Notes

Reductive Cyclization of *o*-Nitrophenylazo Dyes Using Bakers' Yeast in NaOH Solution. A New Synthesis of 2-Aryl-2*H*-benzotriazoles and Their 1-Oxides†

Woonphil Baik* and Tae Hong Park

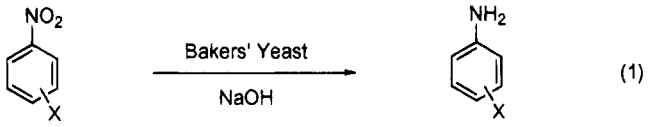
Department of Chemistry, Myong Ji University, Yong In Kun, Kyung Ki-Do, 449-728, Korea

Byeong Hyo Kim and Young Moo Jun

Department of Chemistry, Kwangwoon University, Seoul, Korea

Received November 21, 1994

In recent years, bakers' yeast (*Saccharomyces cerevisiae*) has been widely employed for the stereoselective reduction of β-keto esters,[1a] α-keto esters,[1b] β-keto phenyl sulfides,[1c] or α,β-unsaturated carbonyl compounds.[1d] Among many applications of bakers' yeast in organic synthesis, the reduction of carbonyl groups to their hydroxy groups is one of the most extensively studied. However, the mechanistic details of bakers' yeast reduction of carbonyl compounds have not been explained since its discovery. Furthermore, little attention has been paid to the reduction of nitro compounds by bakers' yeast. We have recently found that aromatic nitro compounds containing *o*-, *m*-, or *p*-electron-withdrawing groups, such as carbonyl, halogen, or nitro, were selectively reduced to their corresponding amino derivatives using bakers' yeast in NaOH solution (eq 1).[2]



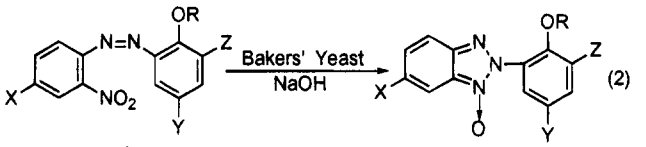
(1)

X = C(=O), C(=O)CH$_3$, C(=O)Ph, Br, Cl, I, OR, NO$_2$

The reductions generally proceeded with excellent yields and showed high selectivity over carbonyl or other labile substituents. In general, it is known that the reduction of nitro compounds to amine proceeds through intermediate stages involving nitroso compounds. Although highly selective reduction of aromatic nitro compounds using the bakers' yeast–NaOH system was observed in eq 1, none of the nitroso, azoxy, or hydroxylamine compounds were detected as intermediates. Presumably, the rate of reduction of the intermediate is so fast that it is difficult to quench the reduction at the nitroso stage. As a part of our continuing study on aromatic nitro compounds with bakers' yeast, we decided to carry out the reductive cyclization of *o*-nitrophenylazo dyes **1** with bakers' yeast to examine the intermediacy of reaction pathways and the products. The products, 2-(2′-hydroxyphenyl)-2*H*-benzotrizoles **3**, are widely used as ultraviolet absorbers for the protection of commercially important plastics against sunlight.[3] A wide variety of reagents have been employed for the conversion of **1** to **3**.[4,5] Rosevear and Wilshire[4] reported that the reduction of *o*-nitrophenylazo dye **1** with thiourea *S*,*S*′-dioxide and NaOH at 85–90 °C gave the corresponding benzotriazoles **3**. Herein we report a unique application of bakers' yeast for the reductive cyclization of aromatic nitro compounds to obtain plastic additives **3** and their reaction pathways.

Results and Discussion

o-Nitrophenylazo dyes **1** (20 mmol), when treated with bakers' yeast[6] (30 g) and NaOH (4 g) in EtOH–H$_2$O at 85 °C for 3–5 h, gave 2-aryl-2*H*-benzotriazole 1-oxides **2**. The suspension was filtered, and the *N*-oxides **2** were isolated in excellent yields. Neither further reduction nor *o*-aminophenyl azo dye formation was observed. In fact, the procedure is more selective than any other literature procedures for the preparation of *N*-oxides from their nitro compounds.

