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The baker's yeast-mediated reduction of conjugated methylene groups in an organic solvent

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Abstract

The baker's yeast-mediated reduction of a series of conjugated methylene compounds was conducted in a petroleum ether reaction system. The methylene ketone, 3-phenyl-3-buten-2-one (**1**), was stereoselectively reduced to (*R*)-3-phenyl-2-butanone; no reduction of the ketone carbonyl was observed. Reduction of 2-phenyl-2-propenenitrile (**7**) also occurred stereoselectively to give (*R*)-2-phenylpropanenitrile (**8**) in good yield. The yeast mediated reduction of the methylene aldehyde, 2-phenyl-2-propenal (**3**), gave a mixture of products arising from reduction of both the methylene and carbonyl groups; stereoselective reduction of the methylene group gives (*R*)-2-phenylpropanal (**6**) which is rapidly reduced to (*R*)-2-phenyl-1-propanol (**5**), whereas reduction of the carbonyl gives 2-phenyl-2-propen-1-ol (**4**) which is slowly reduced to racemic (**5**).

Keywords: Baker's yeast-mediated reduction; Organic solvent; Conjugated methylene groups

1. Introduction

Baker's yeast is an inexpensive reducing agent which has been used for the stereoselective reduction of both carbonyl groups and alkenes [1,2]. Recently, an organic solvent has been used as a medium for yeast reactions, replacing the more conventional aqueous reaction environment [3,4]. The main advantage associated with the use of an organic solvent is the simplicity with which pure product can be isolated and we have shown that significantly better yields and enantioselectivities can be achieved with an organic solvent [5]. Reports describing the yeast-mediated reduction of alkenes in an organic solvent have, to date, only indicated racemic products, due to racemisation [6,7]. We now wish to report the stereoselective yeast-mediated reduction of a range of conjugated methylene groups in an organic solvent.

The yeast-mediated reduction of a conjugated methylene group is an appealing technique for the stereoselective introduction of chiral methyl groups, such as those found in many pharmaceuticals, e.g. Ibuprofen and Naproxen. Yeast is a considerably

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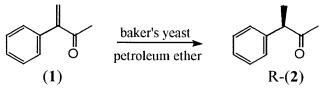


Scheme 1.

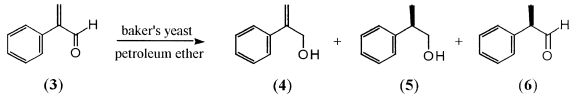
cheaper reducing agent than the metal complexes commonly used for this stereospecific reduction.

2. Reduction of methylene ketone (1)

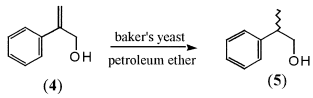
3-Phenyl-3-buten-2-one (**1**) was stirred in petroleum ether with 7 g yeast/mmol substrate and 0.8 ml water/g yeast at room temperature for 24 h and gas chromatographic analysis indicated complete consumption of the starting material. After removal of the solvent, (*R*)-3-phenyl-2-butanone (**2**) was isolated in good yield (76%) as the sole product ($[\alpha]_D = -249°$ (c = 0.75 benzene); Lit. [8] $[\alpha]_D = -333°$ (c = 0.75 benzene)) (Scheme 1). The reaction was completely chemoselective, there being no evidence of reduction of the carbonyl group; this was in marked contrast to the yeast-mediated reaction reported by Sakai [8] in an aqueous system which resulted in reduction of both functional groups. The reaction was also completely stereoselective; chiral gas chromatographic analysis indicated the total absence of the (*S*)-enantiomer.

3. Reduction of methylene aldehyde (3)

Reduction of 2-phenyl-2-propenal (**3**) under similar conditions using 7.5 g yeast/mmol substrate resulted in a 1:1 mixture of the unsaturated 2-phenyl-2-propen-1-ol (**4**) and saturated (*R*)-2-phenyl-1-propanol (**5**) in good yield (52%) (Scheme 2). Gas chromatographic analysis of the reaction mixture shown no sign of the starting material (**3**) or the saturated aldehyde, (*R*)-2-phenylpropanal (**6**). The unsaturated alcohol is obviously formed by reduction



Scheme 2.

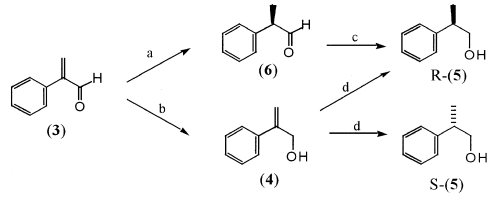


Scheme 3.

of the aldehyde group, while the saturated alcohol results from reduction of both the carbonyl group and the carbon-carbon double bond. The fact that the aldehyde carbonyl group is reduced under these conditions indicates that it is significantly more susceptible to yeast reduction than the corresponding ketone carbonyl in (**1**).

