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Highly Regio- and Enantioselective Reduction of 1-Chloro-2,4-alkanediones Using Baker's Yeast: Effects of Organic Solvents as Additives

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Abstract: Bakers' yeast reduction of 1-chloro-2,4-alkanediones **1a** afforded 1-chloro-2-hydroxy-4-alkanones **2a** regioselectively with low optical purities. Application of inhibitors and heat-treatment of bakers' yeast enhanced the optical purities toward the *S* enantiomer (88–91% ee). Organic solvents added in small amounts were also found to enhance the *S* selectivity significantly. High optical purities of 94–96% ee were achieved by the combined action of the inhibitor, heat-treatment, and organic solvent. © 1997 Elsevier Science Ltd.

Herein we wish to report a novel asymmetric reduction of 1-chloro-2,4-alkanediones **1a** using bakers' yeast, which includes a new aspect of the stereochemical control using organic solvents as additives in the yeast reduction. Various prochiral ketones have been reduced enatioselectively by use of bakers' yeast[1] and, in these reductions, especially interesting is the fact that high regio- and enantioselectivities are achieved in the reduction of β-diketones **1b** to afford β-hydroxy ketones **2b**.[2] Since the optically active β-hydroxy ketone moiety is important in organic synthesis,[3] we have been investigating the preparation of functionalized β-hydroxy ketones by use of bakers' yeast and reported that the bakers' yeast reduction of 1-acetoxy-2,4-alkanediones **1c** afforded (*S*)-1-acetoxy-2-hydroxy-4-alkanones (*S*)-**2c** with high regio- and enantioselectivities.[4] In connection with the work, we have studied the reduction of **1a** to **2a** to adopt the synthetic versatility of the chloro substituent. Recent successes in the stereochemical control in the bakers' yeast reduction of β-keto esters seemed to be promising[5] and urged us to apply the control to attain high enantioselectivity in the reduction of our α-chloro diketones **1a**.

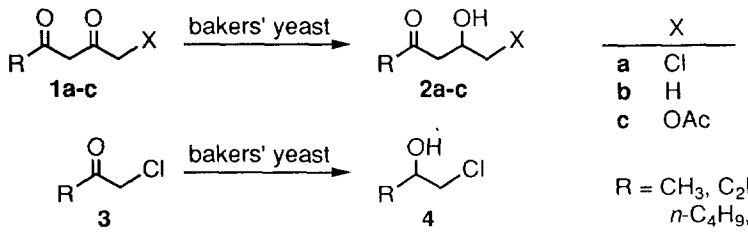

Table 1. Bakers' Yeast Reduction of **1a** to **2a**[a]

R	reaction time h	yield %	ee %	$[\alpha]_D$	*R/S*
CH_3	1.0	53	29	-6.85	*S*
C_2H_5	1.0	70	14	+5.20	*R*
n-C_3H_7	1.0	84	6	-1.88	*S*
n-C_4H_9	1.0	76	39	+12.2	*R*
n-C_5H_{11}	2.5	58	58	+18.2	*R*

a) Substrate 0.5 mmol, dry bakers' yeast 2.0 g, water 38 ml. See ref 6.

The compounds **1a** prepared in one step from methyl ketones and ethyl chloroacetate, were reduced by use of dry bakers' yeast under conventional conditions.[6] The regioselectivity was perfect, as observed in the reduction of **1b**. We could not detect the regioisomer that had a hydroxyl group at the C-4 position, even in the reduction of **1a** (R = CH_3) having a rather easily reducible methyl ketone functionality at the C-4. The enantioselectivity, however, varies from *S* 29% to *R* 58% ee depending on the alkyl chain length, in contrast to that for the reduction of **1b** to **2b** keeping a constancy of *S* 95–98% ee.[2] This tendency is similar to that for the reduction of **3** to **4** varying from *S* 83% to *R* 65% ee.[7] It is clear that 1-chloro-2,4-alkanediones **1a** are reduced by the yeast as derivatives of 1-chloro-2-alkanones **3**, not as those of 2,4-alkanediones **1b** which are seemingly reduced as methyl ketones activated by the β-keto group.

We considered that the low and varying % ee's for **1a** were attributable to the presence of plural reducing enzymes in the yeast cells. In fact, the reduction of β-keto ester using yeast cells is catalyzed by some enzymes producing the *S* enantiomer and by others producing the *R* enantiomer, and thus the enantioselectivity can be controlled by inhibiting either of those enzymes.[5] Therefore we tried to selectively inhibit the reducing enzymes by addition of inhibitors[5a] and heat-treatment of the yeast,[5b] although we had not identified the reducing enzymes concerned.

To begin with, we chose **1a** (R = *n*-C_3H_7) as a probe to select the inhibitor and the reduction conditions, because it was reduced to a nearly racemic product of *S* 6% ee in the conventional reduction (Table 1). Thus we found that allyl alcohol was better than methyl vinyl ketone as an *S* enhancing inhibitor and that the maximal *S* selectivity was obtained when the yeast was heat-treated at 50 °C for 30 min with allyl alcohol prior to the addition of the substrate. An alternate procedure of the heat-treatment followed by addition of allyl alcohol was found less effective. Our choices are shown in Table 2 (entries 2–4).