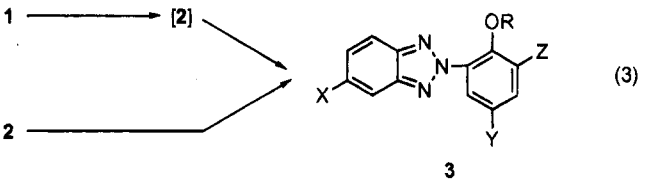


(2)

1 **2**

1-a : X = Cl, Y = *t*-Bu, Z = *t*-Bu, R = H : **2-a**
1-b : X = H, Y = *t*-Bu, Z = *t*-Bu, R = H : **2-b**
1-c : X = H, Y = *t*-pentyl, Z = *t*-pentyl, R = H : **2-c**
1-d : X = H, Y = Me, Z = H, R = H : **2-d**

Surprisingly, when the same reaction was performed using twice the amount of bakers' yeast (60 g)–NaOH (6 g) and a longer reaction time, 2-aryl-2*H*-benzotriazoles **3** were obtained as the single product in good yields (eq 3). In this case, the reduction of nitro compounds **1** to



(3)

3

triazoles **3** proceeded through an intermediate stage involving *N*-oxide **2**. Furthermore, isolated *N*-oxides **2** were also smoothly reduced to give triazoles **3** with

† Dedicated to Professor Glen A. Russell on the occasion of his 70th birthday.

(1) For example, see: (a) Tsuboi, S.; Sakamoto, J.; Kawano, T.; Utaka, M.; Takeda, A. *J. Org. Chem.* **1991**, *56*, 7177 and references cited therein. (b) Tsuboi, S.; Sakamoto, J.; Sakai, T.; Utaka, M. *Synlett* **1991**, 867. (c) Fujisawa, T.; Itoh, T.; Nakai, M.; Sato, T. *Tetrahedron Lett.* **1985**, *26*, 771. (d) Utaka, M.; Konishi, S.; Takeda, A. *Tetrahedron Lett.* **1986**, *27*, 4737.

(2) Baik, W.; Han, J. L.; Lee, N. H.; Kim, B. H.; Hahn, J. T. *Tetrahedron Lett.* **1994**, *35*, 3965.

(3) Gachter, R.; Muller, H. *Plastics Additives Handbook*, 3rd ed.; Hanser Publisher: New York, 1990; p 25.

(4) Rosevear, J.; Wilshire, J. *Aust. J. Chem.* **1984**, *37*, 2489.

(5) (a) Rosevear, J.; Wilshire, J. *Aust. J. Chem.* **1982**, *35*, 2089. (b) White, H. L.; Krolewski, C. V. Ger. Pat. 2620896, 1976; *Chem. Abstr.* **1987**, *86*, 106598s. (c) Ziegler, C. E.; Peterli, H. J. Swiss Pat. 615165, 1980; *Chem. Abstr.* **1980**, *93*, 8181a. (d) White, H. L. Ger. Pat. 2551853, 1976; *Chem. Abstr.* **1976**, *85*, 108646j.

(6) Bakers' yeast was obtained from commercial suppliers and from the food market. Dry activated bakers' yeast was used to obtain the best results.

0022-3263/95/1960-5683$09.00/0

Table 1. Reduction of *o*-Nitrophenylazo Dyes and Their *N*-Oxides by Bakers' Yeast[a]

reactant	condns: BY[d] (g)	condns: NaOH (g)	condns: time (h)	product[b]	yield[c] (%)
1a	30	4	4	**2a**	85
1b	30	4	3.5	**2b**	87
1c	30	4	3.5	**2c**	84
1a	60	6	40	**3a**	85
1b	60	6	36	**3b**	87
1c	60	6	36	**3c**	85
1d	60	6	40	**3d**	80
2a	40	3	24	**3a**	89
2b	40	3	24	**3b**	90
2c	40	3	30	**3c**	86

[a] All reactions were carried out with 20 mmol of reactant in EtOH–H_2O at 85 °C. [b] All products were confirmed by comparing with authentic samples. [c] Isolated yields based on reactants. [d] Dry activated bakers' yeast.

Table 2. Baker's Yeast Reduction of 1a under Various Chemical Environments[a]

entry	condns	yield[b] (%): 2a	3a	1a
1	BY (10 g), NaOH (4 g), 24 h	25	0	71
2	BY (20 g), NaOH (4 g), 24 h	76	0	18
3	NaOH (4 g), 4 h	85	0	0
4	BY (60 g), NaOH (4 g), 24 h	78	16	0
5	BY (60 g), NaOH (6 g), 4 h	79	16	0
6	BY (60 g), NaOH (6 g), 24 h	29	65	0
7	BY (60 g), NaOH (6 g), 40 h	0	85	0
8	BY (40 g), NaOH (0 g), 24 h	0	0	100
9	NaOH (2 g), 24 h	32	0	65
10	NaOH (3 g), 24 h	84	0	5
11	Et_3N (5 g), 24 h	0	0	98
12	pyridine (5 g), 24 h	0	0	92
13	$NaHCO_3$–NaOH Buffer (pH 10.6)[c]	22	0	74
14	Na_2HPO_4–NaOH Buffer (pH 11)[c]	9	0	89
15	KCl–NaOH Buffer (pH 12)[c]	38	0	60

