Baker's Yeast-Mediated Regioselective Reduction of 2,4-Dinitroacylanilines: Synthesis of 2-Substituted 6-Nitrobenzimidazoles

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Abstract: Several 2,4-dinitro-*N*-acylanilines were regioselectively reduced at the C-2 position by baker's yeast in slightly basic media (pH = 7.5) to afford 2-amino-4-nitroacylanilines, which were then cyclized under acidic conditions to the corresponding 2-substituted-6-nitrobenzimidazoles. The benzimidazoles thus obtained can be employed as precursors for bioactive derivatives.

Key words: regioselective, reduction, baker's yeast, dinitroacylanilines, nitrobenzimidazoles

The use of baker's yeast to perform functional group transformations of compounds has become a well-established and valuable methodology in organic synthesis. For instance, baker's yeast has been used to carry out selective reductions of some dinitroarenes,[1] but little work has been done on the application of these reactions for the synthesis of nitrogen heterocycles. Although the selective reduction of dinitroaromatic compounds has been already addressed,[2] only few reported methods provide the desired selectivity when are used for the regioselective reduction of 2,4-dinitroacylanilines. Our research group has previously reported[3] the baker's yeast mediated reduction and further cyclization of 3-nitropropenenitriles to produce 5-aminoisoxazoles and 4-substituted-2-nitroacetanilides to give 6-substituted 2-methylbenzimidazoles and 1-hydroxy-2-methylbenzimidazoles.

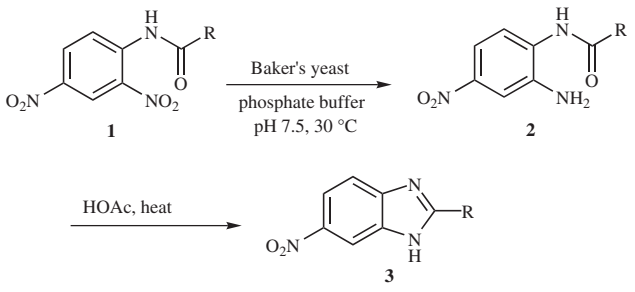
The class of heterocyclic compounds known as benzimidazoles show a variety of biological activities. For example, 2-substituted 5(6)-nitrobenzimidazoles and their derivatives have been studied for their analgesic, anti-inflammatory, anti-proliferative and anti-viral activity,[4] they have also been used as substrates for DT-diaphorase,[5] as starting materials for the synthesis of anti-viral and erythrocyte resistance compounds,[6,7] as well as intermediates for the preparation of potentially bioactive benzimidazoles.[8] Besides, nitrobenzimidazoles are employed as precursors for dye manufacturing and have showed promising applications in nonlinear optics.[9,10]

Simple 2-substituted nitrobenzimidazoles are readily prepared by an intramolecular palladium-catalyzed arylamination reaction,[11] by intramolecular vicarious nucleophilic substitution of alkoxyguanidines with potassium *tert*-butoxide,[12] and by the direct nitration of some benzimidazoles.[13] The most well known procedure for the synthesis of benzimidazoles involves the condensation and further cyclization of *ortho*-arylenediamines, which may contain a nitro substituent, with carboxylic acids or their derivatives under different conditions.[14] In this context, the availability of practical methodologies to efficiently prepare *ortho*-arylenediamines or *ortho*-acylanilines, which might be later transformed into the corresponding benzimidazoles, is highly convenient. A good example of such a method would be the selective reduction of 2,4-dinitroanilines.[15]

As part of our continuing research on the chemo- and regioselective reduction of substituted nitro- and dinitro-aromatic compounds with baker's yeast, we wish to report the conversion of a series of 2,4-dinitro-*N*-acylanilines into the corresponding 2-substituted 6-nitrobenzimidazoles. To the best of our knowledge, the synthesis of nitrobenzimidazoles featuring the regioselective reduction the 2,4-dinitro-*N*-acylanilines **1** by yeast, has not been previously reported.

