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Synthesis of Optically Active α-Phenylpyridylmethanols with Baker's Yeast

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We have synthesized optically active α-phenylpyridylmethanols by using free baker's yeast (FBY) in water, immobilized baker's yeast (IMBY) in water, and IMBY in hexane.

Keywords chiral α-phenylpyridylmethanol; immobilized baker's yeast; microbial reduction; selective reduction; benzoylpyridine

α-Pyridyl alcohols are intermediates of some pharmacological interest,[1-3] and (+)-α-phenyl-2-pyridylmethanol (**2c**) itself has analgetic and anticonvulsant activities.[4] α-Pyridyl alcohols are often synthesized from halogen derivatives or *N*-oxides of pyridine because direct metallation of this heterocycle is deemed impractical.[5-7] Kessar *et al.* have synthesized α-phenyl-2-pyridylmethanol (**2c**) *via* metallation of BF_3-pyridine complex, but optically active alcohol was not obtained from chiral boron compounds.[8] Inouye *et al.* have synthesized (−)-α-phenyl-2-pyridylmethanol (**2c**) by asymmetric reduction with a chiral polymethylene-bridged bis(NADH) model compound.[9]

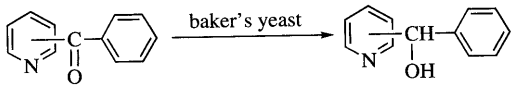
We have investigated the synthesis of optically active α-phenyl-2, 3 or 4-pyridylmethanol (**2a—c**) by fermenting baker's yeast (*Saccharomyces cerevisiae*), which is easily obtainable and cheap. However, while some ketones on reduction with baker's yeast (BY) give alcohols with high stereoselectivity, many others do not. Nakamura *et al.* reported that stereochemical control in the yeast reduction could be achieved by several methods, namely, modification of the substituent in ketones or changing the reaction conditions.[10] Approaches to changing the reaction conditions include immobilization of yeast, and varying the glucose concentration.

Kato *et al.* have reported microbiological asymmetric reduction (using *Rhodosporidium toruloides*) of 2-amino-5-chlorobenzophenone, which was not reduced by BY.[11] Takeshita and his co-workers have reported asymmetric reduction of *p*-nitrobenzophenone[12] and α,β,γ-acetylpyridines[13] with fermenting BY, but few applications of BY to aromatic heterocycles have been reported.[14] In this paper, we wish to report the effect of changing the reaction conditions [immobilization of yeast, concentration of sugar (glucose, saccharose) or solvent (water, organic solvent)] on the stereochemistry in the reduction of 2-, 3-, or 4-benzoylpyridine (**1a—c**) by BY.

These compounds (**1a—c**) were reduced by three methods, that is, with free dry baker's yeast (FBY, Oriental) in water, with immobilized baker's yeast (IMBY) in water, and with IMBY in organic solvent (hexane, CH_2Cl_2, $CHCl_3$, benzene, toluene, ether, diisopropylether, ethanol). IMBY was made by mixing BY with sodium alginate. The resultant polymer was dropped into aqueous calcium chloride and rinsed with water to give IMBY. [BY : sodium alginate = 10 : 1 (w/w), H_2O : IMBY = 8 : 10 (w/w)]. The benzoylpyridines (**1a—c**) were reduced under various incubation conditions (incubation time, yeast : substrate ratio). The yeast : substrate ratio had no influence on the optical yield of α-phenylpyridylmethanol (**2a—c**), but did affect the chemical yield. Finally, the reduction was performed with substrate (1 mmol), dry BY (5 g), glucose (5 g) and water (50 ml), in order to afford high chemical yield and short incubation time. As shown in Table I, the reduction of compounds **1a—c** with BY for 24—144 h at room temperature gave the corresponding (−)-α-phenyl-4-pyridylmethanol [(−)-**2a**],[15] (−)-α-phenyl-3-pyridylmethanol [(−)-**2b**] or (+)-α-phenyl-2-pyridylmethanol [(+)-**2c**][4] in 3—86% chemical and 28—96% optical yields. In the case of IMBY in organic solvent, the reaction proceeded only in hexane among the solvents tested. In the case of the reduction of **1a**, the enantiomeric excess (ee) of the alcohol (−)-**2a** obtained with IMBY in hexane (96% ee) was much higher than those with FBY in water (86% ee) and IMBY in water (84% ee), though the reaction time (72 h) was longer (24 h for FBY in water and 48 h for IMBY in water).

