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Journal of Molecular Catalysis B: Enzymatic 11 (2001) 893–896

JOURNAL OF MOLECULAR CATALYSIS B: ENZYMATIC

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Baker's yeast mediated reduction of β-keto esters and β-keto amides in an organic solvent system

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Abstract

The baker's yeast mediated reduction of four β-keto esters in petroleum ether indicated that the size of the group attached to the keto carbon affected their reactivity. Ethyl 3-phenyl-3-oxopropanoate (**1**), which has a phenyl group directly attached to the keto carbon, is incompletely reduced using 20 g yeast/mmol substrate, ethyl 4-phenyl-3-oxobutanoate (**2**), which has one methylene group between the phenyl and keto carbon, was also incompletely reduced using 20 g yeast/mmol, although the extent of reduction was about double that of (**1**), ethyl 5-phenyl-3-oxopentanoate (**3**), which has two methylene groups between the phenyl and keto carbon, is completely reduced using 10 g yeast/mmol and ethyl 3-oxobutanoate (**4**), which has a methyl group attached to the keto carbon shows complete reduction using only 1 g yeast/mmol. The corresponding β-keto amides are considerably less reactive than the corresponding β-keto esters with only the amides derived from ethyl 3-oxobutanoate indicating any significant reduction using 20 g yeast/mmol.

Keywords: Baker's yeast; β-Keto esters; Organic solvent system

1. Introduction

Homochiral β-hydroxy esters have been used as chiral starting materials for the synthesis of a variety of important chemicals including β-lactams [1] insect pheromones [2] and carotenoids [3]. One of the most widely used means of preparing this class of compound is through the stereoselective reduction of β-keto esters using baker's yeast. The use of organic solvent systems for baker's yeast mediated reactions is becoming more prevalent [4] and recently, we reported the baker's yeast mediated reduction of a series of 3-oxobutanoates in petroleum ether and showed that it gave superior results compared to an aqueous system [5]. This report showed that the size of the ester played a part in determining the reactivity of the β-keto ester; the methyl ester was reduced significantly more readily that the *t*-butyl ester. β-Keto esters with a bulky group at the keto end of the molecule, e.g. ethyl 3-phenyl-3-oxopropanoate (**1**), are less readily reduced by baker's yeast in an aqueous reaction system and we were interested in determining their reactivity in an organic solvent. There have been few reports concerning the baker's yeast mediated reduction of β-keto amides using an aqueous reaction medium [6–8] and the reactivity of

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1381-1177/01/$ - see front matter
PII: S1381-1177(00)00153-3

these compounds in an organic solvent was also of interest.

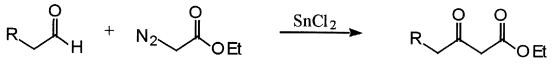
2. Preparation of β-keto esters and β-keto amides

Two β-keto esters, ethyl 4-phenyl-3-oxobutanoate (**2**) and ethyl 5-phenyl-3-oxopentanoate (**3**), were prepared in high yield (88–96%) using a similar method to that described by Sudrik et al. [9] (Scheme 1). Thus, ethyl diazoacetate was reacted with the appropriate aldehyde in the presence of tin(II) chloride for 12 h at room temperature. The product was obtained by distillation after removal of the catalyst by centrifugation. These esters were chosen as it was thought that the steric hindrance about the keto-carbon in these compounds would be intermediate between ethyl 3-phenyl-3-oxopropanoate (**1**) and ethyl 3-oxobutanoate (**4**) which are commercially available.

The *N*-methyl, *N*-benzyl and *N*-phenyl amides of the β-keto esters (**1**–**4**) were prepared in variable yield (12–88%) by reaction of the appropriate amine with the β-keto ester (Scheme 2). The *N*-methyl amides were prepared using a 40% aqueous solution of methylamine at room temperature. A significant amount of the corresponding methyl imine was formed under these conditions and this was hydrolysed to the β-keto amide by washing an ether solution of the imine with 2 M HCl. The other amides were prepared in refluxing xylene and no imine was formed under these conditions.

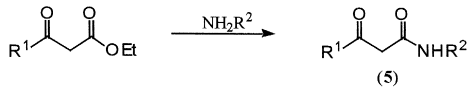
3. Reduction of the β-keto esters

The four β-keto esters (**1**–**4**) were reduced with baker's yeast in petroleum ether containing 0.8 ml water/g yeast at room temperature for 24 h (Table 1). Ethyl 3-oxobutanoate (**4**) is stereoselectively reduced to ethyl (*S*)-3-hydroxybutanoate in good yield (69%) and high enantioselectivity (99% ee) [5]. Reduction of the considerably more bulky ethyl 3-phenyl-3-oxopropanoate (**1**) did not proceed to completion even with 20 g yeast/mmol; a maximum of only 21% conversion could be achieved. While there have been reports concerning the baker's yeast mediated reduction of this compound in an aqueous system, the best results were obtained when the yeast was either immobilised onto calcium alginate [10] or mutated [11]. The use of an organic solvent for the baker's yeast mediated reduction of this compound has been reported, but no reduction was observed [12]. In this report, only 8 g yeast/mmol was utilised, which probably explains why no reduction was observed. Reduction of ethyl 4-phenyl-3-oxobutanoate (**2**) also did not proceed to completion, only 42% conversion was observed using 20 g yeast/mmol substrate. It was, however, possible to achieve complete reduction of ethyl 5-phenyl-3-oxopentanoate (**3**) using 10 g yeast/mmol substrate and ethyl (*S*)-5-phenyl-3-hydroxypentanoate was isolated in good yield (87%).



