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A novel strategy for the preparation of arylhydroxylamines: chemoselective reduction of aromatic nitro compounds using bakers' yeast†

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Using bakers' yeast as a biocatalyst, the chemoselective reduction of aromatic nitro compounds bearing electron-withdrawing groups gave the corresponding hydroxylamines with good to excellent conversion under mild conditions.

Arylhydroxylamines are an important class of compounds frequently used as key intermediates in the construction of numerous fine chemicals,[1] many natural products and other useful biologically active compounds.[2] They also exhibit a wide range of pharmacological and physiological activities.[3] For these reasons, several methods have been developed for the preparation of arylhydroxylamines, including catalytic transfer hydrogenation and metal-mediated reduction of the corresponding nitro compounds.[4] However, it is known that during reduction of aromatic nitro compounds, intermediate derivatives are rapidly reduced to the corresponding amines and often form side products such as hydrazines, azoarenes and azoxyarenes. In addition, many of these procedures still suffer from disadvantages such as the use of high-pressure equipment, flammable hydrogen gas, toxic heavy metals and hazardous reagents. Therefore, an efficient strategy for producing arylhydroxylamines is still a challenge in organic synthesis.

Bakers' yeast has been the most popular whole-cell biocatalyst, particularly for asymmetric reduction of carbonyl compounds.[5] A variety of novel and new applications of bakers' yeast have been reported.[6] Recently, bakers' yeast has been extensively used to carry out reduction of the aromatic nitro compounds to the corresponding amines.[7] However, the hydroxylamine intermediate in the process has so far never been detected.[8] Our interest in developing a novel enzymatic reaction prompted us to explore the possibility of the preparation of these highly valuable compounds using bakers' yeast as a biocatalyst. In this communication, we wish to report the chemoselective reduction of aromatic nitro compounds to the corresponding hydroxylamines using bakers' yeast. To the best of our knowledge, this is also the first example of the preparation of arylhydroxylamines by a biological process.

The *p*-dinitrobenzene **1a** was chosen as a model in order to explore the feasibility of the reaction. In a typical experiment, the substrate **1a** was reduced using 10.0 g of bakers' yeast under conventional conditions and the reaction process was monitored by HPLC. Fortunately, the hydroxylamine **1c** was detected by HPLC and confirmed by a ^{1}H NMR spectrum. Further investigations were carried out to establish the optimal reaction conditions. It is surprising to find that the amount of bakers' yeast plays a very important role in the chemoselectivity of the reduction. The experimental results are listed in Table 1. When the amount of bakers' yeast was decreased to 5.0 g, the reaction proceeded for 0.5 h to give **1c** and **1d** in an optimal ratio of 95 : 5 with 100% conversion. Most significantly, the ratio of **1c** and **1d** was still 90 : 10 after 2 h. Finally, **1c** was converted to **1d** completely after 22 h.

Table 1 Chemoselective reduction of *p*-dinitrobenzene **1a** using bakers' yeast [a]

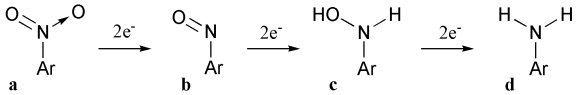
Entry	Yeast/g	Time/h	Conv. (%) [b]	**1c** : **1d**[b]
1	10.0	0.5	100	58 : 42
2	7.5	0.5	100	69 : 31
3	5.0	0.5	100	95 : 5
4	5.0	2.0	100	90 : 10
5	2.5	0.5	85	95 : 5
6	2.5	2.0	100	92 : 8

[a] Reduction conditions: substrate 100 mg, 0.2 M phosphate buffer (pH 6.5) 100 ml, glucose 2.5 g, at 30 °C. [b] The conversion and the ratio of **1c** : **1d** were determined by ^{1}H NMR.

Similar to a previous report,[8] the nitroso compound **1b** was not detected because it is likely to be highly reactive and unstable.

