

REDUCTION OF N-OXIDE WITH BAKER'S YEAST[†]

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Abstract – Reduction of N-oxides with baker's yeast has been examined. In the reduction of acetylpyridine N-oxides, selective reduction takes place to give chiral pyridylethanol N-oxides.

Baker's yeast (*Saccharomyces cerevisiae*) has been recognized as one of potentially useful catalyst for the synthesis of various chiral synthons. Based on its reductive abilities, carbonyl¹ and nitro² groups have been converted to corresponding hydroxyl and amino moieties. Deoxygenation of pyridine N-oxide itself with baker's yeast was reported,³ however, no extensive study on the reduction of N-oxide using this microorganism has been carried out. We now report the reduction of aromatic or aliphatic N-oxides and the chemoselective reduction of acylpyridine N-oxides with baker's yeast. As shown in Table I, when substituted pyridine N-oxides (**1**) were treated with baker's yeast for 161-168 h at 35 °C, the reduction proceeded to give the corresponding deoxygenated pyridine derivatives (**2**) in 0-44 % chemical yields. In these reductions, it was found that by substitution of electron-donating group on pyridine ring, N-oxides were smoothly reduced to afford deoxygenated products (22-44 %)(**Entries a-e**), while by substitution of electron-withdrawing group, the reaction proceeded in poor chemical yields (0-7 %)(**Entries g-l**). The same reaction of aromatic N-oxides (quinoline N-oxide (**3**), isoquinoline N-oxide (**5**)) gave also the corresponding deoxygenated products (**4**), (**6**) in 8 and 44 % chemical yields, respectively. In contrast to the reduction of aromatic N-oxides, however, aliphatic N-oxides (**7**), (**9**), (**11**) were reduced in moderate to good chemical yields (52-84 %)

[†] Dedicated to the memory of Dr. Tetsuji Kametani.

(Table II). Interestingly, when (S)-(-)-nicotine-N, N'-dioxide (**13**)⁴ was treated with baker's yeast, selective reduction between aromatic and aliphatic N-oxides was occurred to give pyridine N-oxide (**14**)⁴ in 32 % chemical yield with (S)-(-)-nicotine (**15**) as a minor product (6 %)(Scheme I).

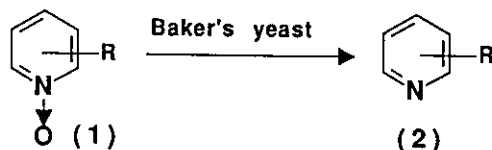


Table I. Reduction of pyridine N-Oxides with Baker's Yeast

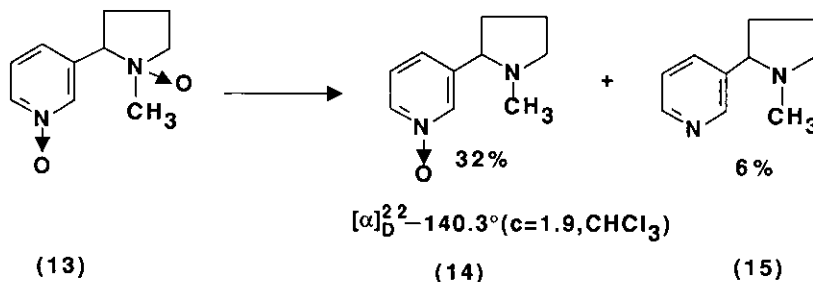
No	R	Time (h) ^{a)}	Yield of 2 (%) ^{b)}
a	2-CH ₃	168	22 (76)
b	3-CH ₃	161	29 (64)
c	4-CH ₃	166	22 (74)
d	3-OH	167	31 (0)
e	4-OCH ₃	161	44 (5)
f	4-C ₆ H ₅	164	35 (58)
g	4-NO ₂	164	0 (0)
h	4-CN	168	0 (84)
i	2-Br	166	7 (54)

a) Temperature is 35 °C.

b) Recovered starting material is given in parenthesis.

