# Reduction of Aromatic Nitro Compounds with Baker's Yeast

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**The reduction of the nitro group of aromatic nitro compounds with baker's yeast was strongly influenced by the nature of the substituent on nitrobenzene, and in the reaction of acyl nitrobenzenes, selective reduction occurred to give optically active nitro alcohol and amino ketone without giving any amino alcohol.**

**Keywords** baker's yeast; aromatic nitro compound; selective reduction; acyl nitrobenzene; chiral nitro alcohol

Baker's yeast (*Saccharomyces cerevisiae*) is a potentially useful tool[1] for the versatile synthesis of optically active materials. Though it is well known that baker's yeast reduces carbonyl compounds to give chiral alcohols, the reduction of other functional groups has not been much studied. Conversion of nitrobenzene into aniline by fermenting with baker's yeast was reported.[2] However, little is known about the influence of substituents on the reduction of aromatic nitro compounds. We report here on the substituent effect in the reduction of aromatic nitro compounds with various substituents on a benzene ring, and on the selective reduction of aromatic nitro acyl compounds with baker's yeast.

As shown in Table I, ferementaiton of aromatic nitro compounds (**1**) with baker's yeast for 24—132 h at 31—35 °C gave the corresponding aromatic amines (**2**) in 4—88% chemical yields. In these reactions, we found that the reduction was influenced significantly by the nature of the substituent on the aromatic ring. When an electron-donating group such as $NH_2$, OH, SH, $CH_3$, $OCH_3$ and Br was substituted, the reduction proceeded very sluggishly or did not proceed at all (No. 1—13). In contrast, when an electron-withdrawing group such as $NO_2$, CN, $CF_3$ and COOEt was substituted, the reduction proceeded smoothly to give the aromatic amine in good yields (No. 14—28).


**1** **2**

Chart 1

TABLE I. Reduction of Aromatic Nitro Compounds (**1**) with Baker's Yeast

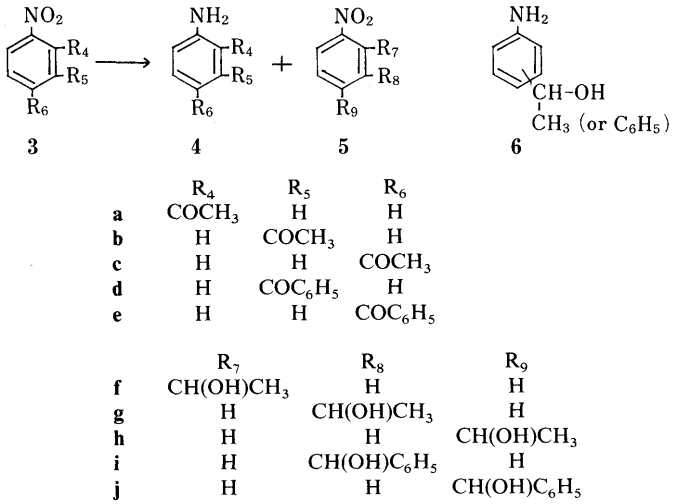
| No. | $R_1$ | $R_2$ | $R_3$ | Reaction[a] time (h) | Yield of **2**[b] (%) | (Recovery of **1** (%)) | mp (°C) [°C/mmHg] of **2**[c] |
|---|---|---|---|---|---|---|---|
| 1 | $NH_2$ | H | H | 72 | 0 | (76) | — |
| 2 | H | $NH_2$ | H | 96 | 0 | (86) | — |
| 3 | H | H | $NH_2$ | 97 | 0 | (80) | — |
| 4 | OH | H | H | 88 | 0 | (13) | — |
| 5 | H | OH | H | 89 | 18 | (34) | 117 |
| 6 | H | H | OH | 61 | 0 | (59) | — |
| 7 | H | H | SH | 72 | 0 | (45) | — |
| 8 | $CH_3$ | H | H | 61 | 0 | (84) | — |
| 9 | H | $CH_3$ | H | 132 | 17 | (39) | [91—93/30] |
| 10 | H | H | $CH_3$ | 114 | 14 | (47) | 42—43 |
| 11 | $CH_3O$ | H | H | 71 | 22 | (72) | [115/20] |
| 12 | H | $CH_3O$ | H | 72 | 25 | (50) | [113/20] |
| 13 | H | H | $CH_3O$ | 67 | 0 | (70) | — |
| 14 | Br | H | H | 74 | 62 | (28) | [115/20] |
| 15 | H | Br | H | 72 | 42 | (46) | [135/20] |
| 16 | H | H | Br | 119 | 37 | (23) | 56—58 |
| 17 | $NO_2$ | H | H | 26 | 87 | (0) | 71—74 |
| 18 | H | $NO_2$ | H | 99 | 66 | (0) | 112—113 |
| 19 | H | H | $NO_2$ | 78 | 87 | (0) | 146—148 |
| 20 | CN | H | H | 96 | 30 | (0) | 47—48 |
| 21 | H | CN | H | 20 | 88 | (0) | 52 |
| 22 | H | H | CN | 97 | 80 | (0) | 84—85 |
| 23 | $CF_3$ | H | H | 48 | 66 | (0) | [68—15] |
| 24 | H | $CF_3$ | H | 94 | 55 | (0) | [143—145/20] |
| 25 | H | H | $CF_3$ | 89 | 48 | (0) | [40/0.7] |
| 26 | COOEt | H | H | 24 | 28 | (44) | [130/10] |
| 27 | H | COOEt | H | 24 | 28 | (27) | [185/20] |
| 28 | H | H | COOEt | 24 | 61 | (0) | 86—88 |
| 29 | $NHCOCH_3$ | H | H | 72 | 25 | (8) | 132[2] |
| 30 | H | $NHCOCH_3$ | H | 72 | 59 | (34) | 85—86[3] |
| 31 | H | H | $NHCOCH_3$ | 96 | 4 | (77) | 161—162 |

