Effect of Inhibitor or Immobilization on Reduction of Benzoylpyridines by Baker's Yeast

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The stereochemical course of the reduction of benzoylpyridine derivatives (1a—e) by baker's yeast can be modified by immobilization or by treating the reduction system with allyl alcohol or ethyl chloroacetate.

Key words chiral α-phenylpyridylmethanol; chiral *p*-chlorophenylpyridylmethanol; immobilized baker's yeast; allyl alcohol; ethyl chloroacetate

α-Pyridyl alcohol derivatives are intermediates of some pharmacological interest,[1-3] and (+)-(*S*)-α-phenyl-2-pyridyl methanol (**2c**) itself has analgetic and anticonvulsant activities.[4] Carbinoxamine,[5] a *p*-chlorophenyl-2-pyridylmethanol derivative, {2-[(4-chlorophenyl)-2-pyridinylmethoxy]-*N*,*N*-dimethylethanamine} is an antihistaminic drug whose (*S*) form is active, while the (*R*) form is inactive. Another *p*-chlorophenyl-4-pyridylmethanol derivative, 4-[1-(*p*-chlorophenyl)-1-propoxymethyl]-piperidine,[6] has antimalarial activity. However, chiral synthesis of *p*-chlorophenyl-4 or 2-pyridylmethanol (**2d, e**) by chemical or biological means has not yet been reported.

In a preceding paper,[7] we reported the first synthesis of optically active α-phenyl-4,3 or 2-pyridylmethanol (**2a—c**) by using fermenting baker's yeast (BY). In the reduction of 4-benzoylpyridine (**1a**), BY could discriminate the phenyl group and pyridinyl group of **1a**, in spite of the apparent stereochemical resemblance between them, affording (−)-**2a** in high optical purity (86% ee). However, *meta* (**1b**) and *ortho* (**1c**) compounds were less well discriminated by BY, which afforded the alcohols **2b** and **2c** in lower optical yields (OY) [(−)-**2b**: 56% ee, (+)-(*S*)-**2c**: 32% ee]. Thus, it seems necessary to investigate enantioselective BY reduction of substrates which possess *ortho* or *meta* substitution.

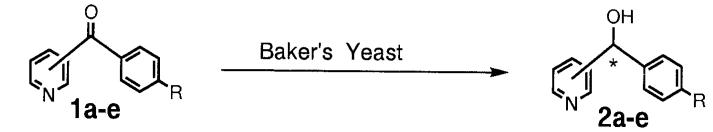
BY is often used as a reducing reagent, because it is cheap and easily obtainable. However, the reduction with BY does not always afford alcohols with the desired configurations in satisfactory ee. Hence, various methods have been tried for controlling the stereochemical course in BY reduction, *i.e.*, immobilization of BY[7] (in water, in organic solvent), addition of inhibitor[8] (ethyl chloroacetate, allyl alcohol, *etc*). We therefore performed BY reduction of **1a—e** using these stereochemical control methods (Chart 1).

First, we performed the BY reduction of **1a—e** using allyl alcohol or ethyl chloroacetate (Table 1). In the case of **1a**, the yeast:allyl alcohol ratio had almost no influence on the optical yield, but did affect the chemical yield (CY) (entries 3—8). Then we used 100 mg of allyl alcohol in the BY reduction of the substrate (1 mmol). Interestingly, the reduction of **1b** without allyl alcohol gave the corresponding alcohol (−)-**2b** in 62% ee (entry 9), while treatment of the same system with 100 mg of allyl alcohol enhanced the ee of (−)-**2b** from 62% to 85% (entry 11). The reduction of **1c** with BY gave (*S*)-**2c** in 39% ee

Table 1. Effect of Allyl Alcohol on Asymmetric Reduction of **1a—e** with Baker's Yeast