[a] Twenty mmol of reactant and 30 g of bakers' yeast were employed, otherwise as indicated. Reactions were carried out in EtOH–H_2O at 85 °C. [b] Determined by GLC with internal standard (dodecane). [c] Buffer solution was employed instead of H_2O.

bakers' yeast (40 g)–NaOH (3 g) (eq 3). The significative results of the reduction are summarized in Table 1.

It is well known that the biotransformation of carbonyl compounds by bakers' yeast is seriously influenced by varying chemical environments:[7] pH, solvents, nutrient (saccharose), amounts of bakers' yeast, reaction time, and heat treatment. In order to investigate the reductive cyclization of **1** by bakers' yeast, we examined the biotransformations varying both chemical environments and aromatic nitro compounds.

Effect of Bakers' Yeast and NaOH. We tried to monitor the formation of intermediate compounds, *N*-oxides **2**, during the transformation of **1** to **3** (eq 3) by TLC or GLC. By varying the amount of bakers' yeast and NaOH, the formation of **2** and **3** could be successfully controlled. For control experiments, a suspension containing **1a** (20 mmol) and NaOH (4 g) was stirred with varying amounts of bakers' yeast. As shown in Table 2, 30 g of bakers' yeast was necessary to exclusively reduce the nitro compound **1a** to *N*-oxide **2a** (entries 1–3). As we increased the amount of bakers' yeast, over-reduction to triazole **3a** started to occur (entry 4). For example, reductive cyclization of a solution of **1a** with 60 g of bakers' yeast and 6 g of NaOH led to the formation of *N*-oxide (79%) and triazole (16%) after 4 h, whereas the nitro compound was completely reduced to *N*-oxide and then over-reduced to triazole after 40 h (entries 5–7). The rates for the reductions of **1** to **3** with our bakers' yeast–NaOH system are faster than those for the reductions of **2** to **3**. In the absence of NaOH, no reduction of **1** was observed under any variations of chemical environments. The unreacted nitro compound was recovered (no evidence on the formation of other byproducts). With 30 g of bakers' yeast and 2 g of NaOH (half the amount of optimum requirement), the reduction of **1a** gave 32% yield of **2a** and 65% of **1a** was recovered after 24 h (entry 9). No other byproducts such as 2-aminophenylazo dye or **3a** were observed. Additional amounts of NaOH enhanced both the yield and the reaction rate. For 20 mmol of substrate, the optimum amount of NaOH for the conversion of **1** → **2** was 4 g. Our experimental results show that the pH of the reaction mixture does not change noticeably during the reduction. In the case of Et_3N, pyridine, or Na_2CO_3 (at pH 10.5–11.5), no reduction of aromatic nitro compounds in eqs 1 and 2 took place (entries 11 and 12). Other basic buffers ($NaHCO_3$–NaOH, Na_2HPO_4–NaOH, or KCl–NaOH) in the range of pH 10.5–12.0 were also studied. As shown in Table 2, entries 13–15, **1a** was merely reduced (9–38% yield) to form **2a**, and no further reduction to **3a** was observed under the same conditions. The results strongly indicate that the presence of NaOH has a substantial influence on the reduction of aromatic nitro compounds by bakers' yeast.

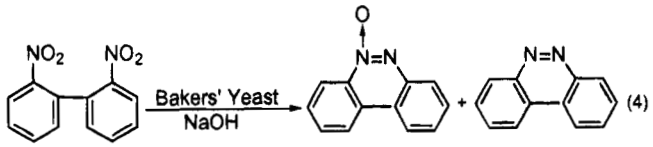
Effect of Solvents. In general, the reduction of a microbe has been carried out in an aqueous medium, and most of the bakers' yeast reduction of carbonyl compounds have been performed in water.[1] One example shows that benzene can be employed as the solvent to reduce α-keto ester with bakers' yeast enantioselectively.[8] This method can be employed to the reduction of water-insoluble substrates such as aromatic nitro compounds. However, in aprotic solvents, such as benzene, hexane, and CH_2Cl_2, both **1** and **3** were not reduced at all under our optimum conditions. And the reductive cyclization of **1a** in H_2O (i.e., without alcohol) afforded only 25% of recovered **2a** and 69% of recovered **1a**. On the basis of these data, the best results were obtained with mixed solvent systems, either H_2O–EtOH or H_2O–MeOH.