*a*) Reaction temperatures were 31—35 °C. *b*) All compounds gave satisfactory IR and $^1$H-NMR spectra. *c*) Identical with authentic samples, purchased from Aldrich Chemical Co., Inc. (except 29 and 30).

TABLE II. Reduction of Acyl Nitrobenzenes with Baker's Yeast

| Substrate 3 | Temp. °C | Time h | Product | Yield (%)[b] of 4/5 | mp (°C) [°C/mmHg] of 4 | $[\alpha]_D$ °C[c] (c, $CHCl_3$) of 5 | %ee[d] of 5 | Config. of 5 | mp (°C) [°C/mmHg] of 5 | Ref. of 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | 32 | 108 | **4a**[a] + **5f** | 80/12 (0) | [130/10] | +45.5 (1.1) | 97 | *S* | [120/10] | 5 |
| | 24 | 36 | | 44/17 (35) | [155/20] | +45.6 (1.3) | 96 | *S* | [130/15] | |
| **3b** | 33 | 93 | **4b**[a] + **5g** | 15/22 (0) | 92—93 | −30.6 (2.3) | 80 | (*S*)[e,f] | 84—86 | |
| | 24 | 36 | | 2/63 (18) | 92 | −38.7 (1.0) | 97 | (*S*)[e,f] | 85—86 | |
| **3c** | 33 | 93 | **4c**[a] + **5h** | 70/10 (0) | 103—105 | −13.6 (1.9) | 73 | *S* | [100—105/1.3] | 5 |
| | 24 | 36 | | 3/84 (3) | 104—105 | −18.5 (1.0) | 80 | *S* | [151—155/20] | |
| **3d** | 33 | 93 | **4d**[6] + **5i** | 15/23 (10) | 81—82 | −52.6 (2.2) | 82 | [e] | 88—90 | 7 |
| | 24 | 36 | | 5/26 (32) | 80—81 | −62.9 (1.0) | 98 | | 88—89 | |
| **3e** | 35 | 80 | **4e**[a] + **5j** | 25/20 (0) | 120—122 | +78.0 (1.0) | 98 | *S* | 65—66 | 7—9 |
| | 24 | 36 | | 12/15 (60) | 119—122 | +68.8 (2.0) | 86 | *S* | 62—63 | |

*a*) All compounds gave satisfactory IR and $^1$H-NMR spectra and were identical with authentic samples, purchased from Aldrich Chemical Co., Inc. *b*) Recovered starting material is given in parenthesis (%). *c*) Temperature: 21—24 °C. *d*) See Experimental. *e*) The configuration is unknown. *f*) Estimated by $^1$H-NMR analysis of the corresponding (−) or (+)-MTPA ester; see Experimental.




| | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|
| **a** | $COCH_3$ | H | H |
| **b** | H | $COCH_3$ | H |
| **c** | H | H | $COCH_3$ |
| **d** | H | $COC_6H_5$ | H |
| **e** | H | H | $COC_6H_5$ |

| | $R_7$ | $R_8$ | $R_9$ |
|---|---|---|---|
| **f** | $CH(OH)CH_3$ | H | H |
| **g** | H | $CH(OH)CH_3$ | H |
| **h** | H | H | $CH(OH)CH_3$ |
| **i** | H | $CH(OH)C_6H_5$ | H |
| **j** | H | H | $CH(OH)C_6H_5$ |

Chart 2

However, some differences of reactivity between *ortho*-, *para*-nitro compounds and the *meta*-isomers were observed. The low chemical yields in the reduction of nitro anilide would be due to the low solubility in water (No. 29—31).