Entry	Substr.	Time (d)	Allyl alcohol (mg)	Glucose (g)	CY (%)	OY[a] (%)	OY[a] (Config.)	
1	**1a**	1	0	0	78	88	(−)	
2		1	0	20	85	92	(−)	
3		2	100	0	65	86	(−)	
4		2	100	20	67	92	(−)	
5		4	200	0	61	84	(−)	
6		4	200	20	65	86	(−)	
7		4	300	0	58	92	(−)	
8		4	300	20	62	87	(−)	
9	**1b**	5	0	0	77	62	(−)	
10		5	0	10	77	56	(−)	
11		4	100	0	62	85	(−)	
12	**1c**	6	0	0	55	39	(+)	(*S*)
13		6	0	5	62	32	(+)	(*S*)
14		7	100	0	5	8	(−)	(*R*)
15		7	100	10	8	13	(−)	(*R*)
16	**1d**	7	0	5	59	57	(−)	
17		7	100	5	0	—		
18	**1e**	7	0	5	6	0		
19		7	100	5	0	—		

Conditions: dry baker's yeast 5 g, water 50 ml, substrate 1 mmol. *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); **2d** (Chiralcel OB, 2-propanol : hexane = 2 : 3).



a ; 4-pyridyl , R = H b ; 3-pyridyl , R = H c ; 2-pyridyl , R = H
d ; 4-pyridyl , R = Cl e ; 2-pyridyl , R = Cl

Chart 1

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Table 2. Effect of Ethyl Chloroacetate on Asymmetric Reduction of **1a—e** with Baker's Yeast

Entry	Substr.	Time (d)	Ethyl chloroacetate (mg)	Glucose (g)	CY (%)	OY[a] (%)	(Config.)	
1	**1a**	2	100	0	70	86	(−)	
2		2	100	20	72	88	(−)	
3	**1b**	5	100	0	65	38	(−)	
4	**1c**	8	100	0	48	52	(+)	(*S*)
5		8	100	10	33	41	(+)	(*S*)
6		8	200	0	18	44	(+)	(*S*)
7		8	200	10	24	40	(+)	(*S*)
8	**1d**	7	100	5	13	81	(−)	
9	**1e**	7	100	5	23	20	(−)	(*R*)

Conditions: dry baker's yeast 5 g, water 50 ml, substrate 1 mmol. *a*) Optical yields were determined by HPLC analysis. **2e** (Chiralcel OJ, 2-propanol : hexane = 1 : 50).

Table 3. Asymmetric Reduction of **1d**, **1e** with Baker's Yeast

Entry	Substr.	Time (d)			CY (%)	OY (%)	(Config.)	
1	**1d**	7	FBY	Water	59	57	(−)	
2		14	IMBY	Water	8	35	(−)	
3		14	IMBY	Hexane	5	96	(−)	
4	**1e**	9	FBY	Water	6	0		
5		17	IMBY	Water	77	68	(−)	(*R*)
6		17	IMBY	Hexane	8	26	(+)	(*S*)

Conditions: entries 1, 4 (dry baker's yeast 5 g, water 50 ml, substrate 1 mmol), entries 2, 5 (including baker's yeast 5 g, water 50 ml, substrate 1 mmol), entries 3, 6 (including baker's yeast 5 g, hexane 100 ml, substrate 1 mmol).

(entry 12), while the addition of allyl alcohol shifted the selectivity toward the L-side to afford (*R*)-**2c** in 8% ee (entry 14). These data show allyl alcohol affects the stereoselectivity in BY reduction of these compounds.

Next, we performed the BY reduction of **1a—e** using ethyl chloroacetate (Table 2). In the case of **1c**, addition of ethyl chloroacetate shifted the stereochemistry toward the D-side to afford (*S*)-**2c** in 52% ee, although the effect is small (entry 4). Similarly, the reduction of **1b** without addition of ethyl chloroacetate gave (−)-**2b** in 62% ee (Table 1, entry 9), whereas addition of ethyl chloroacetate afforded (−)-**2b** in 38% ee (entry 3), *i.e.*, there was a shift towards the (+)-alcohol. Ethyl chloroacetate greatly affected the reduction of **1d** with BY and the ee of (−)-**2d** increased from 57% ee to 81% ee (entry 8).

