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Chemo- and Stereoselective Reduction of an α-Cyanoketone by Bakers' Yeast at Low Temperature

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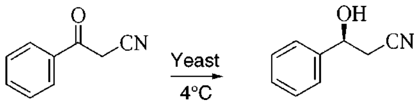
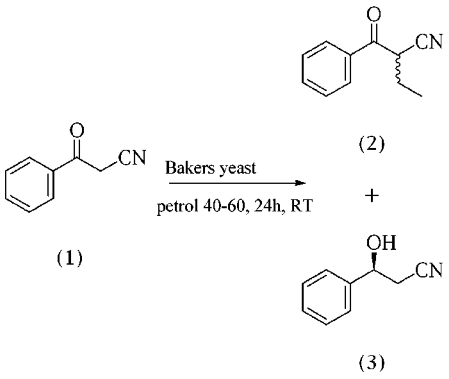
ABSTRACT



The bakers' yeast mediated reduction of 3-oxo-3-phenylpropanenitrile (1) proceeds at 4 °C to give exclusively (*S*)-3-hydroxy-3-phenylpropanenitrile (3) in 59% yield. This is in contrast to the corresponding reaction at room temperature which yields a mixture of reduction and alkylation products. This work demonstrates the use of low temperature to improve yeast selectivity.

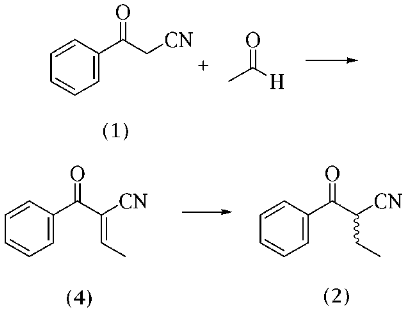
The use of bakers' yeast to stereoselectively reduce α-cyanoketones has been hampered by a competing alkylation reaction which results in the nonstereoselective addition of an ethyl group α to the nitrile.[1−3] For example, treatment of **1** with bakers' yeast in an organic solvent at room temperature gives a mixture of racemic 2-ethyl-3-oxo-3-phenylpropanenitrile (**2**) (40% isolated yield) and (*S*)-3-hydroxy-3-phenylpropanenitrile (**3**) (10%) (Scheme 1).[3] The corresponding reduction in water at room temperature still gives a mixture, but with the hydroxy nitrile (**3**) as the major product (2:1).

Scheme 1



The alkylated compound is thought to be formed via an aldol type condensation between acetaldehyde, present in the yeast, and the α-cyanoketone (**1**) followed by reduction of the resultant alkene (**4**) (Scheme 2). We have previously shown that it is possible to control this reaction in an organic solvent to give exclusively the alkylated product, in good yield, by adding acetaldehyde to the reaction mixture.[3]

Scheme 2



We now wish to report that the use of bakers' yeast in an aqueous medium at low temperature (4 °C) results in the exclusive formation of the reduction product.

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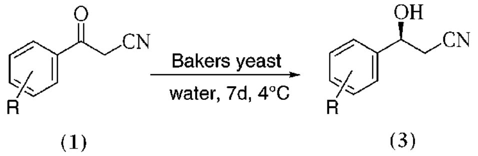
Thus, the cyanoketone (**1**: R = H) (725 mg, 5 mmol) was added to a precooled (4 °C) suspension of bakers' yeast (50 g) in water (450 mL) and stirred at 4 °C for 7 days. The mixture was extracted with ethyl acetate (5 × 150 mL), and the combined extracts were dried and evaporated. Flash-pad chromatography of the residue with ether−petroleum ether afforded the (*S*)-alcohol (**3**: R = H) as a colorless oil (437 mg, 59%), $[\alpha]^{20}_{D}$ −57 (*c* 1.1, EtOH), lit.[4] $[\alpha]^{20}_{D}$ (*R* enantiomer) +58 (*c* 1.0, EtOH) (Scheme 3). Under these reaction conditions, no alkylated material (**2**) could be detected.

Scheme 3



Reaction of the substituted cyano ketones (**1**: R = 2-OMe, 3-OMe) with bakers' yeast at 4 °C for 7 d gave a mixture of starting material and reduced material (**3**: R = 2-OMe, 3-OMe); no trace of alkylated material could be detected in the reaction mixture. The presence of unreacted starting material in the reaction mixture indicates that at the lower reaction temperature the substituted cyanoketones react more slowly than the unsubstituted cyanoketone and longer reaction times would be required to obtain complete conversion. The alkylation reaction is however still totally suppressed in these reactions at the low reaction temperature.

Conducting the reactions in petroleum ether at low temperature did result in more of the reduction product being formed, but it did not prevent alkylation from also occurring.

The mechanism of the alkylation has been proposed to involve the oxidation of ethanol to acetaldehyde which undergoes an aldol reaction with the α-cyanoketone; reduction of the resultant alkene yields the alkylated product (Scheme 2).[2,3] It is highly likely that the alkylation and reduction reactions utilize two (or more) different enzymes and that by lowering the reaction temperature the enzyme(s) involved in the alkylation reaction have been selectively deactivated. This is the first instance of the use of low temperature to alter the selectivity of a yeast reaction although there has been one previous report of the use of low temperature to slow a yeast reduction reaction; reduction of 1-phenyl-1,2-propanedione at reduced temperature results in the reduction of only one of the two ketone groups.[5]

The present work demonstrates the utility of the use of low reaction temperatures to improve the selectivity of a yeast reaction. Coupled with our earlier work[3] it is now possible to alter the reaction conditions for the yeast-mediated reaction of an α-cyanoketone to selectively obtain either the alkylated product (**2**) or the reduced product (**3**).

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