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Regioselective Reduction of Substituted Dinitroarenes Using Baker's Yeast

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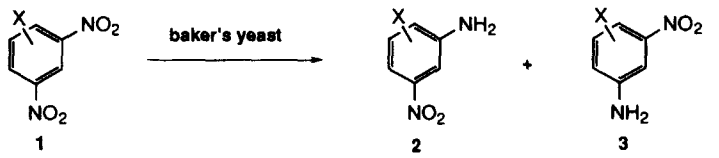
Abstract: A range of substituted dinitroaromatic compounds have been reduced using baker's yeast (*Saccharamyces cerevisiae*), in some cases with very high selectivity. A model is presented to account for the origin of the selectivity together with a possible mechanism for the reduction.

Baker's yeast has been widely used in organic synthesis for the reduction of a variety of functional groups, notably ketones, β-keto esters, and carbon-carbon double bonds.[1] Whilst the literature now contains may examples of these types of reactions, other potentially reducible groups have been relatively unexplored. For example, there are only isolated reports of the reduction of quinones[2], hydroxylamines[3], and oximes.[4] The ability of baker's yeast to effect the reduction of aromatic nitro groups to the corresponding anilines was first reported some 80 years ago[5] and despite some recent reports[6-8], very little is known concerning the scope and limitations of this potentially useful reaction. In this communication we report our investigations into a particular facet of this biotransformation, namely the regioselective reduction of substituted aromatic dinitroarenes **1** (**Scheme 1**), together with a rationale for the observed selectivity, and an insight into the mechanism of the reduction.

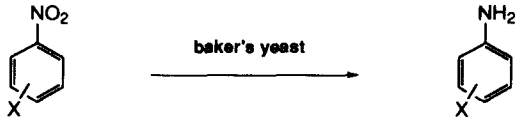


1 **2** **3**

Scheme 1

In order to establish a reproducible protocol for the yeast catalysed reductions, a number of simple mono nitro-containing substrates were screened (**Table 1**).[9] In accord with previous observations[6,8], it was found that electron-withdrawing substituents greatly enhanced the rate of reduction. For example, it is interesting to note that whereas no reduction occurred with the *para*-(methylthio)-nitrobenezene substrate (entry 4), the corresponding sulfoxide (entry 5) was reduced to the aniline in a 25% yield, and furthermore, with the more electron-withdrawing sulphone (entry 6) the yield of the reduction was increased to 71%. Amongst other mono-substituted nitro arenes that failed to undergo reduction were those where X = NH_2, OCH_3, and CH_2CO_2H.

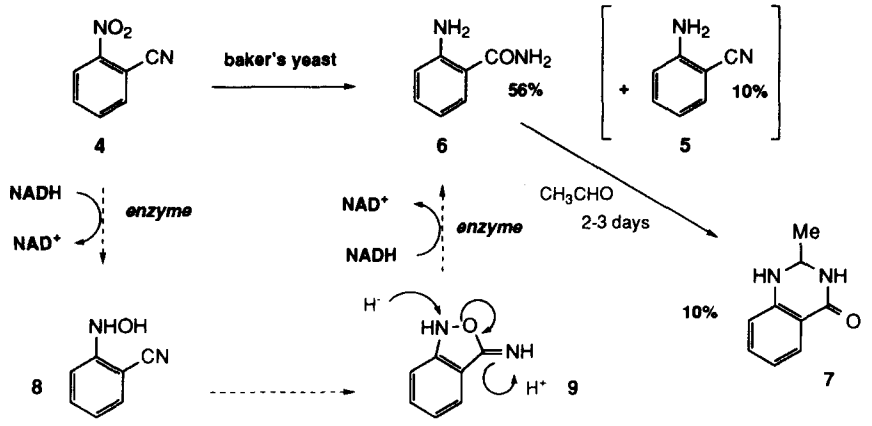
Table 1: Reduction of electron defficient nitroarenes



entry	X	orientation	reaction time/d	yield of aniline/%
1	CN	*para*	4	70
2	$COCH_3$	*para*	4	85[a]
3	$COCH_3$	*ortho*	4	49[b]
4	SCH_3	*para*	4	n.c.[c]
5	$SOCH_3$	*para*	2	25
6	SO_2CH_3	*para*	2	71
7	NO_2	*ortho*	4	78
8	NO_2	*para*	4	60

[a]also isolated *p*-$NO_2C_6H_4CH(OH)CH_3$ (10%); [b]also isolated *o*-$NO_2C_6H_4CH(OH)CH_3$ (12%); [c]n.c. = no conversion