Previously, we have shown that increasing the amount of yeast added to the reaction increases the extent of reduction [5]. When the reaction was carried out using 20 g yeast/mmol, a 1:2 ratio of unsaturated (**4**) to saturated alcohol (**5**) was obtained. Conversely, when the reaction was carried out with only 2-g yeast/mmol substrate, unreacted starting material remained (20%) and the ratio of (**4**):(**5**) was 5:3. No saturated aldehyde (**6**) could be detected by gas chromatography. These results indicate that the aldehyde function is more sensitive to reduction than the methylene group and also suggest that once reduction of the aldehyde has occurred, the methylene group is relatively unreactive. The results also suggest that any saturated aldehyde formed as a result of initial reduction of the double bond is rapidly converted to saturated alcohol.

The relative unreactivity of the alkene group in the unsaturated alcohol was demonstrated by performing a yeast reduction of the unsaturated alcohol (**4**) using 7.5 g yeast/mmol substrate (Scheme 3). Gas chromatography indicated that only 20% of the starting material had been converted into the saturated alcohol (**5**). This allylic alcohol has also been shown to be unreactive in an aqueous reaction system; reaction of 2-phenyl-2-propen-1-ol with baker's



Scheme 4.

yeast (40 g/mmol) in water for 21–25 days led to only small traces of more polar compounds [9].

Examination of the mixture of saturated and unsaturated alcohols obtained from the yeast-mediated reduction of the methylene aldehyde (Scheme 2) using chiral gas chromatography indicated that the saturated alcohol (**4**) was prepared in 70% e.e., optical rotation ($[\alpha]_D = 6.4°$ (c = 0.13 chloroform); Lit. [10] 13.28° (neat)) indicated the (*R*)-enantiomer was the major product. Surprisingly, the alcohol produced from reduction of the unsaturated alcohol (**4**) was shown to be a racemic mixture by chiral gas chromatography, indicating the yeast reduction of this alcohol is not stereoselective.

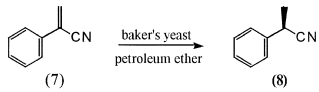
From these results, it is proposed that the reduction of the methylene aldehyde (**3**) proceeds in the following manner (Scheme 4).

- Initial reduction of the methylene aldehyde (**3**) occurs at either the alkene group (path a) or the carbonyl group (path b); both are comparable in rate. The reduction of the alkene group (path a) is a stereoselective process.
- The saturated aldehyde (**6**) is rapidly reduced to the saturated alcohol (**5**) (path c). This is a facile process since no saturated aldehyde can be detected even in reaction mixtures containing unreacted methylene aldehyde (**3**).
- The unsaturated alcohol (**4**) is relatively unreactive and reduction of the alkene group (path d) occurs slowly as evidenced by the yeast-mediated reduction of the alcohol (**4**) which resulted in only a 20% conversion to the saturated alcohol (**5**). This is a non-stereoselective process.

4. Reduction of methylene nitrile (7)

Reduction of 2-phenyl-2-propenenitrile (**7**) under similar conditions to that described above using 10 g yeast/mmol resulted in complete reduction of the methylene group to form (*R*)-2-phenylpropanenitrile (**8**) in 64% yield ($[\alpha]_D = 16°$ (c = 2.47 diethyl ether); Lit. [11] $[\alpha]_D = 12.7°$ (c = 17.6 diethyl ether)) (Scheme 5). Chiral gas chromatography indicated the presence of only one enantiomer.

Reaction of the corresponding carboxylic acid, 2-phenyl-2-propenoic acid, gave a small amount (<



(7) (8)

Scheme 5.

10% conversion) of the reduction product. It was not possible to improve this conversion using more baker's yeast or by adding a buffer to the reaction mixture. Reaction of the methyl ester resulted in no detectable reduction, irrespective of the amount of yeast used.

5. Conclusion

Yeast is capable of reducing methylene groups conjugated to a ketone, aldehyde or nitrile with a high degree of stereoselectivity in good yield. The allylic alcohol reduces much more slowly and with no stereoselectivity. The lack of reactivity of the methylene group in this compound is probably due to the fact that although it remains conjugated to the phenyl group, it is not conjugated to a carbonyl group and is, therefore, less activated towards reduction by the yeast. Methylene groups conjugated to a carboxylic acid or ester showed virtually no reduction.

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