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The baker's yeast reduction of 1-acetoxy-2-alkanones in the presence of a sulfur compound

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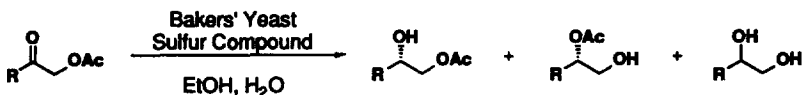
Abstract: Improved enantioselectivity was achieved in the baker's yeast reduction of the 1-acetoxy-2-alkanone derivatives by the addition of a sulfur compound such as L-cysteine and phenyl vinyl sulfide. The reaction rate of the baker's yeast reduction was accelerated using a sulfur compound as an additive. The migration of the acetyl group and the hydrolysis of the acetoxy group of the substrate was suppressed using a sulfur compound. © 1997 Elsevier Science Ltd

Optically active alcohols are important building blocks in the synthesis of natural products. Among the strategies developed for the preparation of the alcohols, the baker's yeast reduction of various carbonyl compounds is one of the most useful methods, because baker's yeast is readily available and inexpensive.[1] However, the baker's yeast reduction does not always afford satisfactory results, in terms of substrate specificity, low chemical yield and/or low selectivity. Particularly, undesirable migration of an acetyl group and hydrolysis of the acetoxy group occurred in the baker's yeast reduction of 1-acetoxy-2-alkanones to give 1-acetoxy-2-alkanols, useful chiral synthons for the synthesis of natural products.[2] A few methods have been reported for the improvement of the selectivity in the baker's yeast reduction of β-keto ester derivatives which involve the use of the long alcohol part of the ester,[3] addition of an additive as an inhibitor of the enzyme,[4] addition of an inorganic salt,[5] thermal treatment of baker's yeast,[6] or use of organic solvents.[7] However, the rate of reduction is usually decreased in such cases because of inhibition of the reductase. On the other hand, the method for improvement of the enantioselectivity in the baker's yeast reduction of 1-acetoxy-2-alkanones has not been reported. Only one example has been available where the hydrolysis of the acetoxy group is suppressed using diisopropyl fluorophosphate, serine protease inhibitor, and baker's yeast cell-free extract.[2d] Therefore, the method of improvement of enantioselectivity and of suppression of the migration of the acetyl group and the hydrolysis of the acetoxy group without using cell-free extract is desirable. We have already reported that the introduction of a sulfur atom in the neighborhood of the carbonyl group of the substrate improves the enantioselectivity and reactivity of the baker's yeast reduction.[8] We were interested in the effect of the sulfur atom as a modifier of the enantiofacial discrimination. Now we wish to report a novel efficient method for improvement of the enantioselectivity and suppression of the migration of the acetyl group and the hydrolysis of the acetoxy group using a sulfur compound as an additive in the baker's yeast reduction of 1-acetoxy-2-alkanones.



Acetoxyacetone **1a** was prepared from acetol. Other acetoxyketones were prepared from the corresponding methylketone by acetoxylation with lead tetraacetate.[9] In a typical procedure of the

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baker's yeast reduction, a suspension of 7.74 g of dry baker's yeast (S. I. Lesaffre) in 77.4 mL of dist. H_2O was stirred for 0.5 h at ambient temperature. To the resulting suspension was added a sulfur compound. After 0.5 h stirring, 7.74 mL of ethanol solution of acetoxyacetone **1a** (300 mg, 2.58 mmol) was added to a suspension of baker's yeast. After disappearance of the substrate on TLC monitoring, Celite and ethyl acetate were added to the reaction mixture, and the whole mixture was stirred for 0.5 h. The resulting mixture was filtered through a Celite pad. The filtrate was extracted with ethyl acetate (5×100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (a 4:1 mixture of *n*-hexane and ether was used as the eluent) followed by distillation (110°C/17 mmHg, bath temp.) to give the mixture of 1-acetoxy-2-propanol **2** and 2-acetoxy-1-propanol **3**.

