Synthesis of Chiral Epoxides from Aldehydes Using Sulfur Ylide Derived from Reduced Product of Bakers' Yeast Reduction

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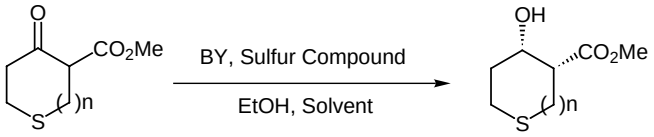
Received 31 May 1999

Abstract: Enantiomerically pure β-hydroxy ester derivatives possessing a sulfide group were obtained in the bakers' yeast reduction of the corresponding β-keto esters in the presence of a sulfur compound as an additive. Highly enantioselective synthesis of epoxides from aldehydes was achieved using sulfur ylide derived from chiral β-hydroxy esters.

Key words: bakers' yeast, sulfur compound, chiral sulfide, sulfur ylide, epoxidation

Optically active epoxide is a useful synthetic intermediate of natural products. Synthesis of epoxide from aldehyde using chiral sulfide as a catalyst is one of the effective methods for the preparation of optically active epoxides.[1] A number of sulfide reagents have been used as a catalyst. However, the preparation of the sulfide needed multiple steps, because chiral sulfide is not readily available in natural products. On the other hand, bakers' yeast reduction is a useful method for preparation of optically active alcohols.[2] However, there have been examples that afforded unsatisfactory results, low chemical yield, and/or low selectivity, mainly because of the participation of multiple enzymes with different enantioselectivity. A number of methods have been reported for the improvement of the enantioselectivity of the bakers' yeast reduction of β-keto ester analogues, involving some modification of the substrate,[3] addition of an additive as a selective inhibitor of reductase,[4] addition of an inorganic salt,[5] immobilization of bakers' yeast,[6] thermal treatment of bakers' yeast,[7] or use of an organic solvent.[8] We have developed an effective method for enhancement of the reactivity and enantioselectivity in the bakers' yeast reduction using a sulfur compound as an additive.[9] In this report, the bakers' yeast reduction of β-keto esters possessing sulfide in the presence of a sulfur compound was investigated, and the corresponding reduced products were applied to synthesis of epoxides from aldehyde derivatives.

2-Methoxycarbonyltetrahydrothiophen-3-one **1** and 3-metoxycarbonyl-tetrahydrothiopyran-4-one **2** were used as substrates. In terms of the structure of sulfur ylide, transformation of the ester moiety into diphenyl carbinol followed by ketalization with the other hydroxy group derived from the yeast reduction may make a suitable environment for the epoxidation of aldehydes via ylide formation in an enantioselective manner. Although the bakers' yeast reductions of 2-methoxycarbonyl-tetrahydrothiophen-3-one **1** and 3-metoxycarbonyltetrahydrothiopyran-4-one **2** have already been reported, the enantioselectivity was not satisfactory.[10] Therefore, the bakers' yeast reduction of those substrate in the presence



1; n = 0
2; n = 1

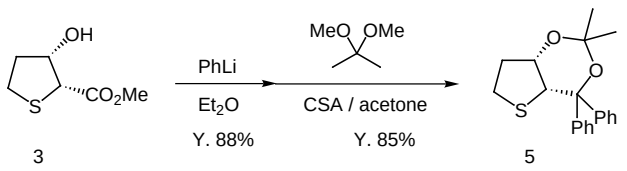
3; n = 0
4; n = 1

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

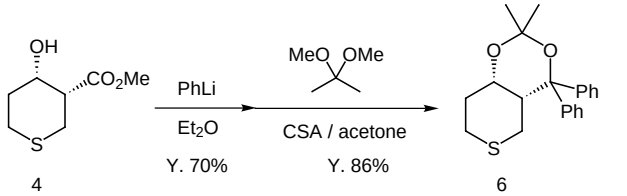
Entry	n	Sulfur Compound (eq)	Solvent	Temp.(°C)	Time(h)	Yield (%)[a]	% de[b]	% ee[b]
1	0	none	buffer	rt	1	36	>99	96
2	0	none	dist.H_2O	rt	1	64	>99	97
3	0	L-Cysteine (3.0)	dist.H_2O	rt	1	51	>99	97
4	0	DMSO (3.0)	dist.H_20	rt	1	54	>99	97
5	0	none	dist.H_2O	2	5	12	>99	>99
6	0	none	dist.H_2O	2-13	6	54	>99	97
7	0	L-Cysteine (3.0)	dist.H_2O	3-14	7	59	>99	>99
8	1	none	dist.H_2O	rt	9	79	96	92
9	1	DMSO (3.0)	dist.H_2O	rt	6	83	82	>99

[a] Isolated yield. [b] Determined by HPLC (Daicel Chiralcel OD) analysis of the corresponding benzoate derivative.

