Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 2, pp. 409-412, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00020-1

Enantio- and Regioselective Reduction of α-Diketones by Baker's Yeast

Kaoru Nakamura,* Shin-ichi Kondo, Yasushi Kawai, Kouichi Hida, Kazutada Kitano,† and Atsuyoshi Ohno

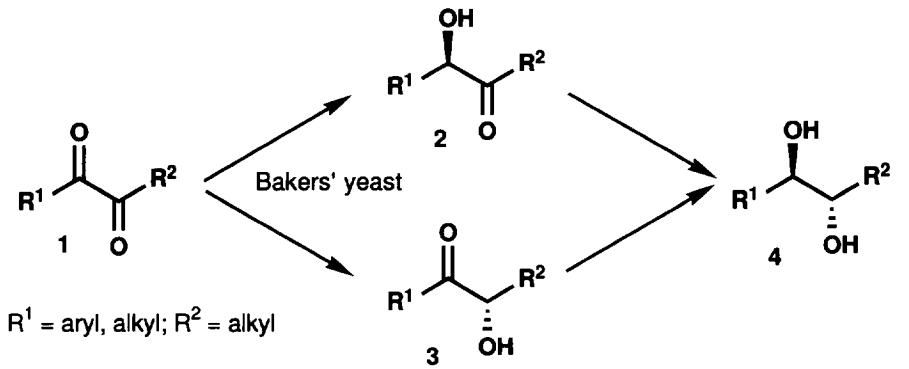
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

Abstract: Although yeast reduction of α-diketones **1** affords a mixture of two α-hydroxy ketones and a *vic*-diol, the use of methyl vinyl ketone as an enzyme inhibitor prevents the production of the diol. Regioselectivity in the reduction to afford α-hydroxy ketones is improved by thermal pre-treatment of baker's yeast. Thus, 1-phenyl-2-hydroxy-1-propanone **3a** is obtained in 80 % yield with >98% e.e.

α-Hydroxy ketones are versatile chiral synthons for the construction of chiral organic compounds due to reactive functional groups: carbonyl and hydroxyl groups, which can easily be transformed to *vic*-diols,[1-6] α-amino ketones,[7] and other functional groups. To obtain chiral α-hydroxy ketones, reduction mediated by yeast is a powerful tool.[8,9] For example, reduction of 1-phenyl-1,2-propandione **1a** by baker's yeast has been reported to produce a mixture of the corresponding α-hydroxy ketones, (*R*)-1-phenyl-1-hydroxy-2-propanone **2a** and (*S*)-1-phenyl-2-hydroxy-1-propanone **3a**, and a diol, (1*R*, 2*S*)-1-phenyl-1,2-propanediol **4a**, although chemical yields of both α-hydroxy ketones are low.[10-12] To improve the yield of α-hydroxy ketones, modification of reaction conditions has been attempted. Chenêvert and Thiboutot have reported yeast reduction conducted in an acidic buffer solution.[10] They obtained one of the α-hydroxy ketones, **3**, selectively. Takeshita and Sato obtained a similar result by lowering the reaction temperature.[11] However, we found that these methods were not reproducible and resulted in the formation of the *vic*-diol. The difference in their results and ours may stem from the difference in the strain of baker's yeast employed for the experiments. Procedures reported in the literature were not effective for our reductions catalyzed by yeast. Besse et al.[13] have reported stereoselective reduction of aliphatic α-diketone using freeze-dried baker's yeast, in which they obtained a chiral diol in a high diastereoselectivity while regioselective synthesis of the corresponding α-hydroxy ketone was difficult. Since selectivities of yeast reduction are not always satisfactory, several methods have been developed to improve the stereochemical result.[14] Here, we would like to report a simple and effective method to improve both chemical yield of an α-hydroxy ketone and regioselectivity of the reduction.

In yeast reduction of **1a**, two regioisomeric α-hydroxy ketones, **2a** and **3a**, are produced, and these α-hydroxy ketones are successively reduced to the diol **4a**. Therefore, chemical yields of the α-hydroxy ketones are very low. For example, the reduction of **1a** with baker's yeast afforded **4a** in 62% yield together with a mixture of α-hydroxy ketones, **2a** and **3a**, in only 38%. From the viewpoint of asymmetric

synthesis, the reduction has three problems: chemoselectivity, regioselectivity, and enantioselectivity. Minimisation of these disadvantages will be reported in this paper.