Interestingly, when a ketocarbonyl group existed on the aromatic ring, selective reduction took place to give amino ketones (**4**) and chiral alcohols (**5**) without giving any amino alcohol (**6**). As shown in Table II, the selective reduction was strongly influenced on the reduction temperature as well as the substituent position. Thus, when *ortho*- or *para*-acyl nitrobenzenes were fermented with baker's yeast for 72—108 h at 32—33 °C, amino ketones (**4**) were preferentially obtained, while the *meta*-isomers gave a slight excess of nitro-alcohols (**5**) over amino ketones (**4**). However, all compounds (except for *ortho*-nitroacetophenone (**3a**)) preferentially gave the nitro alcohols under milder conditions (for 24 h at 24 °C). Unsatisfactory chemical yields of both amino ketones (**4d—e**) and nitro alcohols (**5i—j**), though the latter showed high optical purities, may be owing to the steric bulkiness of the phenyl group, blocking access of the enzyme to the reaction site.

## Experimental

The infrared (IR) spectra were measured with a Hitachi 260-10 spectrometer. The proton nuclear magnetic resonance ($^1$H-NMR) spectra were recorded on JEOL PMX-60si (60 MHz) or JNM-GMX-400 (400 MHz) spectrometers with tetramethylsilane as an internal standard and are given in $\delta$ values. Optical rotation were measured with a JASCO DIP-360 automatic polarimeter. Mass spectra (MS) were recorded on a JEOL JMN-DX 303 at 70 eV. For column chromatography, silica gel (Wacogel C-200, from Wako Pure Chemical Industries, Ltd.) was used. Chemical yields, melting or boiling points, optical rotations and enantiomeric excess (%ee) are shown in Tables I and II.

**General Procedure for the Reduction of Aromatic Nitro Compounds (No. 1—31) with Baker's Yeast** A mixture of an aromatic nitro compound (**1**) (1 g) and baker's yeast (500 g) in distilled water (250 ml) was incubated for 26—132 h at 31—35 °C. The mixture was extracted continuously with $CHCl_3$ using a Soxlet apparatus, and the $CHCl_3$ extract was dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by $SiO_2$ column (20—40 g) chromatography using $CH_2Cl_2$ as the eluent. The product was further purified by recrystallization or distillation.

**2′-Aminoacetanilide (No. 29)** Pale yellow prisms (from benzene) (lit.,[3] mp 132 °C). IR ($CHCl_3$) cm$^{-1}$: 3400, 1670; $^1$H-NMR ($CDCl_3$): 2.13 (3H, s, $COCH_3$), 6.60—7.90 (4H, m, aromatic H). MS *m/z*: 150 ($M^+$), 108.

**3′-Aminoacetanilide (No. 30)** Pale yellow prisms (from benzene) (lit.,[4] mp 86.5—87.5 °C). IR ($CHCl_3$) cm$^{-1}$: 3400, 1680. $^1$H-NMR ($CDCl_3$): 2.13 (3H, s, $COCH_3$), 6.33—7.13 (4H, m, aromatic H). MS *m/z*: 150 ($M^+$), 108.

**General Procedure for the Reduction of Acyl Nitrobenzene (3) with Baker's Yeast** A mixture of acyl nitrobenzene (**3**) (2 g) and baker's yeast (500 g) in distilled water (250 ml) was incubated for 36—108 h at 24—33 °C. The mixture was extracted continuously with $CHCl_3$ using a Soxlet apparatus, and the $CHCl_3$ extract was dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by $SiO_2$ column (30—60 g) chromatography using $CH_2Cl_2$ as the eluent. The resulting nitro alcohols (**4a—e**) and amino ketones (**5a—e**) were further purified by recrystallization or distillation.

**(−)-2′-Nitro-1-phenylethanol (5f)** A colorless oil [lit.,[5] bp 140—150 °C/4 mmHg, $[\alpha]_D^{26}$ +18.77° (*c*=8.37, benzene)]. IR ($CHCl_3$) cm$^{-1}$: 3600, 1600, 1520, 1360. $^1$H-NMR ($CDCl_3$): 1.58 (3H, d, *J*=6.4 Hz, $CH_3$), 5.42 (1H, d, *J*=6.4 Hz, −C<u>H</u>(OH)−), 7.83—7.91 (4H, m, aromatic H). MS *m/z*: 167 ($M^+$), 150, 108. The optical purity of **5f** was determined by 400 MHz $^1$H-NMR ($CDCl_3$) analysis of the corresponding (−)-α-methoxy-α-trifluoromethylphenylacetic acid ester (MTPA ester). In the NMR spectrum of the (−)-MTPA ester, methyl protones were observed as two pairs of doublet signals due to the two diastereoisomers at 1.680 (d, *J*=6.4 Hz) and 1.729 (d, *J*=6.4 Hz) [intensity ratio=93:1.5 (from **5f** prepared at 33 °C), or 98:2.4 (from **5f** prepared at 24 °C)].