The results of baker's yeast reduction of 1-acetoxy-2-alkanones in the presence of a sulfur compound are summarized in Table 1. The baker's yeast reduction of acetoxyacetone **1a**, the simplest 1-acetoxy-2-alkanone, gave (*S*)-1-acetoxy-2-propanol **2a** in enantiomerically pure form, although undesirable 2-acetoxy-1-propanol **3a** was obtained with a ratio of **2a**:**3a**=94: 6 (Entry 1). On the other hand, the use of a sulfur compound as an additive suppressed the migration of the acetyl group to give 2-acetoxy-1-propanol **3a**. In particular, the migration of the acetyl group was completely suppressed using 1 eq of dimethyl sulfide as a sulfur compound (Entry 3). The absolute stereochemistry of **2a** was established by comparison of the specific rotation.[2c] The use of 2 eq of dimethyl sulfide in the baker's yeast reduction of 1-acetoxy-2-hexanone **1b** gave (*S*)-1-acetoxy-2-hexanol **2b** with suppression not only of the migration of the acetyl group but also of the hydrolysis of the acetoxy group to give 1,2-hexanediol **4b**, while the baker's yeast reduction in the absence of a sulfur compound gave low selectivity (Entry 4 and 5).[10] The migration of the acetyl group and the hydrolysis of the acetoxy group were effectively suppressed in the baker's yeast reduction of 1-acetoxy-2-hexanone **1b** in the presence of 1 eq of L-cysteine (Entry 6). Moreover, the reaction rate of the baker's yeast reduction was accelerated using a sulfur compound as an additive. Previously, the acceleration of the baker's yeast reduction using an additive has not been reported.[11] The acetyl migrated product **3b** was obtained with complete enantioselectivity in all cases in the baker's yeast reduction of 1-acetoxy-2-hexanone **1b**, although 1-acetoxy-2-hexanol **2b** was not obtained in enantiomerically pure form. The results indicate that the migration of the acetyl group would be caused by the action of enzyme. Therefore, a kinetic resolution occurred in the migration of the acetyl group. The baker's yeast reduction of acetoxyacetophenone **1c**, an aromatic ketone, was also investigated. The baker's yeast reduction of acetoxyacetophenone **1c** in the absence of a sulfur compound gave (*S*)-2-acetoxy-1-phenylethanol **2c** with 90% ee, 1-acetoxy-1-phenyl-2-ethanol **3c** in enantiomerically pure form and diol **4c** with a ratio of 64: 33: 3.[12] The acetyl migrated product **3b** was obtained in enantiomerically pure form, while the corresponding 1-acetoxyalcohol was not obtained with complete enantioselectivity. The kinetic resolution in the migration of the acetyl group must be due to the action of enzyme. On the other hand, the migration of the acetyl group was slightly suppressed using 2 eq of dimethyl sulfide, although the enantioselectivity was decreased. The use of 1 eq of phenyl vinyl sulfide improved the enantioselectivity of (*S*)-2-acetoxy-1-phenylethanol **2c** in up to 94% ee, while the migration of the acetyl group was not effected. The best enantioselectivity of 98% ee of (*S*)-2-acetoxy-1-phenylethanol **2c** was obtained using 1 eq of 2-aminoethanethiol hydrochloride (Entry 10). The use of L-cysteine effectively improved the enantioselectivity of (*S*)-2-acetoxy-1-phenylethanol **2c**. Moreover, complete suppression of the hydrolysis of the acetoxy group to give 1-phenyl-1,2-ethanediol **4c** was achieved using 2 eq of L-cysteine (Entry 12). The effect of a sulfur compound is not obvious at present. However, the effect could not be due to the role of the inhibitor of the reductase, because the rate of the baker's yeast reduction in the presence of a sulfur compound was accelerated. One assumption is based on the interaction of a sulfur compound with an active site of reductase. A sulfur compound may interact with the active site of reductase to change its cavity. Therefore the reactivity and enantioselectivity were improved. Another assumption is based on the interaction of a sulfur compound with the substrate

Table 1. The baker's yeast reduction of 1-acetoxy-2-alkanones

Entry	Substrate	Sulfur Compound (equiv.)	Time (h)	% yield[a] of (2 + 3)	%yield[a] of 4	2 : 3 : 4 (% ee)[b]
1	1a	none	2	41	-	94 (>99) : 6 : -
2	1a	L-Cysteine (1.0)	2	33	-	97 (>99) : 3 : -
3	1a	Me_2S (1.0)	2	46	-	>99 (>99) : 1 : -
4	1b	none	6	52	28	53 (98) : 12 (>99) : 35 (68)
5	1b	Me_2S (2.0)	1.5	65	14	67 (96) : 10 (>99) : 18 (64)
6	1b	L-Cysteine (1.0)	1	66	8	79 (96) : 10 (>99) : 11 (60)
7	1c	none	5	58	2	64 (90) : 33 (>99) : 3
8	1c	Me_2S (2.0)	6	57	2	68 (87) : 29 (>99) : 3
9	1c	$PhSCH{=}CH_2$ (1.0)	5	62	2	63 (94) : 34 (>99) : 3
10	1c	$HSCH_2CH_2NH_2{\cdot}HCl$ (1.0)	6	58	3	74 (98) : 21 (>99) : 5
11	1c	L-Cysteine (1.0)	3	52	1	74 (98) : 24 (>99) : 2
12	1c	L-Cysteine (2.0)	4	48	-	75 (98) : 25 (>99) : -

[a] Isolated yield. [b] Determined by HPLC (Hibar column, Merck) analysis and 500 MHz ^1H NMR of the corresponding (-)-MTPA ester derivative.

at first in the case of using a sulfur compound possessing a mercapto group such as L-cysteine. It is known that the reaction of a thiol compound with carbonyl compound gives hemithioacetal.[13] The sulfur compound may interact with the substrate and then the resulting species interact with the active site of reductase.

In summary, the improved enantioselectivity and enhancement of the reactivity in the baker's yeast reduction of 1-acetoxy-2-alkanones were achieved using a sulfur compound as an additive. Previously, the improvement and the acceleration have not been reported. The present method is the first example of the suppression of the migration of the acetyl group and the hydrolysis of the the acetoxy group using whole cell in the baker's yeast reduction of 1-acetoxy-2-alkanones.

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