Next, we examined the effect of glucose or saccharose concentration on the reduction of the benzoylpyridines (**1a—c**), as shown in Table II. In the case of the reduction of **1a** (FBY containing glucose), optical yield increased with increasing glucose content between 10 to 20 g, and

TABLE I. Asymmetric Reduction of Benzoylpyridines (**1a—c**) with Baker's Yeast



1a—c **2a—c**

a: 4-, **b**: 3-, **c**: 2-

Substr.	Optical yield[a] chemical yield (%), time, $[\alpha]_D$ (°)[b]		
	FBY in water[c]	IMBY in water[d]	IMBY in hexane[e]
1a	86/78, 24 h, −67.6[15]	84/86, 48 h, −66.0	96/20, 72 h, −75.3
1b	56/77, 120 h, −11.2	45/65, 120 h, −9.0	36/11, 120 h, −7.2
1c	32/62, 114 h, +44.9[4]	28/49, 144 h, +39.3	35/ 3, 144 h, +49.1

a) Optical yields were determined by HPLC analysis. **2a** (Chiralcel OB, 2-propanol/hexane = 2/3); **2b** (Chiralcel OB, 2-propanol/hexane = 2/3); **2c** (Chiralcel OJ, 2-propanol/hexane = 1/30). *b*) In chloroform, *c* = 0.95—1.05. *c*) Reactions were carried out with substrate (1 mmol), FBY (5 g), glucose (5 g) and water (50 ml) at room temperature. *d*) Reactions were carried out with substrate (1 mmol), IMBY (29 g, containing FBY 5 g), glucose (5 g) and water (50 ml) at room temperature. *e*) Reactions were carried out with substrate (1 mmol), IMBY (29 g), and hexane (100 ml) at room temperature.

TABLE II. Effect of Glucose or Saccharose Concentration on the ee of Products **2a**—**c** of the Reduction of Benzoylpyridines **1a**—**c** with FBY in Water or IMBY in Water

Sugar	Conc.[a] (g)	Alcohol			
		2a[b]	**2b**[c]	**2c**[d]	**2a**[e]
		Optical yield[f] (%)/chemical yield (%)			
Glucose	0	88/78	62/77	39/55	90/84
	5	86/78	56/77	32/62	84/86
	10	87/84	52/49	23/54	84/86
	15	90/85	53/52	25/52	84/85
	20	92/85	53/50	24/63	84/87
	25	87/76	53/55	25/63	84/83
	30	86/75	51/53	25/50	84/80
	40	87/75	50/56	22/53	84/82
	50	87/76	50/51	24/52	84/81
Saccharose	0	88/78	62/77	39/55	90/84
	5	87/86	54/65	32/50	84/86
	10	89/83	50/52	30/45	83/84
	15	89/80	50/48	27/48	84/85
	20	86/85	49/50	24/49	84/83
	25	85/78	49/45	20/45	84/82
	30	86/80	47/52	20/50	84/85
	40	85/82	48/51	22/47	83/82
	50	86/76	47/45	20/45	84/70

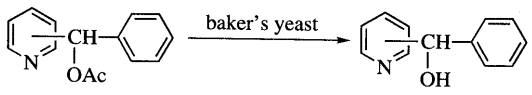
a) g/50 ml water. *b*) Reactions were carried out with 4-benzoylpyridine **1a** (1 mmol), FBY (5 g), glucose or saccharose (0—50 g) and water (50 ml) at room temperature for 24 h. *c*) Reactions were carried out with 3-benzoylpyridine **1b** (1 mmol), FBY (5 g), glucose or saccharose (0—50 g) and water (50 ml) at room temperature for 120 h. *d*) Reactions were carried out with 2-benzoylpyridine **1c** (1 mmol), FBY (5 g), glucose or saccharose (0—50 g) and water (50 ml) at room temperature for 144 h. *e*) Reactions were carried out with 4-benzoylpyridine **1a** (1 mmol), IMBY (29 g, include FBY 5 g), glucose or saccharose (0—50 g) and water (50 ml) at room temperature for 48 h. *f*) Optical yields were determined by HPLC analysis (see Table I).

maximum optical yield (92%) was obtained at the glucose content of 20 g. At glucose contents of 25 to 50 g, optical yield decreased (87%). In the case of FBY containing saccharose, similarly, maximum optical yield (89%) was obtained at the saccharose content of 10 to 15 g. On the whole, in the case of FBY, optical yields with glucose were higher than those with saccharose or starch (85% ee at the starch content of 5 g). In the case of IMBY in water, the reduction of **1a** without glucose or saccharose gave the alcohol (−)-**2a** with high optical yield (90%), but the ee decreased (84%) in the presence of glucose or saccharose (in the range of 5 to 50 g). Further, the reduction of **1b** or **1c** with FBY in water without sugar gave (−)-**2b** (62% ee) or (+)-**2c** (39% ee), and the ee decreased with increasing sugar content.