The use of enzyme inhibitors is a powerful tool to control yeast reduction of β-keto esters.[15-18] We tested several inhibitors to suppress the formation of the diol, **4a**, and found that methyl vinyl ketone (MVK) is the most effective among other inhibitors such as 2-cyclopenten-1-one and ethyl chloroacetate. Thus, the yield of **4a** decreases dramatically on addition of MVK and keeps decreasing with the increase in concentration of MVK up to 50 mM. At higher MVK concentrations, however, the reduction of **1a** is also inhibited resulting in decrease in chemical yields of **3a**.

Next attempt was to improve regioselectivity between **2a** and **3a**. The ratio of 32 : 68 in the absence of MVK was enhanced to 22 : 78 in the presence of 50 mM of MVK. Thus, MVK enhances not only chemoselectivity but also regioselectivity. However, the result was not yet satisfactory to claim the preparation of α-hydroxy ketone as a chiral synthon for asymmetric syntheses, because **2a** and **3a** are barely separable by silica gel column chromatography. Therefore, it was necessary to improve the regioselectivity of the reduction. Previously, we reported that diastereoselectivity in yeast reduction of α-alkyl-β-keto esters can be improved by a combination of two techniques: addition of MVK and thermal pre-treatment of yeast.[19,20] The method has been applied to the present reaction system to improve the regioselectivity. Bakers' yeast was preincubated for 30 min at appropriate temperatures and cooled down to room temperature, then MVK (50 mM) was added to the system and the resulting mixture was stirred for 30 min. Regioselectivity of the reduction (**2a** : **3a**) is improved according to the increase in temperature for the thermal pre-treatment, and the ratio of **2a** to **3a** reaches to 6 : 94 at 55 °C. However, the reduction of **1** was also inhibited by the thermal treatment over 55 °C. Therefore, the temperature for the thermal pre-treatment was set at 53 °C, and the concentration of MVK was kept at 50 mM.

Preincubation time also influences the selectivity. Thus, the regioselectivity is improved at prolonged preheating period (120 min) up to **2a** : **3a** = 4 : 96, although large amount of **1a** remains unreacted under such vigorous preincubation conditions. After several experiments to find optimum conditions, we found that thermal pre-treatment at 53 °C for 65 min followed by yeast reduction in the presence of 50 mM MVK affords the best result, where the α-hydroxy ketones were obtained in the ratio of **2a** : **3a** = 6 : 94 in total 81% isolated yield.

One may expect that the production of **4a** may be inhibited by the thermal pre-treatment of baker's yeast only without addition of MVK. However, reduction of **1a** with thermally treated baker's yeast in the absence of MVK affords the corresponding diol substantially keeping the yield of α-hydroxy ketone at low level. The result indicates that MVK is necessary to inhibit the over-reduction.

Enantiomeric excess (>98%) and absolute configuration (*S*)[11] of **2a** were determined by ^{1}H NMR analysis of the corresponding (*R*)-MTPA ester.[21] α-Hydroxy ketone, **2a**, thus obtained has satisfactory enantiomeric as well as chemical purity to be employed as a chiral synthon in asymmetric syntheses.

To prove the versatility of this method, another eight substrates, **1b–1i**, were reduced, and the results are listed in Table 1. 1-Aryl-1,2-propandiones such as **1a** and **1e–1i** are suitable substrates for the present novel method. However, the reductions of 1-phenyl-1,2-butandione **1b**, 1-phenyl-1,2-pentandione **1c**, and 2,3-octandione **1d** do not afford satisfactory results with this method.

Table 1. Effect of Thermal Pre-treatment and Addition of Methyl Vinyl Ketone on Selectivity in Bakers' Yeast Reduction of α-Diketone

	Substrate		Without treatment				Pre-heating+ MVK[a)]				
	R^1	R^2	Yield of **2** + **3** (%)	**2**	:	**3**	Yield of **2** + **3** (%)	**2**	:	**3**	E.e.[b)] of **3**
a	Ph	Me	38	32	:	68	81	6	:	94	98(*S*)
b	Ph	Et	47	13	:	87	22	64	:	36	---
c	Ph	Pr	19	17	:	83	4	46	:	54	---
d	C_5H_{11}	Me	13	96	:	4	54	62	:	38	---
e	*o*-MeC_6H_4	Me	58	11	:	89	66	5	:	95	98
f	*p*-MeC_6H_4	Me	47	21	:	79	64	9	:	91	>98
g	*p*-$MeOC_6H_4$	Me	56	11	:	88	37	4	:	96	>98
h	*p*-ClC_6H_4	Me	27	35	:	65	53	14	:	86	>98
i	2-Thienyl	Me	36	5	:	95	23	5	:	95	>98

a) Thermal pre-treatment of bakers' yeast at 53 °C for 65 min and addition of methyl vinyl ketone (50 mM).
b) E.e. was determined by ^{1}H NMR of the corresponding (*R*)–MTPA ester.[21]