(**2**) R = $PhCH_2$
(**3**) R = $PhCH_2CH_2$

Scheme 1.



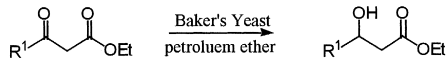
(**5**)

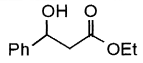
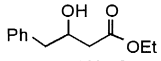
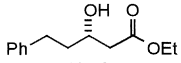
R^1 = Me, CH_2Ph, CH_2CH_2Ph, Ph
R^2 = Me, CH_2Ph, Ph

Scheme 2.

These results indicate that the ease of reduction of these compounds is related to the proximity of the phenyl group to the carbonyl group being reduced. When the phenyl group is attached to the carbonyl carbon (**1**), very little reduction occurs, a one-carbon spacer between the carbonyl and phenyl groups (**2**) increases the extent of conversion, while when the phenyl group is two carbons removed from the site of reduction (**3**), complete reduction is possible. In the absence of the phenyl group (**4**), reduction occurs very readily. This difference in reduction capability is presumably due to the ease with which the substrate fits into the active site of the enzyme. In the case of ethyl 3-phenyl-3-oxopropanoate (**1**), the bulky phenyl group prevents the substrate from binding and very little reduction occurs. The two-carbon chain between the phenyl and carbonyl groups in

Table 1
Yeast mediated reduction of four β-keto ester in petroleum ether



Ester	Product	Yeast (g/mmol)	Conversion (%)	Isolated Yield (%)
1		20	21	16
2		20	42	not isolated
3		10	100	87
4		1	100	69 [5]

ethyl 5-phenyl-3-oxopentanoate (**3**) provides sufficient flexibility for the phenyl group to bend out of the way and allow the substrate to bind to the enzyme.

4. Reduction of the β-keto amides

Nine β-keto amides were reduced using 20 g yeast/mmol of substrate in petroleum ether. Only the amides derived from ethyl 3-oxobutanoate showed any appreciable (> 50%) reduction in 24 h. *N*-Phenyl-3-oxobutanamide (**5**: $R^1 = Me$, $R^2 = Ph$), was completely reduced to give (*S*)-*N*-phenyl-3-hydroxybutanamide in good yield (82%) and with high enantioselectivity (> 99% ee). This amide has been reduced using baker's yeast in an aqueous medium and was reported to give a "satisfactory isolated yield" of almost optically pure material (> 98%) [7]. The corresponding *N*-benzyl amide (**5**: $R^1 = Me$, $R^2 = CH_2Ph$) gave a 56% conversion after 24 h. *N*-Methyl-3-oxo-5-phenylpentanamide (**5**: $R^1 = CH_2CH_2Ph$, $R^2 = Me$) was reduced in only 33% conversion and all of the other amides showed no reduction.

These results clearly show that the amides are considerably less reactive than the corresponding esters. The low reactivity observed for the baker's yeast mediated reduction of β-keto amides has been commented on by Quiros et al. [13] who successfully employed a fungus, *Mortierella isabellina*, for the bioreduction of β-keto amides. We have previously shown that the size of the ester function effects the reactivity of β-keto esters in yeast mediated reactions [5]. While it is possible that the reason for the lowered reactivity of the β-keto amides is attributable to the increased bulk of the amide group compared to the ethyl ester, it is surprising that the bulkiest amide (*N*-phenyl) was the most reactive. It appears more likely that the amide functionality is having a deactivating effect upon the keto carbonyl group, thus lowering the reactivity of these compounds.

5. Conclusion

The baker's yeast mediated reduction of β-keto esters with different size substituents attached to the keto carbon indicated that the ease of reduction is related to the size of the group attached to this carbon. Ethyl 3-oxobutanoate (**4**), with a methyl group attached to the keto-carbon, is completely reduced with 1 g yeast/mmol, while ethyl 3-phenyl-3-oxopropanaote (**1**), with a phenyl group attached to the keto-carbon only proceeds to 21% conversion with 20 g yeast/mmol. Ethyl 5-phenyl-3-oxopentanoate (**3**) with two methylene groups between the phenyl group and the keto-carbon is completely reduced with 10 g yeast/mmol substrate. Conversion

of the ethyl ester into an amide results in considerably lowered activity. Only *N*-phenyl-3-oxobutanoate was reduced to any appreciable extent using yeast in an organic solvent system.

Acknowledgements

The baker's yeast used in this study was Mauripan Instant Dry Yeast and was kindly provided by Kerry Pinnacle Bakery Products, Sunshine, Australia. Financial assistance provided by Polychip Pharmaceuticals (a wholly owned entity of Circadian Technologies) is gratefully acknowledged.

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