Bioreduction with Immobilized Bakers' Yeast in Hexane using Alcohols as an Energy Source

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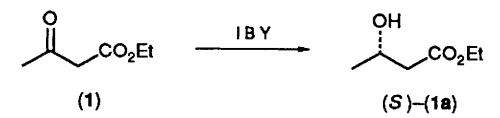
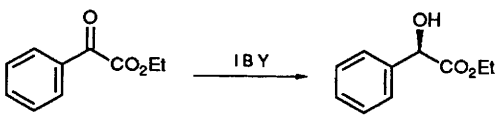
Bioreduction with immobilized bakers' yeast proceeded smoothly in hexane by using alcohols, such as methanol, ethanol, and propan-2-ol, instead of glucose, as an energy source; ethyl 3-oxobutanoate and ethyl benzoylformate were each reduced to the corresponding chiral hydroxy esters with a high enantiomeric purity.

Recently we reported that immobilized bakers' yeast (IBY) entrapped in calcium aliginate beads was active in some organic–water solvent systems such as hexane–water and acetonitrile–water and in other systems, especially in hexane, reduced ethyl 3-oxobutanoate (**1**) to the corresponding (*S*)-alcohol (**1a**) with a high enantiomeric purity.[1] Thus far the energy source and NAD(P)H required in IBY mediated reductions have been provided by the addition of glucose or sucrose to the reaction mixture.[2] However, the use of saccharides was particularly troublesome in organic solvent systems. In an effort to increase the simplicity of IBY mediated reductions, we have carried them out in hexane using alcohols instead of glucose as an energy source.†



(**1**) (*S*)-(**1a**)



(**2**) (*R*)-(**2a**)

The reduction of (**1**) (1 g) with IBY[1] prepared from bakers' yeast (10 g) was examined in hexane (200 ml) in the presence of methanol (1 g). The chemical and optical yields of the resulting (*S*)-hydroxy ester (**1a**) were 56% and 97% and comparable to those of (*S*)-(**1a**) obtained by running the reaction under fermenting conditions using glucose, as shown

† Two NAD(P)H regeneration systems using methanol/alcohol dehydrogenase/aldehyde dehydrogenase/formate dehydrogenase and ethanol/alcohol dehydrogenase/aldehyde dehydrogenase[3] and a bakers' yeast reduction in aqueous solutions using ethanol as an energy source[4] have been reported.

Table 1. Bioreduction of (**1**) and (**2**) with IBY in hexane in the presence of alcohols as an energy source.

	(*S*)-(**1a**)			(*R*)-(**2a**)		
Energy source	% Yield[a]	% E.e.[b]	$[\alpha]_D^{22}$/°[c]	% Yield[a]	% E.e.[d]	$[\alpha]_D^{22}$/°[c]
Methanol	56	97	+43.35	66	94	−130.51
Ethanol	50	95	+42.85	56	93	−125.45
Propan-2-ol	46	95	+41.22	63	93	−127.50
Allyl alcohol	0	—	—	0	—	—
Glucose	51	95	+40.47	51	94	−125.41
None	42	95	+40.28	42	91	−125.00

[a] Purified by a combination of column chromatography and micro-vacuum distillation. [b] Enantiomeric excesses were determined by HPLC analysis of the benzoate ester derived from (*S*)-(**1a**) [Daicel Chiralcel OB, hexane–propan-2-ol (9 : 1), 1.0 ml/min, 220 nm].[2a] [c] Measured in $CHCl_3$. [d] Enantiomeric excesses were determined by HPLC analysis of (*R*)-(**2a**) [Daicel Chiralcel OB, hexane–propan-2-ol (9 : 1), 0.5 ml/min, 254 nm].

in Table 1. Similarly, ethyl benzoylformate (**2**) was reduced in a methanol-containing system to the (*R*)-mandelate (**2a**) with a chemical yield of 66% and an optical yield of 94%. Although these two bioreductions also proceeded without the addition of an energy source,[5] the reductions were much slower than similar ones containing methanol or glucose.‡ The bioreductions of (**1**) and (**2**) were also performed in the presence of ethanol, propan-2-ol, or allyl alcohol. The reductions using ethanol and propan-2-ol progressed smoothly to give (*S*)-(**1a**) and (*R*)-(**2a**), but did not occur using allyl alcohol. The chemical and optical yields were also comparable to those obtained by the analogous glucose-containing systems, although the reduction of (**1**) using propan-2-ol gave a somewhat lower chemical yield of (*S*)-(**1a**).

In conclusion, the present alcohol-containing systems give chemical and optical yields which are similar to those with analogous glucose-containing systems, are more practical than the latter systems, and would make IBY mediated reductions more widely usable in organic synthesis.

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‡ For example, the IBY reduction of (**1**) in the absence of energy sources, such as glucose, required 92 h to reach 95—97% conversion, while in the presence of methanol or glucose the reduction was complete within 24—40 h.

References

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