Typical procedure for the yeast reduction was as follows: baker's yeast (2.0 g) was suspended in potassium-phosphate buffer (pH 7.0, 50 mM, 20 ml) and the suspension was stirred at 53 °C for 65 min. After the mixture was cooled to room temperature with an ice bath, methyl vinyl ketone (81.1 μl, 50 mM) was added and the mixture was stirred at 30 °C for 30 min. The mixture was stirred for 2.5 h after addition of **1a** (59.3 mg, 20 mM). The reaction mixture was poured into 14 g of Hyflo Super-cel and extracted with ethyl acetate (3 × 30 ml). Combined organic layer was dried over anhydrous magnesium sulfate and the solvent was removed by evaporation under reduced pressure. Residual oil was purified by thin-layer chromatography on silica gel (eluent, ethyl acetate : hexane = 1 : 2) to afford the mixture of **2a** and **3a** in

80.9% yield (48.6 mg). IR and ^{1}H NMR spectra gave satisfactory result on comparison with the corresponding authentic samples. The product ratio and regioselectivity(4 : 96) of reduction were determined by ^{1}H NMR analysis of the crude mixture. E.e. of **2a** and **3a** (98%) were determined by ^{1}H NMR analysis of the corresponding MTPA esters. The absolute configurations of **2a** and **3a** were determined according to the literature.[11]

In summary, the inhibition of over-reduction, improvement of regioselectivity, and satisfactory enantioselectivity in the reduction of α-diketone have been achieved by a composite effect of the addition of inhibitor and thermal pre-treatment of baker's yeast.

Acknowledgement: We thank the Ministry of Education, Science and Culture, Japan, for financial support (Grant-in-Aid Nos. 6453063 and 04403066).

References and notes

† On leave from Department of Applied Chemistry, Faculty of Science and Engineering, Kinki University, Kowakae, Higashi-Osaka, Osaka 577, Japan

1. Yamada, S; Koga, K.; *Tetrahedron Lett.*, **1967**, 1711.
2. Katzenenllenbogen, J. A.; Bawlus, S. B. *J. Org. Chem.*, **1973**, *38*, 627.
3. Bawlus, S. B; Katzenenllenbogen, J. A. *J. Org. Chem.*, **1974**, *39*, 3309.
4. Oishi, T.; Nakata, T. *Acc. Chem. Res.*, **1984**, *17*, 338.
5. Fujita, M; Hiyama, T. *J. Org. Chem.*, **1988**, *53*, 5405.
6. Fujita, M; Hiyama, T. *Org. Synth.*, **1990**, *69*, 44.
7. Fujita, M; Oishi, H; Hiyama, T. *Chem. Lett.*, **1986**, 837.
8. Servi, S. *Synthesis*, **1990**, 1.
9. Csuc, R; Glänzer, B. I. *Chem. Rev.*, **1991**, *91*, 49.
10. Chênevert, R.; Thiboutot, S. *Chem. Lett.*, **1988**, 1191.
11. Takeshita, M.; Sato, T. *Chem. Pharm. Bull.*, **1989**, *37*, 1085.
12. Sorrilha, A. E. P.; Marques, M.; Joekes, I.; Moran, P. J. S.; Rodrigues, J. A. R., *Bioorg. & Med. Chem. Lett.*, **1992**, *2*, 191.
13. Besse, P.; Bolte, J.; Fauve, A.; Veschambre, H., *Bioorg. Chem.*, **1993**, *21*, 342.
14. Nakamura, K.; Kondo, S.; Ohno, A. *Bioorg. & Med. Chem.*, **1994**, *2*, 433 and references cited therein.
15. Nakamura, K.; Inoue, K.; Ushio, K.; Oka, S.; Ohno, A. *Chem. Lett.*, **1987**, 679.
16. Nakamura, K.; Kawai, Y.; Ohno, A. *Tetrahedron Lett.*, **1990**, *31*, 267.
17. Nakamura, K.; Kawai, Y.; Miyai, T.; Ohno, A. *Tetrahedron Lett.*, **1990**, *31*, 3631.
18. Nakamura, K.; Kawai, Y.; Nakajima, N.; Ohno, A. *J. Org. Chem.*, **1991**, *56*, 4778.
19. Nakamura, K.; Kawai, Y.; Ohno, A. *Tetrahedron Lett.*, **1991**, *32*, 2927.
20. Kawai, Y.; Kondo, S.; Tsujimoto, M.; Nakamura, K.; Ohno, A. *Bull. Chem. Soc. Jpn.*, **1994**, *67*, 2244.
21. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*, **1969**, *34*, 2543

(*Received in Japan* 4 *December* 1995)