Na_2SO_4. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (30 g) column chromatography usig CH_2Cl_2 : MeOH (99 : 1) as eluent to yield **2c** (0.85 g, 86%).[3,4] The optical yield was calculated by hplc analysis using Chiralcel OD (purchased from DAICEL), eluent: n-hexane: 2-propanol= 95 : 5 (see Table I).

Reduction of 4-benzoylpyridine *N*-oxide (3c) with baker's yeast.

A mixture of 4-benzoylpyridine *N*-oxide (**3c**) (1 g) and baker's yeast (500 g)(purchased from Oriental Yeast Co.) in water (250 ml) was fermented for 72 h at 33° C. The mixuture was extracted continuously with $CHCl_3$ using a Soxlet apparatus and the extract was dried over Na_2SO_4. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (25 g) column chromatography usig $CHCl_3$: MeOH (97 : 3) as eluent to yield 4-(α-hydroxybenzoyl)pyridine *N*-oxide (**4c**)(0.78 g, 79%).[6] The optical yield was calculated by hplc analysis using Chiralcel OD (purchased from DAICEL) after conversion into **2**, eluent: n-hexane: 2-propanol= 95 : 5 (see Table II).

Reduction of 4-(α-hydroxybenzoyl)pyridine *N*-oxide(4c) with Raney Ni.

To a suspention of Raney Ni and MeOH(20 ml), 4-(α-hydroxybenzoyl)pyridine *N*-oxide(**4c**)(0.2 g) was added and the mixture was stirred at room temperature. After 48 h, the mixture was filtered using celite, and the solvent was removed under reduced pressure to give the residue which was purified by silica gel (20 g) column chromatography usig CH_2Cl_2 : MeOH (99 : 1) as eluent to yield **(-)-2c** (0.13 g, 90%)(see Table II).

Asymmetric esterification of 4-(α-hydroxybenzyl)pyridine ((±)-2 c) with lipase PS.

To a mixture of 4-(α-hydroxybenzyl)pyridine **((±)-2 c)** (0.5 g), vinyl acetate ((1.5 g) and t-butyl methyl ether (80 ml), lipase PS (0.5 g) was added, and the mixture was stirred at room temperature. Progress of the reaction was monitored by nmr spectra. After 6 days, the reaction mixture was filtered and the solvent was removed under reduced pressure to give the residue which was purified by silica gel (40 g) column chromatography usig CH_2Cl_2 as eluent to yield **(-)-2c** (0.18 g, 31%). The optical yield of **(-)-2c** was calculated by hplc analysis using Chiralcel OD (purchased from DAICEL), eluent: n-hexane : 2-propanol= 95 : 5 (see Table III).

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