Effects of Nutrient and Temperature. We can generally point out that bakers' yeast reduces carbonyl group in the presence of saccharose at 30–35 °C with high yields. However, in the absence of saccharose, the carbonyl groups are reduced with lower yields and showed lower stereoselectivity.[7] In our case, the addition of saccharose did not improve the product yields. Even by increasing the amount of saccharose, the reductions were performed with low yields. The reaction temperature also critically influenced bakers' yeast reduction of aromatic nitro compounds. The best result was observed at 80–85 °C.

Contrary to the general bakers' yeast reduction of carbonyl compound, our bakers' yeast–NaOH reduction system for aromatic nitro compound is striking in several regards. First, NaOH is absolutely required. Second, saccharose for fermentation is not needed to improve the reaction conditions. Third, the addition of ethanol (or methanol) as a cosolvent improves the yield. Fourth, heat is required for reduction to occur.

In an extension of reaction pathway investigation, we have studied the reduction of 2,2′-dinitrobiphenyl (0.5 g) **4** using our bakers' yeast (40 g)–NaOH (4 g) system.

(7) Fantin, G.; Fogagnolo, M.; Guerzoni, M. E.; Medici, A.; Pedrini, P.; Poli, S. *J. Org. Chem.* **1994**, *59*, 924 and references therein.



4 5 6

Benzo[c]cinnoline *N*-oxide (**5**) was isolated in 83% yield (the structure was confirmed by comparison with authentic samples prepared independently[9]), and a trace amount of benzo[c]cinnoline (**6**) was observed on GC. Similar to eq 3, the yield of **6** was improved by applying additional bakers' yeast and NaOH. Apperently, the reduction of **4** is also strongly influenced by the chemical environment. In addition, *N*-oxide **5** can be selectively prepared by controlling the amount of bakers' yeast and NaOH.

In summary, the reductive cyclization of aromatic nitro compounds using bakers' yeast–NaOH system provides an efficient and selective method for the synthesis of *N*-oxides **2** and trizoles **3**. According to a previous result in eq 1, intermediates, such as nitroso and hydroxylamine cannot be detected. However, the present study shows that the reduction pathway proceeds *via* intermediate *N*-oxide to form triazole. These findings indicate that the reduction of simple aromatic nitro compounds in eq 1 to the corresponding amine is so fast that an intermediate such as nitroso is not detected under the bakers' yeast–NaOH system. In addition, the use of a nonmetallic reducing agent has a crucial advantage as far as the environmental problem is concerned. Work is now in progress to apply this reductive cyclization to the construction of heterocyclic ring system and to provide more detailed mechanistic information to other systems having substituted nitrosobenzenes.

Experimental Section

^{1}H NMR spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ solution. Mass spectra were obtained at a 70 eV *via* GC–MS coupling. GC analyses were performed using a capillary column (25 m × 0.2 mm i.d.). Melting points were determined on a Mel-Temp II apparatus and were uncorrected. *o*-Nitrophenylazo dyes **1a–d** were prepared by the coupling of diazonium salt with hindered phenols according to the published procedure.[10] All reagents and solvents were used as purchased, without any further purification. All products (**2a–c**, **3a–d**) were identical in all respects (mp, IR, MS, and NMR) with those previously reported.[4,5d]

General Procedure for the Preparation of 2-(5′-Chloro-2′*H*-benzotriazol-2′-yl)-4,6-di-*tert*-butylphenol 1′-Oxide (2a). A mixture of **1a** (7.75 g, 20 mmol), NaOH (4 g), and bakers' yeast (30 g) in EtOH (90 mL) and H_2O (30 mL) was vigorously stirred at rt for 30 min. The resulting mixture was heated for 4 h at 80–85 °C. After the reaction was completed, dilute hydrochloride acid and CH_2Cl_2 were poured into the flask. The separated organic layer was filtered through a Celite pad, washed with brine solution, and dried over sodium sulfate. 2-(5′-Chloro-2′*H*-benzotriazol-2′-yl)-4,6-di-*tert*-butylphenol 1′-oxide (**2a**) was purified by recrystallization from EtOH: mp 191–102 °C (lit.[4] mp 191–193 °C); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 1.50 (s, 9H), 7.45–7.58 (m, 3H), 7.75 (dd, J = 1.5 Hz, 2H), 9.48 (s, 1H); MS (from GC–MS) 375 (M^+ + 2), 373 (M^+).