These results show that allyl alcohol and ethyl chloroacetate both affect the outcome, but the influence of allyl alcohol is opposite to that of ethyl chloroacetate. For example, allyl alcohol enhanced the ee of **2b** from 62% ee to 85% ee (Table 1, entry 11), whereas ethyl chloroacetate lowered the ee from 62% ee to 38% ee (Table 2, entry 3). Similarly, allyl alcohol acted oppositely to ethyl chloroacetate in the BY reduction of **1c** (Table 1, entry 15 ; Table 2, entry 4).

Next, we performed the IMBY reduction of **1d, e** in water or hexane. These results are summarized in Table 3. In the case of the reduction of **1d**, the ee of the alcohol (−)-**2d** obtained with IMBY in hexane (96% ee, entry 3) was much higher than that with FBY in water (57% ee, entry 1) or IMBY in water (35% ee, entry 2), though the chemical yield (isolated yield) was not good. Furthermore, it is noteworthy that IMBY in water enantioselectively reduced **1e** to the corresponding alcohol *R*-(−)-**2e** in an excellent optical yield of 68% ee (entry 5) as compared with FBY in water (0% ee, entry 4). This system also increased the chemical yield to a satisfactory level (from 6% to 77%). On the other hand, IMBY in hexane shifted the selectivity toward the D-side and the product was (*S*)-**2e** in 26% ee (entry 6).

The mechanism of such changes in the ee and configuration of the products is not clear yet. However, it has been demonstrated that the method cited above is convenient and useful for enhancing the ee of the product in the reduction of benzoyl pyridine derivatives. In paticular, we succeeded in the chiral synthesis of (−)-**2b** (CY 62%, OY 85%, allyl alcohol), (−)-**2d** (CY 13%, OY 81%, ethyl chloroacetate), (−)-**2d** (CY 5%, OY 96%, IMBY in hexane) and (*R*)-**2e** (CY 77%, OY 68%, IMBY in water).

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. High-performance liquid chromatography (HPLC) was carried out on a Waters 600E (with 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).

General Procedure for BY Reduction of Benzoylpyridines (1a—e) with Allyl Alcohol or Ethyl Chloroacetate Dry BY (5 g, Oriental Yeast Co., Ltd.) and water (50 ml) were placed in a 100 ml flask in the presence of allyl alcohol (100—300 mg) or ethyl chloroacetate (100—200 mg) and the mixture was stirred at room temperature with a magnetic stirrer for 1 h. Then, a benzoylpyridine (**1a—e**, 1 mmol) and glucose (5—20 g) were added, and the mixture was stirred at room temperature. At the conclusion of the reaction, CH_2Cl_2 was added to the flask. The mixture was stirred for 30 min, and filtered with the aid of 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 with CH_2Cl_2 to give the corresponding alcohol (**2a—e**). The reaction time, the chemical yields and the optical yields are listed in Tables 1 and 2. (−)-**2b**: mp 80—81 °C. $[\alpha]_D^{20}$ −18.2 (c = 1.50, $CHCl_3$). OY 85% ee (lit[10]: mp 80—81 °C. $[\alpha]_D^{20}$ −16.9° (c = 1.38, $CHCl_3$). OY 85% ee).

IMBY Reduction of 1d and 1e in Water Substrate (1 mmol), IMBY[7] (consisting of BY 5 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 filtered and the IMBY was washed with CH_2Cl_2. The filtrate and washing were combined and treated by the same procedure as described for the method with allyl alcohol. The reaction time, the chemical yields and the optical yields are listed in Table 3. (−)-**2e**: mp 90—91 °C. $[\alpha]_D^{23}$ −79.5° (c = 1.0, $CHCl_3$). OY 68% ee (lit[9]: mp 95—97 °C. $[\alpha]_D^{17}$ −123.2° (c = 0.5, $CHCl_3$)).

IMBY Reduction of 1d and 1e in Hexane Substrate (1 mmol), IMBY (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 treated by the same procedure as described for the method with allyl alcohol. The reaction time, the chemical yields and

the optical yields are listed in Table 3. (−)-**2d**: mp 166—167 °C. $[\alpha]_D^{23}$ −55.9° (c=0.8, $CHCl_3$). OY 96% ee.

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