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Asymmetric Reduction of α,β-Unsaturated Ketones with Bakers' Yeast[1]

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Abstract: Bakers' yeast reduction of 3-methyl-4-phenyl-3-buten-2-one affords the corresponding saturated (3*S*)-ketone selectively, while 4-(2-furyl)-3-methyl-3-buten-2-one is selectively transformed to the corresponding (2*S*)-allylic alcohol.

Bakers' yeast, *Saccharomyces cerevisiae*, is now well recognized as a valuable reagent in asymmetric synthesis. The asymmetric reduction of simple carbonyl groups with this microbe has been studied extensively, while little is known about the reduction of α,β-unsaturated carbonyl compounds.[2] It is interesting that controversial results were obtained from the reduction of α,β-disubstituted enones such as 3-methyl-4-phenyl-3-buten-2-one. Fuganti *et. al.* reported that bakers' yeast reduction of the enone gives the corresponding (2*S*)-allylic alcohol in 15% yield containing small amount of the corresponding saturated alcohol.[3] In contrast, Sakai *et. al.* reported the production of saturated (3*S*)-ketone by the same reaction.[4] The carbonyl group of the enone is reduced predominantly in the former case, whereas in the latter case the carbon-carbon double bond is reduced exclusively. Since there remain ambiguities in the mode of the reduction and stereoselectivities of these reductions, we investigated detailed structural feature influencing the mode of bakers' yeast reduction of α,β-disubstituted α,β-unsaturated carbonyl compounds.

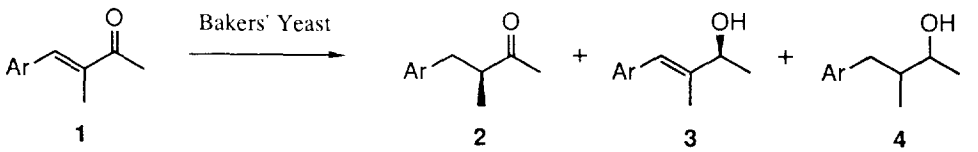
Enones, **1a-g**, were prepared from the reaction of the corresponding aryl aldehyde with 2-butanone in 1M H_2SO_4 of acetic acid solution. Furyl enones, **1h-i**, were prepared from the reactions of furfural and 5-methylfurfural with propionaldehyde followed by the methylation of formyl group with methyllithium, and oxidation of the hydroxyl group with dichlorodicyanobenzoquinone. The enones were reduced with dry bakers' yeast at 35 °C. After usual work-up, chemical yield was determined by GLC,[5] and enantiomeric excess in the product was determined by using a chiral capillary GC-column.[6] The results are listed in Table 1.

The reduction of phenyl enone, **1a**, with bakers' yeast affords (3*S*)-(+)-3-methyl-4-phenyl-2-butanone **2a** in 42% yield and 71% e.e., in which allylic alcohol, **3a**, and saturated alcohol, **4a**, were also detected as minor components.[7] The stereoselectivity of the reduction of carbon-carbon double bond is strongly influenced by a substituent on the phenyl ring. The introduction of a hydroxyl group at the *para*-position retards the reduction and decreases the stereoselectivity. In addition, the site of a substituent plays a crucial role in the stereoselectivity of the reduction. The presence of a methoxy substituent in the *para*-position decreases stereoselectivity of the reduction, whereas substitution at the *ortho*- or *meta*-position drastically improves the stereoselectivity up to satisfactory level. The reduction of *meta*, *para*-disubstituted compound, **1f**, also affords the saturated (3*S*)-ketone, **2f**, in excellent stereoselectivity.[8]

It is interesting that replacement of the phenyl group by a heterocycle changes the mode of the reduction. The bakers' yeast reduction of 2-pyridyl enone, **1g**, affords racemic saturated ketone, **2g**, whereas 2-furyl enone, **1h**, is transformed selectively to the corresponding (2*S*)-allylic alcohol, **3h**, in more than 99% e.e. The reduction rate is retarded enormously by the presence of a methyl substituent on the 5-position of furyl ring.

In conclusion, bakers' yeast reduces α-methyl-β-phenyl-α,β-unsaturated carbonyl compounds, **1**, to the corresponding saturated ketones, **2**, with excellent stereoselectivity. The presence of an *ortho*- or *meta*-substituent plays a crucial role in this stereoselective carbon-carbon double bond reduction. The reported result is believed to be a useful method for obtaining chiral ketones in excellent stereoselectivity.

Table 1. Asymmetric Reduction of Enones with Bakers' Yeast[a]



1 **2** **3** **4**

	Ar	Time/h	Yield/% (E.e./%)		
a	Ph	30	42 (71)	3	9
b	4-HO-Ph	76	20 (58)	0	0
c	2-MeO-Ph	48	13 (>95)	0	0
d	3-MeO-Ph	48	72 (>95)	0	7
e	4-MeO-Ph	20	73 (61)	0	16
f	3,4-*di*MeO-Ph	60	59 (>95)	1	6
g	2-Py	50	59 (1)	7	23
h	2-Furyl	80	5 (67)	30 (>99)	13
i	5-Me-2-Furyl	24	8	0	0

[a] Conditions: Enone, **1**: 0.5 mmol, Dry bakers' yeast: 5 g, Water: 30 mL.

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References and Notes

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4. Sakai, T.; Matsumoto, S.; Hidaka, S.; Imajo, N.; Tsuboi, S.; Utaka, M. *Bull. Chem. Soc. Jpn.*, **1991**, *64*, 3473-3475.
5. Chemical yields were determined by using a capillary GC-column, OV-1701 bonded 30 m. Dodecane was used as a standard compound.
6. Enantiomeric excesses were determined by using a chiral capillary GC-column, Chiraldex G-TA and CHROMPACK CP-Cyclodextrin-B-2,3,6-M-19 capillary column.
7. Absolute configuration of saturated ketone, **2a**, was determined to be *S*: *cf.* ref. 4.
8. Absolute configuration of saturated ketone, **2f**, was determined to be *S* by comparing its optical rotation with that reported: $[\alpha]_D^{27}$=+33.6 (c=4.30, $CHCl_3$); reported value for *R* configuration: $[\alpha]_D^{20}$=-35.3 (c=4.30, $CHCl_3$). *cf.* A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **79**, 3827 (1957).

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