Secondly, we tried the asymmetric hydrolysis of racemic 4-(α-acetoxybenzyl)pyridine (**3a**),[16] 3-(α-acetoxybenzyl)-pyridine (**3b**) or 2-(α-acetoxybenzyl)pyridine (**3c**)[17] using FBY in water, IMBY in water or IMBY in hexane. As shown in Table III, the hydrolysis of racemic **3a**—**c** with BY for 24—192 h at room temperature gave the corresponding α-phenylpyridylmethanols **2a**—**c** (6—36% chemical and 0—53% optical yields) and recovered acetates **3a**—**c** (30—81% chemical and 0—23% optical yields). Generally, optical yields of the alcohols **2a**—**c** in the case of hydrolysis with BY were much lower than those in the case of reduction with BY. But, interestingly, hydrolysis of racemic **3a** and **3c** afforded (−)-**2a** and (+)-**2c** as in the case of BY reduction, whereas, hydrolysis of racemic **3b** in all cases (BY in water, FBY in water or FBY in hexane) afforded (+)-**2b**, in contrast to BY reduction.

Thus, we have succeeded in the synthesis of optically

TABLE III. Asymmetric Hydrolysis of (±) **3a**—**c** with Baker's Yeast



(±) **3a**—**c** **2a**—**c**

a: 4-, **b**: 3-, **c**: 2-

Entry	Substr.	Time (h)	BY	Solvent	Alcohol		$[\alpha]_D$ (°)[a] (*c*)	Recovered acetate	
					CY (%)	OY (%)		CY (%)	OY[b] (%)
1	**3a**	24	F[c]	Water	12	51	−40.1 (1.30)	70	8
2	**3a**	72	F[c]	Water	10	49		30	16
3	**3a**	120	F[c]	Water	18	42		50	15
4	**3a**	24	F[d]	Water	16	53		54	15
5	**3a**	48	IM[e]	Water	30	40	−31.4 (1.10)	51	23
6	**3a**	192	IM[e]	Hexane	12	40	−31.8 (1.00)	61	8
7	**3b**	24	F[c]	Water	6	31	+6.2 (1.48)	70	2
8	**3b**	24	F[d]	Water	10	28		57	4
9	**3b**	48	IM[e]	Water	18	33	+6.6 (1.40)	54	10
10	**3b**	192	IM[e]	Hexane	8	32	+6.4 (2.50)	81	3
11	**3c**	24	F[c]	Water	36	3		51	2
12	**3c**	48	F[d]	Water	17	4	+5.9 (2.60)	70	1
13	**3c**	48	IM[e]	Water	30	2		40	2
14	**3c**	192	IM[e]	Hexane	30	0		34	0

F, free bakers' yeast; IM, immobilized bakers' yeast; *a*) In chloroform. *b*) Optical yields were determined by HPLC analysis. **3a** (Chiralcel OJ, 2-propanol/hexane = 1/5); **3b** (Chiralcel OJ, 2-propanol/hexane = 2/3); **3c** (Chiralcel OJ, 2-propanol/hexane = 1/30). *c*) Reactions were carried out with substrate (1 mmol), FBY (5 g) and water (50 ml) at room temperature. *d*) Reactions were carried out with substrate (1 mmol), FBY (5 g), glucose (10 g in entry 4, and 15 g in entries 8, 12) and water at room temperature. *e*) Reactions were carried out with substrate (1 mmol), IMBY (29 g, include FBY 5 g) and solvent (50 ml in entries 5, 9, 13, and 100 ml in entries 6, 10, 14) at room temperature. CY, chemical yield; OY, optical yield.

