CHEMISTRY LETTERS, pp. 129-132, 1987.

Enantioselective Synthesis of Optically Pure Amino Alcohol Derivatives by Yeast Reduction

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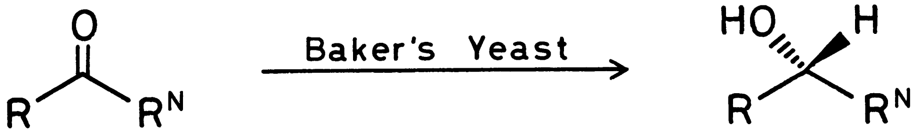
Baker's yeast reduction of nitro- and imide-containing ketones gives the corresponding secondary alcohols in good yields with excellent optical purity. Among the imide groups examined, the ketones with saccharin moiety give the products in the best chemical and optical yields.

Chiral amino alcohols and their derivatives are widely found in natural products or in pharmaceutical agents,[1a)] and also used as chiral auxiliaries in the asymmetric synthesis.[1b)] Typical method for their synthesis is reduction of easily available chiral amino acids, whose products are restricted to chiral secondary amines with primary hydroxy group. On the other hand, baker's yeast reduction of nitrogen-functionalized ketones would give chiral secondary alcohols with amino groups. Baker's yeast mediated reduction of ketones often gives highly optically pure secondary alcohols.[2)] Concerning the reduction of nitrogen-functionalized ketones, however, only limited works have been reported, i.e. reduction of α-ketoamide,[3)] γ-amino-α-ketoester,[4)] and ketones with isoxazole moiety,[5)] but optical purities of these products are not always high. Now we wish to describe here the baker's yeast reduction of nitro- and imide-containing ketones to give the corresponding secondary alcohols in high yields with excellent optical purities.



Since aminoketones are difficult to isolate as the free state because of Schiff base formation, and amino alcohols are too soluble to extract from water, yeast reduction of masked aminoketone derivatives is investigated instead of aminoketone itself. Nitro group can be easily reduced to amino group, so then yeast reduction of easily prepared nitroketones[6)] was firstly examined. 3-Methyl-3-nitro-2-butanone (**1**) was reduced in the suspension containing baker's yeast and saccharose at rt to give 3-methyl-3-nitro-2-butanol in 57% yield after distillation. The optical purity of the product was determined to be more than 96%ee by NMR using chiral shift reagent Eu(hfc)$_3$, and the other enantiomer could not be detected.[7)] Generally

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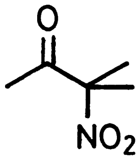
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.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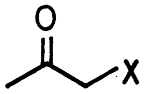
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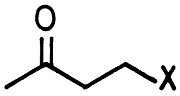
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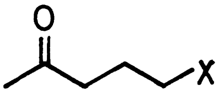
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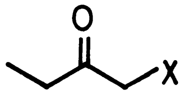
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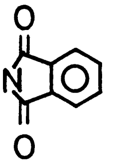

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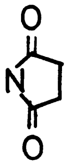

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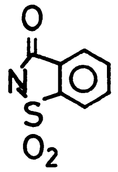


nitroalcohols, however, are relatively unstable under conditions of the yeast reduction, because of decomposition by a retro-nitroaldol reaction.

Yeast reduction of phthalimide-containing ketones, easily prepared by the reaction of halo ketone and potassium phthalimide,[8] was then investigated. N-(2-Oxopropyl)-phthalimide (2a) afforded N-(2-hydroxypropyl)-phthalimide in 74% yield by the baker's yeast reduction for 3 days. The optical purity of the product alcohol showed 94%ee determined by ^1H NMR of acetyl signal for the corresponding α-methoxy-α-trifluoromethylphenylacetyl (MTPA) ester.[9] This alcohol could be purified to optically pure state by recrystallization from ethyl acetate.

The yeast reduction of ketones with various kinds of imide groups was investigated as shown in Table 1. N-(2-Oxopropyl)-succinimide (2b), and N-(2-oxopropyl)-o-benzoic sulfimide (-saccharin) (2c)[8] gave the corresponding alcohols in 48% and 81% yields respectively, whose optical purity was determined to be more than 96%ee by the MTPA method. The lower yield in the case of succinimide derivative 2b depends on the difficulty for extraction because of the high water-

Table 1. The baker's yeast reduction of ketones

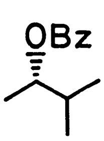
Ketone	Time	Yield/%	Mp of alcohol/°C	%ee	$[\alpha]_D^{23}$	(c, $CHCl_3$)	Abs. config
1	7.5 h	57	oil	>96[b]	+ 25.6	(2.31)	S
2a	3 d[a]	74	99.5—100.5	94[c]	+ 15.7[d]	(1.53)	S
2b	3 d[a]	48	oil	>96[c]	+ 32.1	(1.45)	S
2c	1 d	81	83—87	>96[c]	+ 9.6	(2.81)	S
3a	4 d[a]	94	73—74	95[c]	+ 27.2[d]	(0.48)	S
4a	9 d[a]	41	oil	45[c]	+ 2.6	(3.42)	S
4c	6 d[a]	52	oil	75[c]	+ 3.2	(2.45)	S
5a	10 d[a]	9	50—51	15[c]	+ 5.6	(1.08)	S
5c	6 d[a]	54	oil	>96[c]	+ 8.2	(0.61)[e]	S

a) Saccharose 6 g and yeast 5 g in 40 ml water / ketone (1 mmol) were added everyday when the reaction time exceed one day. b) Determined by ^1H NMR using chiral shift reagent $Eu(hfc)_3$. c) Determined by ^1H NMR of the corresponding MTPA esters. d) Specific rotation of optically pure sample after recrystallization. e) In ethanol.

solubility of the corresponding alcohol. Saccharin derivative 2c showed the best result of chemical yield and optical purity in the yeast reduction.