To explore the scope of this chemoselective reaction, a variety of substrates were examined under the optimal conditions (Table 1, entry 3), and the results are summarized in Table 2. Similar to the case of *p*-dinitrobenzene **1a**, reduction of *o*-dinitrobenzene **2a** gave **2c** and **2d** in an 89 : 11 ratio with 86% conversion after 2 h (entry 2). Other nitroarenes bearing an electron-withdrawing group, such as methylsulfonyl **3a**, acetyl **4a** and cyano **5a**, were successfully reduced to give the corresponding hydroxylamines **3–5c**, respectively (entries 3–5). The heterocyclic compound bearing a halide group **6a** was also reduced to the corresponding hydroxylamine with good selectivity (entry 6). Further, reduction of nitroarenes bearing two electron-withdrawing groups **7–10a** showed excellent chemoselectivity (ratios > 90 : 10) in shorter times (entries 7–10). The highest chemoselectivity was achieved in the reduction of 4-nitrophthalonitrile **7a** (the ratio > 98 : 2). Obviously, the stronger and more electron-withdrawing groups favored enhanced reaction rate and chemoselectivity. We also tried the reduction of some nitroarenes bearing electron-donating groups such as methyl and methoxyl, and found that the reductions did not proceed.

On the basis of the known reductive metabolism of nitroaromatics by nitroreductase (Scheme 1),[9] a plausible explanation for the chemoselective reduction is as follows: the aromatic nitro compound is first reduced *via* two electrons to form the arylnitroso, which accepts another two electrons to form arylhydroxylamine. In the final reduction step, the hydroxylamine is converted to amine, by a two electron reduction. The nitrogen atom of the nitro group bears a partial positive charge and the electron-withdrawing groups intensify this positive charge, activating the molecule for reduction of a nitro group. However, the produced hydroxylamine is relatively difficult to reduce further because the N–O bond is

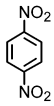
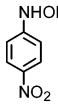
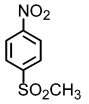
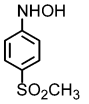
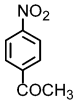
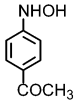
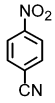
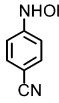
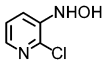
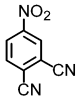
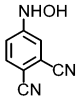
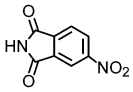
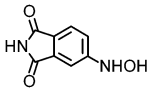
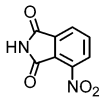
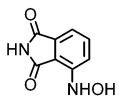
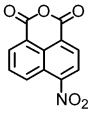
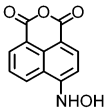


Scheme 1

† Electronic supplementary information (ESI) available: experimental procedures and analytical data for **1–10c**. See http://www.rsc.org/suppdata/cc/b4/b408566c/

DOI: 10.1039/b408566c

Table 2 Chemoselective reduction of various aromatic nitro compounds using bakers' yeast[a]

Entry	Subtrate	Product	Time/h	Conv.[b](%)	**c : d**[b]
1			0.5	100	95 : 5
2			2	86	89 : 11
3			2	90	71 : 29
4			2	87[c]	75 : 25
5			6	88	70 : 30
6			3	81	70 : 30
7			1	99	>98 : 2
8			1	100	93 : 7
9			2	87	91 : 9
10			3	91	90 : 10

[a] Reduction conditions: bakers' yeast 5.0 g, subtrate 100 mg, 0.2 M phosphate buffer (pH 6.5) 100 ml, glucose 2.5 g, 30 °C. [b] The conversion and the ratio were determined by ^{1}H NMR. [c] Also isolated 1-(4-nitrophenyl)ethanol (7%).

strengthened by electron-withdrawing groups. Therefore, the rate of reduction of hydroxylamine to amine is slower than the rate of formation of hydroxylamine, which permits its isolation over a period of time.

In all cases, apart from amines, only a few side products (<2%) were detected by the ^{1}H NMR spectrum of the crude products. It was noteworthy that many readily reducible or labile functional groups such as cyano, imide, ester and halide did not undergo any change under the reaction conditions. The only exception was the carbonyl group; reduction of **4a** proceeded to give 7% of 1-(4-nitrophenyl)ethanol (Table 2, entry 4).

In summary, we have described a novel method for the preparation of arylhydroxylamines using bakers' yeast in aqueous solution. The enzyme-catalyzed procedure is simple, mild, efficient and environmentally friendly. The research will facilitate the understanding of the microbial degradation of nitroaromatic compounds and the mechanism of nitroreductase-mediated prodrug therapy. Further studies to optimize reaction conditions and to expand the substrate scope as well as to synthesize new biologically active compounds *via* arylhydroxylamines are currently under way in our laboratory.

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