**(−)-3′-Nitro-1-phenylethanol (5g)** Colorless needles (from benzene–hexane). IR ($CHCl_3$) cm$^{-1}$: 3600, 1600, 1520, 1360. $^1$H-NMR ($CDCl_3$): 1.55 (3H, d, *J*=6.4 Hz, $CH_3$), 5.30 (1H, q, *J*=6.4 Hz, −C<u>H</u>(OH)−), 7.52—8.26 (4H, m, aromatic H). MS *m/z*: 167 ($M^+$), 152, 108. *Anal.* Calcd for $C_8H_9NO_3$: C, 57.49; H, 5.39; N, 8.39. Found: C, 57.59; H, 5.43; N, 8.45. The optical purity of **5g** was determined from the 400 MHz $^1$H-NMR spectrum of the (−)-MTPA ester. Methyl protons were observed at 1.616 (d, *J*=6.4 Hz) and 1.670 (d, *J*=6.4 Hz) [intensity ratio=83:9 (from **5g** prepared at 35 °C), or 79.3:1.3 (from **5g** prepared at 24 °C)]; (+)-MTPA ester [intensity ratio=1.5:83.4 (from **5g** prepared at 24 °C)].

**(−)-4′-Nitro-1-phenylethanol (5h)** A colorless oil [lit.,[5] bp 160—165 °C/4 mmHg, $[\alpha]_D^{28}$ −6.4° ($c$=3.42, benzene)]. IR ($CHCl_3$) $cm^{-1}$: 3600, 1600, 1500, 1360. $^1$H-NMR ($CDCl_3$): 1.52 (3H, d, $J$=6.4 Hz, $CH_3$), 5.03 (1H, q, $J$=6.4 Hz, –CH(OH)–), 7.53 (2H, d, $J$=8.3 Hz, aromatic H), 8.18 (2H, d, $J$=8.3 Hz, aromatic H). MS $m/z$: 167 ($M^+$), 152, 107. The optical purity of **5h** was determined by 400 MHz $^1$H-NMR ($CDCl_3$) analysis of the (+)-MTPA ester. Methyl protons were observed at 1.599 (d, $J$=6.4 Hz) and 1.651 (d, $J$=6.4 Hz) [the ratio of the intensity=14.2:92.4 (from **5h** prepared at 33 °C), and 11:90 (from **5h** prepared at 24 °C)].

**(−)-3′-Nitrodiphenylmethanol (5i)** Colorless needles (from benzene) [lit.,[7] mp 91—92 °C, $[\alpha]_D^{19}$ −64.1° ($c$=2, $CHCl_3$)]. IR ($CHCl_3$) $cm^{-1}$: 3600, 1600, 1500, 1350. $^1$H-NMR ($CDCl_3$): 5.93 (1H, br, PhCH–), 7.37—8.30 (9H, m, aromatic H). MS $m/z$: 229 ($M^+$), 150, 105. The optical purity was determined based on reported data.[7]

**3′-Aminobenzophenone (4d)** Colorless needles (from benzene) (lit.,[6] mp 87 °C). IR ($CHCl_3$) $cm^{-1}$: 3400, 1630, 1600. $^1$H-NMR ($CDCl_3$): 6.77—8.03 (9H, m, aromatic H). MS $m/z$: 197 ($M^+$), 120, 105.

**(+)-4′-Nitrodiphenylmethanol (5j)** Pale yellow prisms (from benzene) [lit., mp 80—81 °C,[7,9] $[\alpha]_D^{20}$ +79.5° ($c$=1.3, $CHCl_3$),[8] $[\alpha]_D^{19}$ +78.2° ($c$=1, $CHCl_3$)[7]]. IR ($CHCl_3$) $cm^{-1}$: 3600, 1600, 1495, 1350. $^1$H-NMR ($CDCl_3$): 5.92 (1H, br, PhCH–), 7.29—8.18 (9H, m, aromatic H). MS $m/z$: 229 ($M^+$), 150, 105.[10] The optical purity was determined based on reported data.[8]

**References and Notes**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10) The spectra obtained were identical with those of a racemic sample. Though the melting point was low compared to the literature values (refs. 7, 9), we also confirmed the structure by elemental analysis. *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.12; H, 4.80; N, 6.11. Found: C, 68.07; H, 4.81; N, 6.11.