COMMUNICATION

Reductive cyclization with baker's yeast of 4-alkyl-2-nitroacetanilides to 6-alkylbenzimidazoles and 1-hydroxy-2-methyl-6-alkylbenzimidazoles

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Reduction of 4-substituted 2-nitroacetanilides by baker's yeast in acid media effected cyclization, resulting in the formation of 6-substituted 2-methylbenzimidazoles and 6-substituted 1-hydroxy-2-methylbenzimidazole *via* the chemo- and regioselective reduction of the 2-nitro aromatic group to amine or hydroxylamine.

Benzimidazole (1,3-dideazapurine) is an important heterocyclic nucleus, which has been extensively used in medicinal chemistry, notable clinical examples being the antihistamine Astemizole and the antiulcerative Omeprazole.[1] In addition, benzimidazole-based compounds have shown diverse biological activities including anti-tumour, anti-helmintic, antihistaminic, anti-microbial and anti-viral properties.[2]

The standard route to benzimidazoles involves the condensation of *o*-arylenediamine with carbonyl-containing compounds.[3] This method is simple to perform and yields are often high. Other methods include the reductive cyclization of *ortho*-substituted nitrobenzene derivatives[4] or a recently developed solid-phase approach to the synthesis of benzimidazoles using polymer-bound *o*-fluoronitroaromatic compounds that react with an amine. Reduction of *o*-nitroaniline derivatives, followed by cyclization and cleavage, gave a library of benzimidazoles with 70–95% crude yield.[5] Simple 1-hydroxybenzimidazoles are also accessible by cyclization of *N*-alkyl-*o*-nitroanilines and by the acid-catalyzed condensation of substituted *o*-nitrosoanilines.[4,6] In addition, conventional oxidative methods to convert benzimidazoles to the corresponding 1-hydroxy derivatives have been unsuccessful and alternative routes to 1-hydroxybenzimidazoles are therefore important.

Reduction of carbonyl compounds by baker's yeast has become a valuable strategy in organic synthesis.[7] A variety of new and novel applications of baker's yeast have been reported. Some examples include the biooxidative conversion of a thio to an oxo functionality,[8] reduction of aryl azide to aryl amines,[9] oximes to chiral amines,[10] oxidation of sulfides to chiral sulfoxides,[11] the preparation of pyridylethanol *N*-oxides,[12] isoquinoline and morpholine,[13] and the reduction of the nitro group to the corresponding amine.[14]

Baker's yeast has been extensively used to carry out reductions of the aromatic nitro group, but there has been little work on the application of this reaction to the synthesis of heterocycles. In a previous paper, we showed the reductive cyclization of 3-nitropropenenitriles for the synthesis of 5-aminoisoxazoles by baker's yeast.[15]

As part of our continuing study on the reductive cyclization of nitro compounds with baker's yeast, we decided to carry out the conversion of a series of 4-substituted 2-nitroacetanilides to 6-substituted 2-methylbenzimidazoles and 6-substituted 1-hydroxy-2-methylbenzimidazoles. Some representative substituted 2-nitroacetanilides **1a**–**h** were reduced by baker's yeast in acidic media to afford the corresponding 2-methylbenzimidazoles, **2** and 6-substituted 1-hydroxy-2-methylbenzimidazoles, **3**, as illustrated in Scheme 1.

When the *p*-substituted *o*-nitroacetanilides **1a**–**h** are treated with baker's yeast in acid media (pH = 4) at 35 °C, reductive cyclization occurs resulting in the formation of 6-substituted 2-methylbenzimidazoles, **2**, and 6-substituted 1-hydroxy-2-methylbenzimidazole, **3**, as the products, which are summarized in Table 1.

