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The use of liquefied petroleum gas (LPG) as a solvent for yeast reactions

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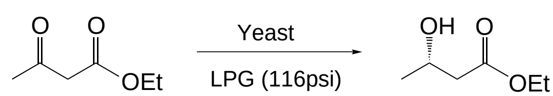
Abstract—The yeast mediated reduction of ethyl acetoacetate to ethyl (*S*)-3-hydroxy butyrate proceeds with good yield and high enantioselectivity in liquefied petroleum gas (LPG). It was found that slightly more water (2 ml/g yeast) and more yeast (1.6 g/mmol substrate) were required to effect complete conversion than was the case with more conventional organic solvents, such as petroleum spirit. © 2001 Published by Elsevier Science Ltd.

Yeast is becoming a widely utilized chiral reducing agent in organic synthesis due to its low cost and high efficiency. Recently it has been demonstrated that yeast reactions can be carried out in a variety of organic solvents rather than the more conventional aqueous reaction systems; solvents such as benzene,[1] petroleum ether,[2] toluene[3] and carbon tetrachloride[3] have all been successfully employed. The main advantage with using an organic solvent for the reaction is the ease with which the product can be isolated and that generally superior isolated yields and enantioselectivity can be achieved.[4] The main drawback associated with the use of organic solvents is their potential toxicity and problems associated with their disposal. It was thought that liquefied hydrocarbon gases may prove to be a 'greener' alternative to organic solvents since they are cheap, non-toxic and readily recyclable.

Reduction of ethyl acetoacetate (**1**) with dry baker's yeast in LPG[5] (116 psi) in a stainless steel reaction vessel using the reaction conditions determined to be optimal for reaction in petroleum ether (0.8 ml water/g yeast, 1 g yeast/mmol substrate) gave ethyl (*S*)-3-hydroxy butyrate (**2**) in 33% conversion after 12 h (Scheme 1).

The yeast:water and yeast:substrate ratios were altered in order to determine the optimal conditions for the reaction. It was found that with 2 ml water/g yeast and 1.6 g yeast/mmol substrate complete conversion of ethyl acetoacetate to ethyl (*S*)-3-hydroxy butyrate was obtained. This is slightly more water and yeast than is required to effect complete conversion in petroleum spirit where only 0.8 ml water/g yeast and 1 g yeast/mmol substrate is required. It has been shown that an enzyme becomes fully hydrated when surrounded by a few layers of water molecules and this hydration layer acts as a microreactor for the enzyme and protects it from any detrimental effects of the bulk organic solvent.[6,7] Solvents that interact with this water layer and either remove or distort it, will have a detrimental effect upon the activity of the enzyme(s) involved in the reaction. Solvents which are hydrophilic or water miscible will have the greatest effect and are generally unsuitable solvents for enzymatic reactions. For yeast mediated reactions, non-polar solvents have been shown to be the most suitable whilst in polar solvents such as acetonitrile, acetone or dimethyl formamide, yeast is inactive. LPG is partially miscible with water and it is probable that the LPG is partitioning some of this essential water away from the yeast enzymes; more water is therefore required to maintain the enzymic activity. The requirement for more yeast is an indication that either the yeast is less active in LPG than in petroleum spirit or that the yeast enzyme system is deactivated faster in LPG than in petroleum ether.[8] Diethyl ether, which is also partially miscible with water, shows a similar requirement for a higher yeast:substrate ratio.[4]

The product from the reaction, conducted under optimal conditions, was isolated to give ethyl (*S*)-3-hydroxy butyrate in 74% yield and 95% ee. The ee was measured on the trifluoroacetyl derivative using chiral gas chro-



(**1**) (**2**)

Scheme 1.

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matography as described earlier.[4] This compares very favorably with the reaction conducted in petroleum ether which produces ethyl (*S*)-3-hydroxy butyrate in 69% yield and 99% ee.

This work clearly demonstrates the viability of LPG as a solvent for yeast mediated reduction reactions. The applicability of LPG as a solvent for other classes of yeast mediated reactions is under examination.

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