active α-phenyl-2, 3 or 4-pyridylmethanol (**2a—c**) by using fermenting BY (reduction or hydrolysis). It is very interesting that in spite of the apparent stereochemical resemblance between the phenyl group and the pyridinyl group, BY could discriminate the phenyl group and pyridinyl group of 4-benzoylpyridine (**1a**), affording (−)-α-phenyl-4-pyridylmethanol (**2a**) in high optical purity. Furthermore, we investigated the effect of changing the reaction conditions [immobilization of yeast, concentration of sugar (glucose, saccharose, starch) or solvent (water, organic solvent)] on the stereochemistry in the reduction of 2-, 3-, or 4-benzoylpyridine (**1a—c**) by BY. In the reduction of **1a**, we succeeded in achieving asymmetric reduction by using immobilized BY in organic solvent (hexane) to afford the alcohol [(−)-**2a**] in high optical purity (96% ee). Furthermore, sugar influenced the optical yield of the alcohol. In the case of the reduction of **1a**, the addition of sugar increased the optical yield of the alcohol **2a**, whereas, in the cases of **1b** and **1c**, the addition of sugar decreased the optical yield. Furthermore, in the IMBY–water system, the addition of sugar tended to decrease the optical yield of alcohol.

Experimental

Melting points were determined on a micro-melting point apparatus (Yanagimoto) and are uncorrected. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. IR spectra were taken on JASCO IR-810 IR spectrophotometers and values are given in cm^{-1}. ^{1}H-NMR spectra were recorded on a JEOL JNM PMX 60SI (60 MHz) spectrophotometer in $CDCl_3$. Chemical shifts are given in δ (ppm) downfield from tetramethylsilane, and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet. High-performance liquid chromatography (HPLC) was carried out with a Waters 600E (ultraviolet detection) equipped with a column packed with Chiralcel OB (Daicel Chemical Industries Ltd., 2-propanol/hexane) or Chiralcel OJ (Daicel Chemical Industries, 2-propanol/hexane). Thin layer chromatography (TLC) was performed on silica gel (Kieselgel $60F_{254}$ on aluminum sheets, Merck). All compounds were located by spraying the TLC plate with a 10% solution of phosphomolybdic acid in ethanol and heating it on a hot plate. Preparative TLC was performed on preparative layer chromatography plates (Kieselgel $60F_{254}$ 2 mm and 0.5 mm, Merck). Column chromatography was performed on silica gel (Kieselgel 60, 70—230 mesh, Merck).

Preparation of IMBY with Calcium Alginate Sodium alginate (7 g) was added to stirred, boiling water (350 ml) and the mixture was stirred for 4 h to afford a uniform solution. After the solution had cooled, 35 g of BY (Oriental Yeast Co., Ltd.) was added and the mixture was stirred for 2 h. The solution was transferred into a separatory funnel and dropped into aqueous calcium chloride (10%, 350 ml) to afford IMBY. This IMBY was added to boiled water (750 ml) and stirred slowly for about 30 min. As a result, about 203 g of IMBY was obtained; 203 g of IMBY consisted of BY (35 g), calcium alginate (7 g), and water (161 g).

General Procedure for Reduction of Benzoylpyridines (1a—c). With FBY in Water A benzoylpyridine (183 mg, 1 mmol), FBY (5 g), glucose or saccharose (0—50 g), and water (50 ml) were placed in a 100 ml flask and the mixture was stirred at room temperature with a magnetic stirrer. At the conclusion of the reaction, CH_2Cl_2 was added to the flask. The mixture was stirred for 30 min, and filtered over Celite. The filtrate was extracted with CH_2Cl_2, and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using CH_2Cl_2 as an eluent to give the corresponding phenylpyridylmethanol (**2a—c**). The reaction time, the chemical yields, the optical yields (OY) and the optical rotations are listed in Tables I and II.

(−)-**2a**: mp 155—156 °C. $[\alpha]_D^{20}$ −75.3 (c=1.30, $CHCl_3$). OY 96% ee. (lit.[15] mp 131—132 °C. $[\alpha]_D^{18}$ −55.5 (c=3.66, $CHCl_3$).

(−)-**2b**: mp 80—81 °C. $[\alpha]_D^{20}$ −13.1 (c=1.48, $CHCl_3$). OY 66% ee. IR (neat): 3346 (OH). *Anal.* Calcd for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.69; H, 5.87; N, 7.57. MS m/z: 185 (M^+). ^{1}H-NMR: 4.17 (1H, s, OH), 6.05 (1H, s, side chain H), 7.40 (1H, dd, $J_{4,5}$=7.6, $J_{5,6}$=3 Hz, C_5-H), 7.52 (5H, s, phenyl), 7.90 (1H, tt, $J_{4,5}$=7.6, $J_{2,4}$=2, $J_{4,6}$=2 Hz, C_4-H), 8.55 (1H, dd, $J_{4,6}$=2, $J_{5,6}$=3 Hz, C_6-H), 8.68 (1H, d, $J_{2,4}$=2 Hz, C_2-H).