When some representative 2,4-dinitro-*N*-acylanilines **1** were reduced by baker's yeast under basic media (phosphate buffer, pH = 7.5) at 35 °C, regioselective reduction of the 2-nitro group took place, resulting in the formation of 2-amino-*N*-acyl-4-nitroanilines **2** (Scheme 1). These *ortho*-acylamines were then cyclized using Phillips' protocol to provide 2-substituted 6-nitrobenzimidazoles **3**.[16] The results of these transformations are summarized in Table 1.

The starting materials namely 2,4-dinitro-*N*-acylanilines **1a–j** were readily prepared in one step by reacting the corresponding amine with the appropriate acid anhydride by procedures described elswere.[17]



Scheme 1

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As shown in Table 1, the preferential reduction of the C-2 nitro group of the acylanilines was completed within several hours and lead to the formation of 2-aminoacylanilines as the major isolated products.

Table 1 Regioselective Reduction of **1a–j** by Baker's Yeast and Cyclization of **2a–j** into **3a–j**

Entry	Starting material[a,b]	R	Time (h)	Yield of **2** (%)[a]	Yield of **3** (%)[a]
1	**1a**	H	12	40	80
2	**1b**	CH_3	4	82	92
3	**1c**	CH_2CH_3	4	84	94
4	**1d**	$(CH_2)_2CH_3$	4	85	91
5	**1e**	$(CH_2)_3CH_3$	4	90	90
6	**1f**	$(CH_2)_4CH_3$	4	83	93
7	**1g**	$(CH_2)_6CH_3$	4	79	86
8	**1h**	CF_3	12	36	94
9	**1i**	CH_2Cl	12	47	80
10	**1j**	$(CH_2)_2COOH$	4	86	90

[a] All the starting materials, intermediates and products were identified by spectroscopic means (^1H NMR, ^{13}C NMR, IR, and MS).
[b] The starting materials (compounds **1a–j**) were prepared by the reaction of 2,4-dinitroaniline with acid anhydride and few drops of concentrated H_2SO_4 as the catalyst at reflux temperature, according to a reported procedure.[17]

It is noteworthy to mention that reduction of the C-2 nitro group of 2,4-dinitro-*N*-acylanilines occurred without affecting the chemical integrity of other functionalities present in the molecule, and that the reaction time for the regioselective reduction was influenced by the nature of the acyl group in **1** (entries 1, 8, 9 and 2–7).

In most cases, 2,4-dinitro-*N*-acylanilines **1b–g** and **1j** (entries 2–7 and 10) were easily reduced by baker's yeast in basic media to provide **2b–g** and **2j** in good yields. Only in few cases, **1a** and **2h**,**i** (entries 1 and 8, 9) the yields for the reduction were low, due to the formation of 2,4-dinitroanilines, caused from the hydrolysis of the starting materials promoted by yeast.

Once the regioselective reduction was achieved, the next step was the acid-catalyzed cyclization of amines **2**; thus when 2-amino-*N*-acyl-4-nitroanilines **2a–j** were treated with glacial acetic acid at 60 °C, cyclization took place resulting in the formation of benzimidazoles **3** as yellow solids in good isolated yields (80–94%).

In summary, we have been able to show for the first time, that baker's yeast may be efficiently used for the regioselective reduction of 2,4-dinitro-*N*-acylanilines, and that the reduced products can be conveniently transformed afterwards into the corresponding 2-substituted 6-nitrobenzimidazoles.[18] The regioselective reduction is influenced by the nature of the substrate's acyl group: when R (Scheme 1) is an alkyl group, the reaction proceeded with good yields, while reduction where R is an alkyl group bearing halogen substituents or hydrogen, proceeded very sluggishly and with modest yields. The reaction with baker's yeast is simple and highly selective, attributes that make this methodology an attractive tool for the synthesis of precursors of highly functionalized bioactive benzimidazoles.