Incidentally we noticed that a small amount of organic solvent used to dissolve the substrate could enhance the enantioselectivity toward the *S* enantiomer. Our search for the effect of organic solvents, hexane and diethyl ether as additives, is included in Table 2 (entries 5–6). The *S* enhancing effect of organic solvents was found to be considerable and superior to that of the heat-treatment. Other organic solvents such as THF, cyclohexane, octane, ethyl acetate, acetone, methanol, and ethanol as additives were also effective to enhance the *S* selectivity. Although organic solvents so far have been used as bulk solvents[8] or substrate-dissolving solvents,[9] such an effect as additives has never been reported.

Since the *S* selectivity reached was 89% ee at the highest by use of allyl alcohol as an additive and heat-

Table 2. Effects of Inhibitor, Heat-treatment, and Organic Solvents in the Bakers' Yeast Reduction of **1a** to **2a** (R = n-C_3H_7)[a]

entry	allyl alcohol mM	heat-treatment	org. solvent (mL)	yield %	ee %	$[\alpha]_D$	*R/S*
1	none	none	none	84	6	-1.88	*S*
2	67	none	none	87	80	-28.3	*S*
3	none	50 °C, 30 min	none	86	39	-14.0	*S*
4	67	50 °C, 30 min	none	51	89	-31.6	*S*
5	none	none	hexane (0.5)	82	60	-17.0	*S*
6	none	none	Et_2O (0.5)	55	45	-16.2	*S*
7	none	50 °C, 30 min	Et_2O (0.5)	72	47	-16.6	*S*
8	67	50 °C, 30 min	Et_2O (0.5)	63	91	-31.7	*S*
9	67	50 °C, 30 min	hexane (0.25) + Et_2O (0.25)	70	94	-34.1	*S*

a) Substrate 0.5 mmol, dry bakers' yeast 2.0 g, water 38 ml. See ref 6.

Table 3. Control of the Enantioselectivity Using Additives and Heat-treatment in the Bakers' Yeast Reduction of **1a** to **2a**[a]

R	allyl alcohol + heat-treatment					allyl alcohol + heat-treatment + hexane-Et_2O				
	time (h)	% yield[b]	% ee	$[\alpha]_D$	*R/S*	time (h)	% yield	% ee	$[\alpha]_D$	*R/S*
CH_3	4.0	21	91	-28.1	*S*	3.0	54	95	-32.6	*S*
C_2H_5	2.5	23	88	-30.3	*S*	1.0	68	96	-35.4	*S*
n-C_3H_7	3.0	51	89	-31.6	*S*	1.0	70	94	-34.1	*S*
n-C_4H_9	4.0	24	78	-21.8	*S*	2.0	52	81	-29.5	*S*
n-C_5H_{11}	5.0	23	64	-18.2	*S*	3.0	41	66	-18.9	*S*

a) Substrate 0.5 mmol, dry bakers' yeast 2.0 g, water 38 ml. Allyl alcohol 2.5 mmol (67 mM), heat-treatment at 50 °C for 30 min, hexane–Et_2O 0.25 mL each. See ref 6. b) See ref 10.

treatment (Table 2, entry 4), we tried to cumulate the effect of organic solvent on it. Unexpectedly the cumulative effect was small or negligible (Table 2, entry 8), but we achieved 94% ee by use of a mixture of hexane and diethyl ether (entry 9). This significant enhancement was commonly realized for the substrates **1a** having R = CH_3 (from 91% to 95% ee), C_2H_5 (from 88% to 96% ee), and n-C_3H_7 (from 89% to 94% ee) as shown in Table 3. The rather lower values of *S* 81% ee and *S* 66% ee for R = n-C_4H_9 and n-C_5H_{11}, respectively, could be attributable to the predominance of enzymes producing the *R* enantiomers.

The mechanism that the organic solvents used in small quantities caused significant enhancements in the enantioselectivity is worthy of a further study. At present we suggest the following two factors. One is the enhanced concentration of substrate due to the solubilizing or dispersing power of organic solvents. We found that the *S* 6% ee of **2a** (R = n-C_3H_7) obtained by the yeast reduction without organic solvent, allyl alcohol, and heat-treatment at a 13 mM substrate concentration, was increased to *S* 48% ee at 62 mM, probably owing to the higher substrate concentration kept during the reduction. Table 3 also indicates the shorter reaction times

realized by the addition of organic solvents, the reductions apparently being accelerated by increased effective concentrations of the substrate. We consider that the function of organic solvents is to change the state of the substrate in the aqueous reaction mixture. This function is essentially different from that of the organic solvents used in bulk,[8] where the substrate is partitioned between organic and aqueous layers.

The other factor is the action of organic solvents as inhibitors. It is well-known that enzymes are denatured in aqueous–organic mixtures, but further investigations are needed to clarify the effect of organic solvents in the present work.

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6. Typically, the substrate (0.5 mmol), neat or dissolved in a small quantity of organic solvent, was added to a fermenting mixture of dry bakers' yeast (2.0 g, Nissin Milling), glucose (2.0 g) and boiled water (38 ml) and stirred at 30 °C until exhaustion of the substrate. The ee's were determined by ^{1}H NMR of the corresponding (*R*)-MTPA ester. The $[\alpha]_D$ values were measured using $CHCl_3$ with *c* 1.9–2.3. The absolute configurations were determined by comparing the $[\alpha]_D$ values of dechlorinated derivatives with those of the corresponding 2-hydroxy-4-alkanones. Similar results were obtained in the experiments using dry bakers' yeast from Sigma.
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10. We obtained furanones in 3–7% yield, recovered the substrates in 5–10% yield (R = *n*-C_4H_9, *n*-C_5H_{11}), and estimated 15–20% of the products lost by decomposition.

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