Tetrahedron Letters, Vol 32, No 6, pp 761-762, 1991
Printed in Great Britain

0040-4039/91 $3 00 +
Pergamon Press plc

ENZYMES IN ORGANIC SYNTHESIS VII
ENZYMATIC ACYLATION OF AMINES

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ABSTRACT Lipases and esterases catalyze amide synthesis from primary amines in the presence of various esters Lipase SP 382 exhibited a very high activity and specificity

Enzymatic synthesis in organic solvents is now well recognized (1,2) Transesterification catalyzed by hydrolases has been widely used (2,3) whereas only a few results have been reported concerning the acylation of amines Among these results,the enzymatic synthesis of peptides (4,5,6) and enantioselective acylation of amino alcohols (7,8) are particularly efficient The enzymatic resolution of racemic amines with subtilisine is also well known (9) Although the reaction between ethyl propiolate and aromatic amines is known to be catalyzed by a lipase (10), there are no results concerning the regioselectivity of the enzymatic acylation of amines

Enol esters, suitably used in transesterification reactions (11), could not be employed as acylating agents with primary amines, since they react exothermally without catalyst In the presence of ethyl butyrate, enzymatic acylation of n-hexylamine was performed with some lipases and esterases the lipase from Candida rugosa, Pig Pancreatic Lipase, the lipase from Pseudomonas sp., lipase SP 382 (from Candida sp.) and horse-liver acetonic powder We observed that lipase SP 382 was the most efficient catalyst when the reaction was carried out with ethyl butyrate as the solvent The reaction times were longer when the enzyme powder was suspended in heptane as solvent Accordingly, reactions of amines (250 mM) in ethyl butyrate (20 mL) were carried out at 40°C with lipase SP 382 (1g) , n-butylamine and n-hexylamine reacted in 1 hour with quantitative yield These results indicated that butanol was not an inhibitor for lipase SP 382 at these concentrations We can also conclud that the reverse reaction is a very slow process in these experimental conditions More hindered isobutylamine and cyclohexylamine were less reactive (91% and 62% chemical yield in 24 hours)

Surprisingly, the reaction with anilin was very slow (15% chemical yield in 40h) Tertiobutylamine was not a substrate for lipase SP 382 Estimation of competitive factors between two acyl acceptors could be used for the prediction of separation efficiency by enzymes (12) Some selected amines pairs were examined α_1 (n-butylamine / isobutylamine) = 1 6 , α_2 (n-butylamine / cyclohexylamine) = 6 , α_3 (isobutylamine / cyclohexylamine) = 3 3 There was a good correlation between these values of α the ratio $\alpha_2/\alpha_3 = \alpha_1$ (within experimental errors), indicated that the reactivity of each amine was not modified by the other

In conclusion, lipase SP 382 is an excellent catalyst for the acylation of amines in organic media Furthermore, this study emphasizes the difference in reactivity between primary amines as acyl acceptors

ACKNOWLEDGMENT: The generous gift of lipase SP382 by NOVO-NORDISK is gratefully acknowledged

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(Received in France 1 October 1990)