(+)-**2c**: mp 64—65 °C. $[\alpha]_D^{20}$ +49.1 (c=2.60, $CHCl_3$). OY 35% ee. [lit.[4] mp 64—65 °C. $[\alpha]_D^{25}$ +17.2 (c=1.54, $CHCl_3$), lit.[9] (−)-**2c**: $[\alpha]_D^{25}$ −114.6 (c=2.81, $CHCl_3$). OY 93% ee.]

With IMBY in Water A benzoylpyridine (183 mg, 1 mmol), IMBY (29 g, consisting of BY 5 g), glucose or saccharose (0—50 g), and water (50 ml) were placed in a 100 ml flask and the mixture was stirred at room temperature with a magnetic stirrer. At the conclusion of the reaction, the mixture was separated by filtration and the IMBY was washed with CH_2Cl_2. The filtrate was treated by the same procedure as described for FBY in water. The reaction time, the chemical yields, the optical yields and the optical rotations are listed in Tables I and II.

With IMBY in Hexane A benzoylpyridine (183 mg, 1 mmol), IMBY (29 g, consisting of BY 5 g), and hexane (100 ml) were placed in a 200 ml flask and the mixture was stirred at room temperature with a magnetic stirrer. At the conclusion of the reaction, the mixture was separated by filtration, and the IMBY was washed with hexane. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using CH_2Cl_2 as an eluent to give phenyl pyridyl methanol. The reaction time, the chemical yields, the optical yields and the optical rotations are listed in Tables I and II.

Preparation of Racemic Acetates (3a—c) Racemic **2a**,[15] **2b**,[18] or **2c**[8] (740 mg, 4 mmol) was added to a stirred solution of acetic anhydride (3 ml), pyridine (192 mg), dimethylaminopyridine (DMAP, 80 mg) and CH_2Cl_2 (5 ml), and the mixture was stirred for 17 h. The reaction solution was concentrated *in vacuo* and the residue was subjected to column chromatography on SiO_2 using CH_2Cl_2 as an eluent to give the corresponding racemic acetate (**3a—c**).

3b: IR (neat): 1740 (C=O). *Anal.* Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.96; H, 5.63; N, 6.02. MS m/z: 227 (M^+). ^{1}H-NMR: 2.13 (3H, s, CH_3), 6.73 (1H, s, side chain H), 7.06 (1H, dd, $J_{4,5}$=7.5, $J_{5,6}$=7.5 Hz, C_5-H), 7.45 (1H, tt, $J_{4,5}$=7.5, $J_{2,4}$=2, $J_{4,6}$=2 Hz, C_4-H), 8.29 (1H, dd, $J_{4,6}$=2, $J_{5,6}$=7.5 Hz, C_6-H), 8.40 (1H, d, $J_{2,4}$=2 Hz, C_2-H).

General Procedure for Hydrolysis of Racemic Acetates (3a—c). With FBY in Water One of **3a—c** (183 mg, 1 mmol) was placed in a 100 ml flask, together with FBY (5 g), glucose (0—15 g), and water (50 ml), and the mixture was stirred at room temperature with a magnetic stirrer. At the conclusion of the reaction, CH_2Cl_2 was added to the flask. The mixture was stirred for 30 min, and filtered over Celite. The filtrate was extracted with CH_2Cl_2, and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using CH_2Cl_2 as an eluent. The first fraction gave **3a—c** and the second fraction gave **2a—c**. The reaction time, the chemical yields, the optical yields and the optical rotations are listed in Table III.

With IMBY in Water One of **3a—c** (183 mg, 1 mmol) was placed in a 100 ml flask, together with IMBY (29 g; BY 5 g) and water (50 ml), and the mixture was stirred at room temperature with a magnetic stirrer. At the conclusion of the reaction, the mixture was separated by filtration and the IMBY was washed with CH_2Cl_2. The filtrate was treated by the same procedure as described for FBY in water. The reaction time, the chemical yields, the optical yields and the optical rotations are listed in Table III.

With IMBY in Hexane One of **3a—c** (183 mg, 1 mmol) was placed in a 200 ml flask, together with IMBY (29 g; BY 5 g) and hexane (100 ml), and the mixture was stirred at room temperature with a magnetic stirrer. At the conclusion of the reaction, the mixture was separated by filtration, and the IMBY was washed with hexane. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using CH_2Cl_2 as an eluent. The first fraction gave **3a—c** and the second fraction gave **2a—c**. The reaction time, the chemical yields, the optical yields and the optical rotations are listed in Table III.

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