2-(2′*H*-Benzotriazol-2′-yl)-4,6-di-*tert*-butylphenol 1′-Oxide (2b): mp 179–181 °C (lit.[4] mp 180–183 °C); ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9H), 1.48 (s, 9H), 7.43–7.52 (m, 4H), 7.83 (dd, J = 2 Hz, 2H), 9.65 (s, 1H); MS (from GC–MS) 339 (M^+).

2-(2′*H*-Benzotraizol-2′-yl)-4,6-di-*tert*-pentylphenol 1′-oxide (2c): mp 119–121 °C (lit.[4] mp 118–120 °C); ^{1}H NMR ($CDCl_3$) δ 0.68 (dt, 6H), 1.31 (s, 6H), 1.43 (s, 6H), 1.65 (q, J = 7 Hz, 2H), 1.96 (q, J = 7 Hz, 2H), 7.40–7.52 (m, 4H), 7.85 (dd, J = 2 Hz, 2H), 9.67 (s, 1H); MS (from GC–MS) 367 (M^+).

General Procedure for the Preparation of 2-(5′-Chloro-2′*H*-benzotriazol-2′-yl)-4,6-di-*tert*-butylphenyl (3a). Reaction of **1a** (7.75 g, 20 mmol) with bakers' yeast (60 g) and NaOH (6 g) in EtOH (150 mL) and H_2O (60 mL) was carried out for 40 h under the typical reaction condition described above. Then the resulting mixture was poured into dilute hydrochloric acid and CH_2Cl_2. The resulting mixture was partitioned between CH_2Cl_2 and H_2O. The organic layer was filtered through a Celite pad, washed, dried, concentrated, and purified by recrystallization from ethanol: mp 151–153 °C (lit.[4] mp 151–154 °C); ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.50 (s, 9H), 7.45 (d, J = 2 Hz, 1H), 7.47 (d, J = 1 Hz, 1H), 7.85–7.95 (m, 2H), 8.36 (d, J = 2 Hz, 1H), 11.52 (s, 1H); MS (from GC–MS) 359 (M^+ + 2), 357 (M^+).

2-(2′*H*-Benzotriazol-2′-yl)-4,6-di-*tert*-butylphenol (3b): mp 153–155 °C (lit.[4] mp 154–156 °C); ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.51 (s, 9H), 7.40 (d, J = 2 Hz, 1H), 7.50 (m, 2H), 7.95 (m, 2H), 8.30 (d, J = 2 Hz, 1H), 11.76 (s, 1H); MS (from GC–MS) 323 (M^+).

2-(2′*H*-Benzotriazol-2′-yl)-4,6-di-*tert*-pentylphenol (3c): mp 85–87 °C (lit.[4] mp 86–88 °C); ^{1}H NMR ($CDCl_3$) δ 0.65–0.85 (m, 6H), 1.36 (s, 6H), 1.45 (s, 6H), 1.68 (q, J = 7 Hz, 1H), 2.00 (q, J = 7 Hz, 2H), 7.28 (d, J = 2 Hz, 1H), 7.45 (m, 2H), 7.95 (m, 2H), 8.23 (d, J = 2 Hz, 1H), 11.74 (s, 1H); MS (from GC–MS) 351 (M^+).

2-(2′*H*-Benzotriazol-2′-yl)-4-methylphenol (3d): mp 129–130 °C (lit.[4] mp 128–130 °C); ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 7.10 (m, 2H), 7.45 (m, 2H), 7.95 (m, 2H), 8.25 (d, J = 2 Hz, 1H), 11.13 (s, 1H); MS (from GC–MS) 225 (M^+).

Acknowledgment. The financial support from the Korea Science and Engineering Foundation (93-0500-09-01-3) is greatly acknowledged. We are greateful to Prof. Lee, K. H. of Myong Ji University for his careful editing of this manuscript.

Supporting Information Available: Physical data (^{1}H NMR) for **2a–c** and **3a–d** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9419697

(8) Nakamura, K.; Kondo, S.; Kawai, Y.; Ohno, A. *Tetrahedron Lett.* **1991**, *32*, 7075.

(9) Yun, T. H.; Park, M. K.; Han, B. H. *J. Chem. Res., Synop.* **1992**, 336.

(10) Furniss, B. S.; Hannaford, A. J.; Smith, P. W.; Tatchell, A. R. Vogel's *Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific & Technical: England, 1989; p 946.