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(18) **Representative Reduction of Substituted 2,4-Dinitro-*N*-acylanilines with Baker's Yeast**.
In a typical experiment, the substrate 2,4-dinitroacylaniline **1e** (0.5 mmol) was dissolved in 5 mL of acetone–EtOH 1:1 v/v and the resulting solution was added to a prehydrated (30 min) suspension of 10 g dried yeast (Saf-instant) in 100 mL of 0.5 M phosphate buffer (pH = 7.5) and containing 10 g of sucrose at 30 °C. The mixture was stirred on an orbital shaker (150 rpm) and the pH was kept constant by adding portions of 0.5 M NaOH. The stirring was continued until all the substrate was consumed or remained unchanged as judged by TLC. The mixture was then saturated with NaCl, diluted with 100 mL of EtOAc and combined with 20 g of celite. After vigorous stirring, the cells were removed by vacuum filtration over a bed of celite, the two phases of the filtrate were separated and the aqueous layer extracted with EtOAc (3 × 100 mL); the filter cake was rinsed with EtOAc (3 × 100 mL) and the combined organic extracts were dried over anhyd Na_2SO_4 and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel. Elution with CH_2Cl_2–MeOH (95:5) yielded 2-amino-4-nitroacylaniline **2e**:
^{1}H NMR (300 MHz, $CDCl_3$-d_6–DMSO): δ = 9.14 (1 H, s, NH), 7.73 (1 H, d, *J* = 9.0 Hz, ArH^6), 7.65 (1 H, d, *J* = 2.7 Hz, ArH^3), 7.47 (1 H, dd, $J_{5\text{-}6}$ = 8.8 Hz, $J_{5\text{-}3}$ = 2.8 Hz, ArH^5), 5.05 (2 H, s, NH_2), 2.44 (2 H, t, CH_2, C-1), 2.44 (2 H, sext, CH_2, C-3), 1.69 (2 H, q, CH_2, C-2), 0.95 (2 H, t, CH_3, C-4). ^{13}C NMR (75 MHz, $CDCl_3$-d_6–DMSO): δ = 172.00, 144.17, 140.11, 129.78, 123.03, 111.83, 110.171, 35.92, 27.14, 21.75, 13.33. IR (KBr): ν_{max} = 3452 (Ar-NH_2), 3374, 3255 (-NH), 2916, 2847 (CH_2, CH_3), 1653 (C=O), 1347 (Ar-NO_2), 876, 739 (NH_2, Ar) cm^{-1}. MS (EI): *m/z* (%) = 237 (40) [M$^+$], 180 (12), 177 (29), 153 (100), 107 (12), 85 (25), 57 (35). Yield: 214 mg (90%); mp 123–125 °C.
A typical example for the cyclization of 2-amino-4-nitroacylanilines into substituted nitrobenzimidazoles is as follows: 2,4-dinitroacylaniline **2e** (118.5 mg, 0.5 mmol) was dissolved in 5 mL of glacial acetic acid and then this solution was carried out at 60 °C for 6 h. After completion, the solution was concentrated in a rotary evaporator to remove the HOAc and the residue was recrystallized from MeOH–H_2O to afford 2-butyl-6-nitrobenzimidazole (**3e**):
^{1}H NMR (300 MHz, $CDCl_3$-d_6–DMSO): δ = 12.14 (1 H, s, NH^1), 8.50 (1 H, d, $J_{7\text{-}5}$ = 2.0 Hz, ArH^7), 8.19 (1 H, dd, $J_{5\text{-}4}$ = 8.8 Hz, $J_{5\text{-}7}$ = 2.0 Hz, ArH^5), 7.60 (1 H, d, $J_{4\text{-}5}$ = 8.8 Hz, ArH^4), 3.00 (2 H, t, CH_2, C-1), 1.89 (2 H, q, CH_2, C-2), 1.46 (2 H, sext, CH_2, C-3), 0.96 (3 H, t, CH_3, C-4). ^{13}C NMR (75 MHz, $CDCl_3$-d_6–DMSO): δ = 159.59, 142.50. 114.44, 118.48, 143.57, 111.56, 138.41, 29.95, 29.21, 22.42, 13.69. IR (KBr): ν = 3430 (NH), 3000–2800 (NH), 2980, 2939 (CH_2, CH_3), 1625 (Ar), 1592, 1472, 1452 and 1418 (C=N and C=C), 1514 and 1341 (Ar-NO_2), 825, 734 (Ar) cm^{-1}. MS (EI): *m/z* (%) = 219 (6) [M$^+$], 218 (1), 204 (5), 190 (24), 177 (100), 158 (7), 144 (12), 131 (32). Yield: 98.5 mg (90%); mp 134–135 °C (Lit.[19] 139–141 °C).

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