As shown in Table 1, 2-nitroacetanilides **1d**–**h** (entries 4–8) were reduced by baker's yeast in acidic media (pH = 4) to provide **2** and **3** in moderate yields. The regioselectivity of the reduction was influenced by the phenyl ring substituents in the reductive cyclization of the series of aromatic nitroacetanilides. Only the reduction of the *p*-nitroacetanilide derivatives **1** possessing an electron-withdrawing group afforded the reductive cyclization products (entries 4–8). For substrates with electron-donating groups (entries 1–3), such as methoxy or hydroxy groups, reduction did not proceed. In fact, this result concurs with the case of nitroarenes.[20]

According to a previous study on the reduction of the aromatic nitro group by yeast, the nitro group is initially reduced to a nitroso group, followed by reduction to hydroxylamine, which is further transformed into an amino group.[14]

The conversion of 2-nitroacetanilides to benzimidazoles **2** and **3** presumably follows the reaction sequence shown in Scheme 1. Initial four-electron reduction of the nitro group to the hydroxylamine, **4** is followed by nucleophilic intramolecular attack of the amino group of **4** on to the carbonyl carbon of the amide to give the 1-hydroxybenzimidazole, **3**. A second two-electron reduction of hydroxylamine **4** results in the formation of the benzimidazole **2** *via* nucleophilic intramolecular attack of the amino group on to the carbonyl carbon of the amide **5**. The use of sucrose, which is metabolized rapidly, causes a rapid acidification of the medium,[21] that promotes the spontaneous cyclization of the intermediates **4** and **5**. Interestingly, reduction of *N*-(2,4-dinitrophenyl)acetamide occurred regiospecifically to deliver the benzimidazoles. Reduction of the *ortho*-nitro group to the acetamide occurred without affecting the nitro group on the *para*-position. This example of regioselective reduction appears to be chemically challenging.

In summary, we have shown for the first time that baker's yeast may be conveniently used for the chemo- and regioselective reduction–cyclization of nitroacetanilides affording the corresponding 6-substituted 2-methylbenzimidazoles **2** and 6-substituted 1-hydroxy-2-methylbenzimidazoles **3**. The reductive cyclization is strongly influenced by the substitution pattern of the substrate: those with electron-withdrawing substituents undergo reaction in good yields, while the reductions of those with electron-donating groups do not proceed or proceed very sluggishly.

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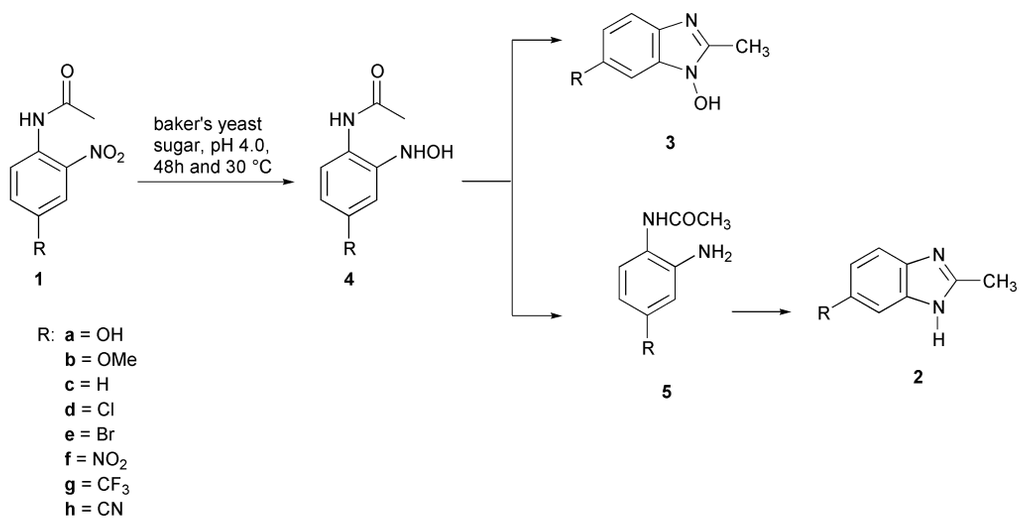
Table 1 Reductive cyclization of *p*-substituted *o*-nitroacetanilides[a] by baker's yeast

