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Control of Enantioselectivity in the Bakers' Yeast Reduction of β-Keto Ester Derivatives in the Presence of a Sulfur Compound

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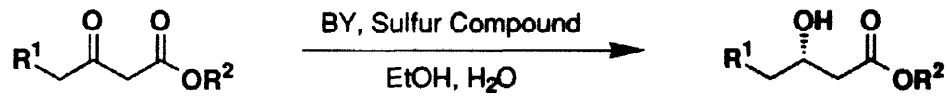
Abstract. Improvement of the enantioselectivity and enhancement of the reactivity were achieved in the bakers' yeast reduction of the β-keto ester derivatives by the addition of a sulfur compound.

Optically active alcohols are important building blocks in the synthesis of natural products. Among the strategies developed for their preparation, microbial reduction of carbonyl compounds into the alcohols has been widely investigated. The microorganism most popular and frequently used for this purpose is bakers' yeast.[1] In most cases so far reported, the results are satisfactory with high chemical yields and high stereoselectivity. However, it should be emphasized that there have been some examples to afford unsatisfactory results, arising from substrate specificity, low chemical yields and/or low selectivity.[2] A few methods have been reported to improve the enantioselectivity in the bakers' 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 enzyme,[4] addition of an inorganic salt,[5] immobilization of bakers' yeast,[6] or use of an organic solvent.[7] However, the rate of reduction is usually decreased in such cases. Therefore, more effective methods to improve the enantioselectivity without decrease of the reactivity have been desired. On the other hand, we have already reported that the introduction of a sulfur atom into the neighborhood of the carbonyl group of the substrate improved the enantioselectivity and reactivity of the bakers' yeast reduction.[8] We have been interested in the effect of a sulfur atom as a modifier of the enantiofacial discrimination. With a view to extending the scope of this type of bakers' yeast reduction, the reduction of β-keto ester by bakers' yeast in the presence of various sulfur compounds has been examined under the assumption that the cavity of the reaction site would, when a sulfur compound is added, be changed. Therefore, the improved enantioselectivity would be achieved using a sulfur compound as an additive, instead of introduction of a sulfur atom into the substrate as a substituent. We report herein a novel efficient method of the bakers' yeast reduction of β-keto ester derivatives in the presence of a sulfur compound.



1: R^1 = H, R^2 = Et **3**: R^1 = Cl, R^2 = Bu
2: R^1 = Me, R^2 = Bu **4**: R^1 = Cl, R^2 = Hexyl
5: R^1 = OBn, R^2 = Et

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Table 1. The Bakers' Yeast Reduction of β-Keto Ester Derivatives

Entry	Substrate	S-Compound (equiv)	Time (h)	% Yield[a]	% ee[b]
1	1	none	8	60	94
2	1	Me_2S (1.0)	3	59	98
3	1	Me_2S (2.0)	4	42	99
4	1	Bu_2S (1.0)	3	52	99
5	1	$PhSCH{=}CH_2$ (1.0)	3	64	99
6	1	L-Cysteine (1.0)	2	49	98
7	2	none	36	44	77
8	2	L-Cysteine (1.0)	19	75	81
9	2	L-Cysteine (3.0)	5.5	75	90
10	2	L-Cysteine (5.0)	6.5	72	92
11	2	L-Alanine (1.0)	3	69	76
12	2	L-Methionine (1.0)	4	77	77
13	2	$PhSCH{=}CH_2$ (1.0)	10	68	86
14	2	$PhSCH{=}CH_2$ (3.0)	36	67	93
15	3	none	2	65	22
16	3	$HSCH_2CH_2NH_2{\cdot}HCl$ (1.0)	2	65	46
17	3	$HSCH_2CH_2NH_2{\cdot}HCl$ (5.0)	1	20	69
18	4	none	3	62	64
19	4	$HSCH_2CH_2NH_2{\cdot}HCl$ (1.0)	3	38	75
20	4	$PhSCH{=}CH_2$ (1.0)	5	76	88
21	4	$PhSCH{=}CH_2$ (3.0)	96	12	97
22	5	none	5	74	34[c]
23	5	L-Cysteine (2.0)	9	61	54[c]
24	5	$PhSCH{=}CH_2$ (3.0)	9	64	70[c]
25	5	$PhSCH{=}CH_2$ (3.0) + L-Cysteine (2.0)	12	18	76[c]
26	5	$PhSCH{=}CH_2$ (2.0) + $HSCH_2CH_2NH_2{\cdot}HCl$ (2.0)	23	58	83[c]
27	5	$PhSCH{=}CH_2$ (3.0) + $HSCH_2CH_2NH_2{\cdot}HCl$ (2.0)	35	46	87[c]

[a]Isolated yield. [b]Determined by HPLC of the corresponding (-)-MTPA ester derivative. [c]Determined by chiral HPLC of the corresponding benzoate derivative.

