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The Yeast Mediated Reduction of Ethyl acetoacetate in Petroleum Ether

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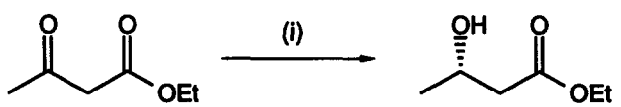
Ethyl acetoacetate is smoothly reduced with high selectivity and good yield to (S)-ethyl 3-hydroxybutyrate using freeze-dried yeast in petroleum ether.

Yeast is capable of catalysing a wide variety of different classes of reactions with high selectivity but its use in synthetic organic chemistry has been limited due to the obligatory use of aqueous solvent systems.[1] For yeast to become a more widely applicable reagent/catalyst in synthetic chemistry it needs to retain its activity in solvents more compatible with organic compounds than is water. Recently three reports appeared indicating that yeast was capable of reducing α- and β-keto esters in essentially non-aqueous systems if it was first immobilised onto a calcium alginate or polyurethane support.[2] Immobilisation of yeast is time consuming and expensive and a system utilising commercially available freeze-dried yeast would be a much simpler and more cost effective approach.

Reduction of ethyl acetoacetate (1) with freeze-dried yeast (*Saccharomyces Cerevisiae*, Mauri Foods Ltd., Australia) in petroleum ether (bp. 40-60°C) in the presence of a small amount of water (1.6%v/v) gave (S)-ethyl 3-hydroxy butyrate (2) in 58% isolated yield and 94%ee [3] after 24h at room temperature (Scheme 1).



(1) (2)

(i) 1mmol (1), 1g yeast, 50ml pet. ether, 0.8ml water, RT, 24h

Scheme 1

In an aqueous system NADPH, the coenzyme necessary for the reduction of carbonyl groups, is continuously recycled by the various metabolic pathways within the yeast. In contrast, in organic solvents regeneration of coenzymes cannot occur so that the extent of the reaction is limited by the initial concentration of coenzyme in yeast. One gram of freeze dried yeast is required for the complete reduction of 1mmol of ethyl acetoacetate as judged by glc. In this case the yeast is providing both the catalyst and reagent for the reaction. It appears that a significant amount of product remains tightly bound to the yeast since only 58% recovered yield could be obtained from a reaction which, according to glc, had proceeded to completion and given a single product. The use of an internal standard to monitor the absolute amount of product indicated a 78% yield. This yield did not decrease when reaction times were extended suggesting that the loss of yield was not a function of product degradation but rather an indication of some sort of binding.

It has been shown that the inactivation of enzymes in organic solvents can be avoided if the enzyme is surrounded by a layer of water.[4] This is also a requirement for yeast activity. A minimum of 0.8ml of added water is required per gram of freeze-dried yeast in order to obtain complete reduction of ethyl acetoacetate in petroleum ether (Figure 1).

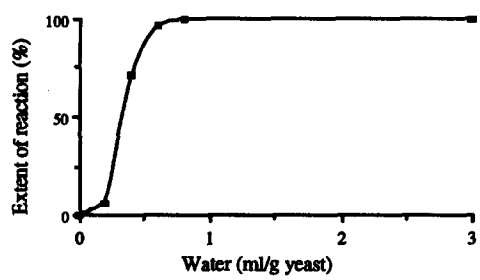


Figure 1: Effect of water on yeast reduction of ethyl acetoacetate.

This is the first example of a reaction promoted by freeze-dried yeast in an organic solvent and it clearly establishes an expanded potential for yeast in synthetic organic chemistry.

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[1] S. Servi, *Synthesis*, 1990, 1.

[2] a) Y. Naoshima, J. Marda, Y. Munakata, T. Nishiyama, M. Kamczawa, H. Tachibana, *J. Chem. Soc. Chem. Commun.*, 1990, 964.

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[3] $[\alpha]_D$ = +40.1 (B. Wipf, E. Kupfer, R. Berlazzi, H. G. W. Leuenberger, *Helv. Chim. Acta.*, 1983, **66**, 485: $[\alpha]_D$ = +41.3 ee:97%)

[4] S. S. Katyar, K. De Tapas, *Biochem. Ind.*, 1990, **20**, 1127.

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