Entry	Starting material[b]	R	Yield **2** (%)	Yield **3** (%)	Recovered **1** (%)
1	**1a**	OH	—	—	All
2	**1b**	OMe	—	—	All
3	**1c**	H	9[4]	—	84
4	**1d**	Cl	63[18]	16	11
5	**1e**	Br[17]	67[4]	12	13
6	**1f**	NO_2	64[4]	32[19]	—
7	**1g**	CF_3[a]	28	53	10
8	**1h**	CN[17]	32	58	—

[a] All of the acetanilides were characterized by comparison of spectral data with known published values available in handbooks or in the reference indicated. Spectral data for CF_3 are not available in the literature. However, compound **1g** and all of the products were identified by spectroscopic means (^{1}H NMR, ^{13}C NMR, IR and MS). [b] The starting materials (compounds **1a**–**h**) were prepared by the reaction of *p*-substituted *o*-nitroanilines with acetic anhydride and a few drops of concentrated sulfuric acid as catalyst at reflux temperature, according to a reported procedure.[16]



Scheme 1 Proposed mechanism for the formation of compounds **2** and **3**.

Experimental

Representative reduction with baker's yeast

In a typical experiment, the substrate **1f** (113 mg, 0.5 mmol) was dissolved at 30 °C in 5 mL of acetone–ethanol (1 : 1 v/v) and the solution was added to a prehydrated (30 min) suspension of 10 g dried yeast (Saf-Instant) in 100 mL of water containing 10 g of sucrose. The mixture was stirred on an orbital shaker (150 rpm) until all the substrate was consumed or when no changes were observed by TLC. The mixture was then saturated with sodium chloride and 20 g of Celite and 100 mL of ethyl acetate were then added. After vigorous stirring, the cells were removed by vacuum filtration over a bed of Celite. The filtrate was alkalinized with ammonium hydroxide and extracted with ethyl acetate (3 × 100 mL). The bed was also extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated at 60 °C for 60 min. The resulting oil was purified by column chromatography on silica gel, where **2f** was eluted firstly with hexane–ethyl acetate (6 : 4), followed by elution of **3f** with ethyl acetate–methanol (8 : 2).

2-Methyl-6-nitrobenzimidazole (2f). ^{1}H NMR (300 MHz, $CDCl_3$–d_6-DMSO, 1 : 1): δ 12.17 (s, 1H, NH), 8.43 (d, J = 2.1 Hz, 1H, arom.), 8.10 (dd, J = 8.9, 2.3 Hz, 1H, arom.), 7.54 (d, J = 9.0 Hz, 1H, arom.), 2.65 (s, 1H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$–d_6-DMSO): δ 14.53, 55.73, 110.92, 113.31, 116.95, 142.32. IR (KBr) ν_{max}/cm^{-1} 3566, 3330, 2926, 2819, 1516, 1472, 1337, 830. MS *m*/*z* 177 (M^+), 147, 131, 104. Yield: 57 mg (64%). Mp 214–215 °C (lit.[4] 214 °C).

1-Hydroxy-2-methyl-6-nitrobenzimidazole (3f). ^{1}H NMR (300 MHz, $CDCl_3$–d_6-DMSO): δ 12.30 (s, 1H, OH), 8.19 (d, J = 2.3 Hz, 1H, arom.), 8.02 (dd, J = 8.9, 2.3 Hz, 1H, arom.), 7.65 (d, J = 8.9 Hz, 1H, arom.), 2.53 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$–d_6-DMSO): δ 12.07, 104.82, 116.61, 118.66, 131.27, 142.07, 142.30, 153.57. IR (KBr) ν_{max}/cm^{-1} 3447, 3078, 2410, 1606, 1524, 1349, 1301, 1270, 1216, 1158, 887, 734. MS *m*/*z* 193 (M^+), 177, 163, 147, 130. Yield: 31 mg (32%). Mp 290 °C (decomp.) (lit.[19] 290–294 °C).

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