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, carbonyl[1] and nitro[2] 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).

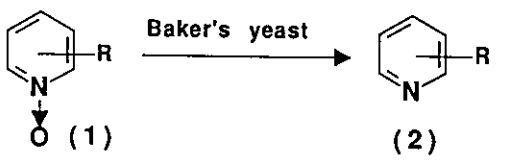


Table I. Reduction of pyridine N-Oxides with Baker's Yeast

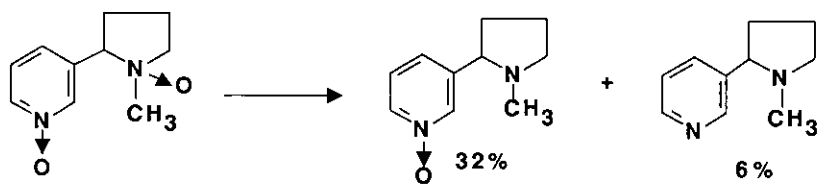
No	R	Time (h)[a]	Yield of 2 (%)[b]
a	2-CH_3	168	22 (76)
b	3-CH_3	161	29 (64)
c	4-CH_3	166	22 (74)
d	3-OH	167	31 (0)
e	4-OCH_3	161	44 (5)
f	4-C_6H_5	164	35 (58)
g	4-NO_2	164	0 (0)
h	4-CN	168	0 (84)
i	2-Br	166	7 (54)

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-Methylmorphorine N-oxide (9)	168	35	N-Methylmorphorine (10)	78
N-Phenylmorphorine N-oxide (11)	168	33	N-Phenylmorphorine (12)	84

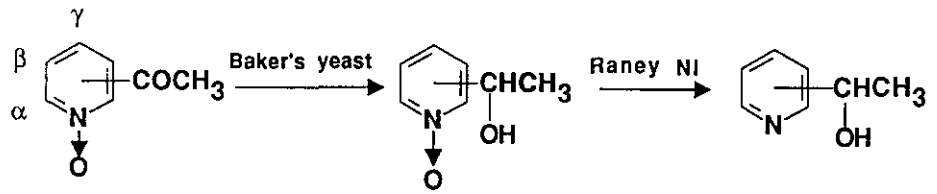


$[\alpha]_D^{22}$ −140.3°(c=1.9,$CHCl_3$)

(13) (14) (15)

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 pyridylethanols **(18)**[7]. The optical purities of the alcohols derived from both α- and β-isomers **(17α,β)** were significantly higher (96-97% ee), but the optical purity of γ-isomer **(17γ)** was somewhat lower (65% ee).



(16) **(17)** **(18)**

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 ^{1}H-nmr($CDCl_3$) analysis of the corresponding (−)-α-methoxy-α-trifluoromethylphenylacetic acid ester (MTPA 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 $CHCl_3$ using a Soxlet apparatus and the extract was dried over

Na_2SO_4. The solvent was removed under reduced pressure to give the residue which was purified by silica gel (12 g) column chromatography using CH_2Cl_2 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 $CHCl_3$ using a *Soxlet apparatus and the extract was dried over* Na_2SO_4. *The sovent was removed under* reduced pressure to give the residue which was purified by silica gel (15 g) column chromatography using CH_2Cl_2-MeOH (98:2) as an eluent to give (**17α**)[6](0.96 g, 95 %). $[\alpha]_D^{22}$ +16.8 °(c= 9.5, $CHCl_3$), (96 % ee).

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Received, 31st August, 1989