of a sulfur compound was investigated. In a typical procedure of the bakers' yeast reduction, a suspension of 2.82 g of dry bakers' yeast (S. I. Lesaffre) in 28 mL of dist. H_2O was stirred for 0.5 h at ambient temperature. To the resulting suspension was added L-cysteine (342 mg, 2.82 mmol). After 0.5 h stirring, 2.8 mL of an ethanol solution of 2-methoxycarbonyltetrahydrothiophen-3-one (150 mg, 0.94 mmol) was added to the suspension of bakers' yeast at 0 °C. After 7.0 h stirring, 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 (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography. The bakers' yeast reduction of β-keto esters was investigated, and the results are summarized in Table 1. Diastereomerically pure reduced product **3** was obtained in the bakers' yeast reduction of 2-methoxycarbonyltetrahydrothiophen-3-one **1** with 96% ee, while the chemical yield was low because of the low stability under the reaction conditions (Entry 1). The absolute configuration was established by comparison of the optical rotation with reported data.[10] Therefore, dist. H_2O was used as a solvent. The bakers' yeast reduction in the presence of a sulfur compound such as L-cysteine or DMSO was investigated (Entries 3 & 4). However, the enantioselectivity was not increased, which may be due to the high reactivity of the reduction. Accordingly reaction temperature was investigated. Enantioselectivity was improved at 0 °C, while the yield was low. The enantiomeically pure reduced product was obtained in 59% yield using L-cysteine as an additive at 3-14 °C (Entry 7). The bakers' yeast reduction of 3-methoxycarbonyl-tetrahydrothiopyran-4-one gave (3*R*,4*S*)-4-hydroxy-3-methoxy-carbonyltetrahydrothiopyrane with 92% ee. Improved enantioselectivity and acceleration of the reactivity were observed using 3 eq of DMSO as an additive with up to >99% ee (Entry 9). These reduced products obtained with enantiomerically pure form was transformed to apply to epoxidation of aldehydes as a catalyst as follows. Diphenyl carbinol was obtained by diphenylation of the ester, which was ketalized with 2,2-dimethoxypropane.



3 5



4 6

In a typical procedure of synthesis of epoxides, 0.4 mL of acetonitrile solution of the chiral sulfide (0.11 mmol) was stirred at 0 °C. To the solution was added 2 equiv of benzylbromide. After 10 min. stirring, 0.44 mL of an acetonitrile solution of 2 equiv of aldehyde and powder of 2.8 equiv of NaOH were added at the same temperature. The reaction temperature was allowed to rise to ambient temperature. The reaction was quenched by addition of brine. The resulting mixture was extracted with ethyl acetate (15 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified on preparative TLC. The results are summarized in Table 2.

Synthesis of epoxide from benzaldehyde using sulfur ylide derived from chiral sulfide **6** gave (*R*,*R*)-stilbene oxide in 64% yield, while the enantioselectivity was only 7% ee. The absolute configuration was established by comparison of the optical rotation with an authentic sample. The low selectivity may be due to the distance of the chiral center to the reaction point. Therefore, tetrahydrothiophene derivative **5** was used as a catalyst instead of the tetrahydrothiopyrane derivative. The enantioselectivity was increased with up to 78% ee. The turnover cycle for the reaction of benzaldehyde was observed using NaOH as a base, which has not been previously reported without using excess aldehyde (Entry 3).[1a] Benzyl benzoate was produced *via* Cannizzarro reaction of benzaldehyde using KOH as a base. The reaction with various aldehydes was investigated under the same conditions. Increased enantioselectivity was observed by introduction of a chloro group to the ortho-position of benzaldehyde (Entry 5). The highest enantioselectivity was achieved in the reaction of tolaldehyde with up to 92% ee (Entries 6 & 7).

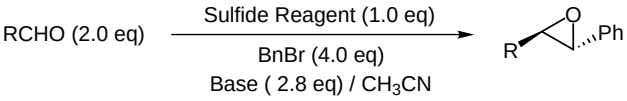


Table 2. Synthesis of Epoxides from Aldehydes with Sulfur Ylide.

Entry	R	sulfide reagent	Base	Time (h)	Yield (%)[a]	%ee[b]
1	Ph	**6**	KOH	20	64	7
2	Ph	**5**	KOH	23	79	78
3	Ph	**5**	NaOH	23	105	78
4	*trans*-PhCH=CH	**5**	NaOH	25	71	34
5	*o*-ClC_6H_4	**5**	NaOH	18	112	86
6	*p*-Tol	**5**	NaOH	21	78	92
7	*o*-Tol	**5**	NaOH	21	79	92

a Isolated yield based on the sulfide reagent. b Determined by HPLC (Daicel Chiralcel OD) analysis.

In conclusion, homo chiral sulfide derivatives were easily synthesized utilizing the bakers' yeast reduction in the presence of a sulfur compound. Subsequent manipulation of the reduction products allows a highly enantioselective

synthesis of epoxides from aldehydes without tedious isolation of intermediary sulfur ylides.

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Article Identifier:
1437-2096,E;1999,0,08,1328,1330,ftx,en;Y11499ST.pdf