Concerning the effect of the number of methylene group between imide and carbonyl groups, N-(3-oxobutyl)-phthalimide (3a) gave N-(3-hydroxybutyl)-phthalimide in 94% yield with 95% optical purity, which can be purified to optically pure state by recrystallization from ethyl acetate-hexane. In the case of 4-oxopentane derivatives, N-(4-oxopentyl)-saccharin (4c) gave N-(4-hydroxypentyl)-saccharin with much higher optical purity of 75%ee compared with the corresponding phthalimide alcohol derived from ketone 4a. Generally, in the yeast reduction of ethylketones, optical yield of the product is not so high10) with only few exceptions.11) The fitness of saccharin derivatives for the yeast reduction was typically shown in the reduction of ethyl ketones 5a and 5c. Actually N-(2-oxobutyl)-phthalimide (5a) gave N-(2-hydroxybutyl)-phthalimide with low optical purity of 15%, while N-(2-oxobutyl)-saccharin (5c) gave the corresponding alcohol with excellent optical purity of over 96%ee.

Absolute configuration of the alcohols obtained by the present baker's yeast reduction was determined by transformation into known compounds and comparison of the signs of the specific rotation of them with reported values. 3-Methyl-3-nitro-2-butanol obtained from ketone **1** was benzoylated and reduced12) to (2S)-3-methylbut-2-yl benzoate (6) ($[\alpha]_D^{23}$ +41.1° (c 2.45, $CHCl_3$)).13a) N-(2-Hydroxypropyl)-phthalimide, -succinimide, and -saccharin derived from ketone 2a, 2b, and 2c respectively, are converted12) to (2S)-N,O-dibenzoyl-1-amino-2-propanol (7) ($[\alpha]_D^{23}$ +72.1° (c 0.33, EtOH), +70.3° (c 0.35), +69.0° (c 0.41)).13b) N-(3-Hydroxybutyl)-phthalimide from ketone 3a was hydrazinolized14) to (3S)-1-amino-3-butanol hydrochloride (8) ($[\alpha]_D^{23}$ +7.01° (c 0.97, H_2O)).13c) N-(4-Hydroxypentyl)-phthalimide and -saccharin derived from ketone 4a and 4c were transformed to (2R)-1-tosyl-2-methylpyrrolidine (9) by hydrazinolysis or hydrolysis, tosylation and cyclization14,15) ($[\alpha]_D^{23}$ -29.2° (c 0.47, EtOH), $[\alpha]_D^{23}$ -51.4° (c 0.070)).13d) This pyrrolidine 9 is R form due to inversion during the cyclization. N-(2-Hydroxybutyl)-saccharin was hydrolyzed16) to (2S)-1-amino-2-butanol oxalate (10) ($[\alpha]_D^{23}$ +9.9° (c 0.19, H_2O)).13e) Accordingly all alcohols obtained by the present yeast reduction showed S-form, as predicted from the Prelog's rule.17)



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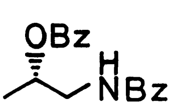

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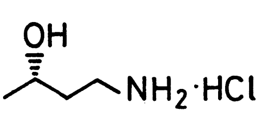

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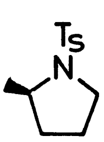

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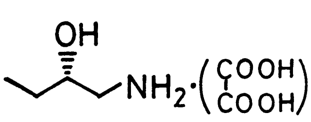

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A typical procedure for the baker's yeast reduction of N-(2-oxopropyl)-saccharin (2c) is as followes: A suspension of 6 g of saccharose and 5 g of the baker's yeast (Oriental Yeast Co.) in 40 ml of water was stirred for 30 min at rt, and then 5 ml of ethanol suspension of finely powdered 2c (1 mmol) was added to the yeast suspension. The reaction was monitored by silica-gel TLC analysis until the disappearance of the starting ketone. After the ketone faded (1 day), celite and ethyl acetate were added, and the mixture was stirred for 30 min and then filtered through a celite pad. The filtrate was extracted with ethyl acetate and purification by TLC on silica-gel gave N-(2-hydroxypropyl)-saccharin in 81% yield.

In conclusion, by the yeast reduction of nitrogen-functionalized ketones, chiral amino alcohol derivatives were obtained with excellent optical purities. Among imide ketones examined, saccharin-containing ketones gave the corresponding products with excellent optical yields. Since imide group or nitro group can easily be converted to amino group, this procedure provides a usuful method for the synthesis of chiral amino alcohols.

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(Received October 1, 1986)