The bakers' yeast reduction of ethyl acetoacetate, one of the most popular β-keto esters, is investigated. In a standard procedure of the bakers' yeast reduction, a suspension of dry bakers' yeast (S. I. Lesaffre) in 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, an ethanol solution of the substrate was added to the suspension of bakers' yeast. The results are summarized in Table 1. The improved enantioselectivity in the bakers' yeast reduction of ethyl acetoacetate was obtained using a sulfur compound such as dimethyl sulfide, dibutyl sulfide, or phenyl vinyl sulfide with up to 99% ee, while the reduction of ethyl acetoacetate in the absence of a sulfur compound gave ethyl (*S*)-3-hydroxybutanoate with 94% ee. The absolute stereochemistry was determined by the comparison of the optical rotation.[9] Accelerated reaction rate was achieved using a sulfur compound. The acceleration of the bakers' yeast reduction using an additive has not been previously reported.[10] The highest rate acceleration effect was obtained using L-cysteine as a sulfur compound (entry 6). The use of 5 eq of L-cysteine enhanced the reactivity and improved the enantioselectivity up to 92% ee, while the bakers' yeast reduction of butyl 3-oxopentanoate in the absence of a sulfur compound gave butyl (*S*)-3-hydroxypentanoate with 77% ee, in which

the reaction did not reach completion even after 36 h (entry 8).[11] The mercapto group of cysteine would be effective to increase the enantioselectivity and the amino acid part would enhance the reactivity, because other amino acids, such as L-alanine or L-methionine, enhanced the rate of the bakers' yeast reduction, although the enantioselectivity was not changed (entry 11 & 12). The best enantioselectivity was achieved by the use of 3 eq of phenyl vinyl sulfide (entry 14).

Optically active 4-chloro-3-hydroxybutanoate is a useful intermediate for the synthesis of natural products, such as carnitine.[3b] Thus, the effect of a sulfur compound in the reduction of 4-chloroacetoacetate was also investigated. 2-Aminoethanethiol hydrochloride effectively enhanced the enantioselectivity.[12] The best enantioselectivity was obtained using 5 eq of 2-aminoethanethiol hydrochloride, although the chemical yield was low because 2-aminoethanethiol hydrochloride reacted with butyl 4-chloroacetoacetate to give by-products. 4-Chloroacetoacetate possessing a longer alcohol part was used as a substrate to improve the enantioselectivity of the bakers' yeast reduction. The use of 1 eq of 2-aminoethanethiol hydrochloride or phenyl vinyl sulfide in the bakers' yeast reduction of hexyl 4-chloroacetoacetate improved the enantioselectivity in which cases hexyl (*R*)-4-chloro-3-hydroxybutanoate was obtained with 75 or 88% ee, respectively (entry 19 & 20).[12] The highest enantioselectivity of 97% ee was achieved using 3 eq of phenyl vinyl sulfide (entry 21). The use of an excess amount of a sulfur compound decreased the chemical yield and/or reactivity of the baker' yeast reduction, although the enantioselectivity was improved. These results would be due to inhibition of the reductase of bakers' yeast or production of byproducts by the reaction of the substrate with a sulfur compound.

On the other hand, chiral 3-hydroxybutanoate possessing a hetero-substituent such as an oxygen or sulfur atom at the C-4 position is a useful intermediate for the synthesis of a β-lactam compound[8a,13] and, thus, the bakers' yeast reduction of ethyl 4-benzyloxyacetoacetate in the presence of a sulfur compound was also investigated. The use of a sulfur compound such as L-cysteine or phenyl vinyl sulfide increased the enantioselectivity (entry 23 & 24). The absolute stereochemistry was determined by comparison of the optical rotation.[2d] The use of 3 eq of phenyl vinyl sulfide and 2 eq of L-cysteine enhanced the enantioselectivity more effectively than that of phenyl vinyl sulfide or L-cysteine alone (entry 25). The combined use of phenyl vinyl sulfide and 2-aminoethanethiol hydrochloride was the most effective. The best enantioselectivity was achieved using 3 eq of phenyl vinyl sulfide and 2 eq of 2-aminoethanethiol hydrochloride in up to 87% ee (entry 27).

In summary, improved enantioselectivity was demonstrated using a sulfur compound in the bakers' yeast reduction of β-keto esters. Moreover, acceleration of the reduction rate, which has not been observed previously, was achieved in the bakers' yeast reduction of 3-oxoalkanoate. Therefore, the effect of a sulfur compound could not be due to the role of inhibitor of the reductase, because the rate of the bakers' yeast in the presence of a sulfur compound was accelerated. The sulfur compound possessing a mercapto group such as L-cysteine and 2-aminoethanethiol hydrochloride may act as a hydride source to reproduce of NAD(P)H in the reduction.[14] Although the effect of a sulfur compound has not been substantiated, one assumption is based on the interaction of the sulfur compound with an active site of reductase. The sulfur compound may interact with the active site of bakers' yeast to change the cavity of reductase. Therefore, the reactivity and enantioselectivity were improved. Another assumption is based on the initial interaction of the sulfur compound with the substrate in the case of using a sulfur compound possessing a mercapto group.[15] In particular, the reaction of a thiol compound with a carbonyl compound gives hemithioacetal.[16] A hemithioacetal compound was actually obtained under the present reduction conditions from 1-phenyl-1,2-propanedione and thiophenol. The sulfur compound interacted with the substrate, and then the sulfur atom in the resulting species interacted with the thiophilic part of the active site of reductase. High enantioselectivity in the bakers' yeast reduction of β-keto ester derivatives was achieved by combination of an addition of a sulfur compound with an appropriate selection of the alcohol part of the ester.

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10 It has been reported that an accelerated reaction rate was observed using glucose, the energy-gaining and NAD(P)H-producing glycolysis system of yeast, in the bakers' yeast reduction of β-keto ester derivatives (ref. 4b).

11 The absolute stereochemistry was established by its derivatization to the known methyl ester, and comparison of the optical rotation. (ref. 2a)

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