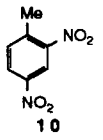
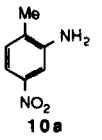
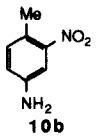
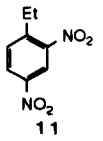
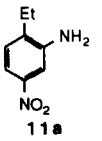
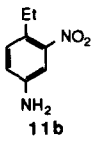
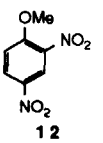
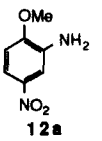
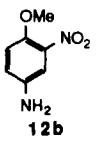
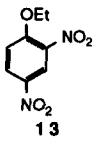
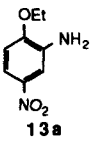
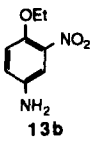
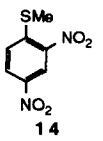
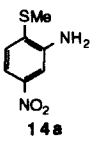
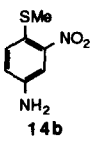
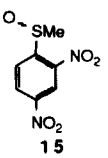
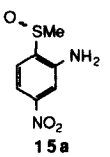
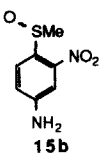
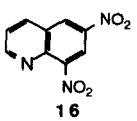
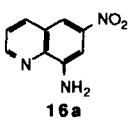
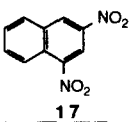
Exposure of 2-nitrobenzonitrile **4** to baker's yeast gave rise to an unexpected result. This substrate has been previously reported[6] to be converted to the expected product 2-cyanoaniline **5**. However, in our hands the major product isolated was 2-aminobenzamide **6** with only a small amount of the aniline **5** (10%). Extended reaction times lead to formation of 2-methyl-2,3-dihydro-(1*H*)-quinazolin-4-one **7**, presumably resulting from reaction of 2-aminobenzamide with acetaldehyde derived from oxidation of ethanol used as the solvent.[10] The conversion of 2-nitrobenzonitrile to **6** may arise *via* the mechanism shown in **Scheme 2**, whereby an initial 2-electron reduction of the nitro group to the hydroxylamine **8** is followed by intramolecular attack of the hydroxyl group onto the nitrile to give the benzo-isoxazolidine **9**. A second 2-electron reduction of **9** would result in cleavage to the product benzamide **6**.



Scheme 2: Possible mechanism of reduction of 2-nitrobenzonitrile.

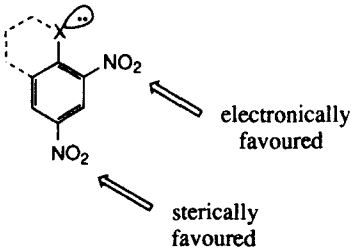
We next examined the reduction of a series of dinitroarenes, the results of which are presented in **Table 2**. In most cases, one regioisomer of the two possible aniline products was found to predominate. Examination of the results suggests that the regioselectivity of the reduction is controlled by two competing

Table 2: Baker's yeast reduction of substituted dinitroarenes

substrate	products	time/d	yield/%
 **10**	 **10a**  **10b**	4	**10a:10b** 1:1 22%:22%
 **11**	 **11a**  **11b**	4	**11a:11b** 1:3 11%:26%
 **12**	 **12a**  **12b**	4	**12a:12b** 5:1 30%:6%
 **13**	 **13a**  **13b**	4	**13a:13b** 3:1 20%:7% (30% s.m.)
 **14**	 **14a**  **14b**	4	**14a:14b** 1:2 13%:27% (9% s.m.)
 **15**	 **15a**  **15b**	0.25	**15a:15b** ~1:1 7%:7%
 **16**	 **16a**	1	**16a** 35%
 **17**	no reduction	4	

factors, namely i) a steric factor favouring reduction of the *para*-nitro group and ii) an electronic factor (*i.e.* presence of a lone pair of electrons) favouring reduction of the *ortho*-nitro group (**Scheme 3**). Thus, 2,4-dinitroanisole **12** gives mainly the *ortho*-product whereas 2,4-dinitrotoluene **10** gives an equal mixture and 2,4-dinitroethylbenzene **11** undergoes reduction predominantly in the *para*-position. Similarly, with 2,4-dinitrothioanisole **14** the more sterically demanding sulfur atom directs reduction towards the *para* position. In the case of the quinoline derivative **16**, in which a single regioisomer **16a** was obtained, we believe that the electronic effect now completely overrides any steric factor leading to complete regioselectivity. It is also interesitng to note that this substrate reacts very efficiently, presumably due to the activating effect of the electron defficient pyridine ring.

In summary, we have shown for the first time that baker's yeast may be conveniently used for the regioselective reduction of dinitroarenes, in some cases leading to the isolation of single isomer products.



Scheme 3: Proposed model to account for the regioselectivity of reduction.

Acknowledgements: We wish to thank SmithKline Beecham Pharmaceuticals for the provision of a studentship (C.L.D.).

References and Notes:

1. For useful reviews see; Csuk, R.; Glänzer, B.I. *Chem. Rev.*, 1991, **91**, 49; Servi, S. *Synthesis*, 1990, 1; Poppe, L.; Novák, L. *Selective Biocatalysis*; VCH: Weinheim. 1992; pp. 191-246.
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8. Baik, W.; Han, J.L.; Lee, K.C.; Kim, B.H.; Hahn, J.-T. *Tetrahedron Lett.*, 1994, **35**, 3965.
9. *Typical conditions for the baker's yeast reduction of nitroarenes*: Baker's yeast (Sigma type II) (10g) was suspended in tap water (40 ml) and incubated at ~32 °C for 1h, after which the substrate (100 mg) dissolved in DMSO or hot ethanol (~5 ml) was added. The reaction was shaken at 32 °C, in an orbital shaker, and the conversion monitored by t.l.c. Upon completion of the reaction, Celite® (5-10g) was added to the flask, which was left to stand with occasional shaking, followed by filtration of the resulting mixture through a bed (~1 cm) of Celite® on a sintered funnel. The filter bed was washed with additional aliquots of water (50 ml) and the combined aqueous fractions were then basified to pH 7 with 1M NaOH followed by saturation with solid NaCl. The aqueous phase was extracted with EtOAc and combined with the EtOAc washings of the filter bed. Standard work-up procedures lead to the isolation of the aniline products.
10. The use of dioxan as cosolvent led to smaller amounts of **7**. In this case the origin of the acetaldehyde is probably the baker's yeast.

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