Table II. Reduction of Aromatic and Aliphatic N-Oxides with Baker's Yeast

Substrate	Time (h)	Temp. (°C)	Product	Yield (%)
Quinoline N-oxide (3)	166	35	Quinoline (4)	8
Isoquinoline N-oxide (5)	168	33	Isoquinoline (6)	44
N,N-Dimethylaniline N-oxide (7)	156	33	N,N-Dimethylaniline (8)	52
N-Methylmorpholine N-oxide (9)	168	35	N-Methylmorpholine (10)	78
N-Phenylmorpholine N-oxide (11)	168	33	N-Phenylmorpholine (12)	84



Scheme I

As shown in Table III, when acetylpyridine N-oxides (16)⁵ were incubated with baker's yeast, chemoselective reduction was occurred to give the chiral pyridylethanol N-oxides (17)⁶. Namely, carbonyl group was reduced in preference to N-oxide in this reaction. The alcohols (17) thus obtained were found to have (S)-configuration by conversion of 17 with Raney Nickel into the chiral pyridylethanol (18)⁷. The optical purities of the alcohols derived from both α - and β -isomers (17 $_{\alpha,\beta}$) were significantly higher (96-97% ee), but the optical purity of γ -isomer (17 $_{\gamma}$) was somewhat lower (65% ee).

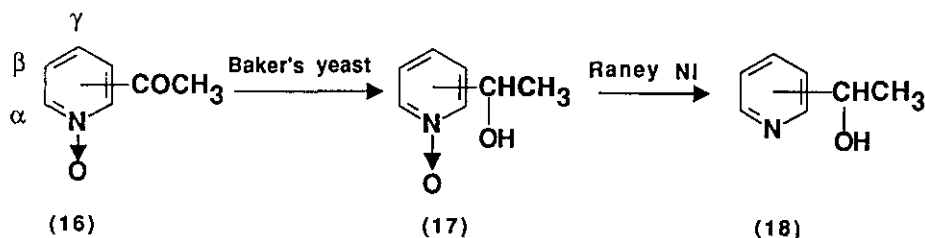


Table III. Asymmetric Reduction of Acetylpyridine N-Oxides with Baker's Yeast

	Temp. (°C)	Time (h)	Yield of (17) (%)	$[\alpha]_D$ of (17) ^a In CHCl ₃	% ee ^b of (17)	Config ^c of (17)	Yield of (18) (%)	$[\alpha]_D$ of (18) ^a In CHCl ₃
α	35	96	95	+16.8° (c=9.5)	96	S	20	-21.7° (c=0.8)
β	27	95	36	+7.0° (c=1.0)	97	S	47	-56.6° (c=1.8)
γ	29	73	31	-2.6° (c=1.0)	65	S	30	-33.5° (c=2.6)

a) Temperature: 22-23 °C. b) Optical purities are determined by 400 MHz ¹H-nmr(CDCl₃) analysis of the corresponding (-)- α -methoxy- α -trifluoromethylphenylacetic acid ester (MPA ester) of (17). c) Determined from the configuration of (18).

Thus, we found that aliphatic N-oxide could be reduced easier than aromatic N-oxides by baker's yeast and in the reduction of acetylpyridine N-oxides, only carbonyl group was reduced to give the pyridylethanol N-oxides.

EXPERIMENTAL

Reduction of N-oxides (1a) with baker's yeast.

A mixture of α -picoline N-oxide (1a)(0.5 g) and baker's yeast (500 g)(purchased from Oriental Yeast Co.) in water (250 ml) was incubated for 161-168 h at 30-35 °C. The mixture was extracted continuously with CHCl₃ using a Soxhlet apparatus and the extract was dried over

Na₂SO₄. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (12 g) column chromatography using CH₂Cl₂ as an eluent to yield (2a)⁸ (0.19 g, 22 %). bp 130 °C.

Synthesis of (S)-2-pyridylethanol N-oxide (17α) with baker's yeast.

A mixture of 2-acetylpyridine N-oxide (16α)(1.0 g) and baker's yeast (500 g) in water (250 ml) was incubated for 96 h at 35 °C. The mixture was extracted continuously with CHCl₃ using a Soxhlet apparatus and the extract was dried over Na₂SO₄. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (15 g) column chromatography using CH₂Cl₂-MeOH (98:2) as an eluent to give (17α)⁶(0.96 g, 95 %).

$[\alpha]_D^{22} + 16.8^\circ$ (c= 9.5, CHCl₃), (96 % ee).

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