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ENZYME-MEDIATED ENANTIOSELECTIVE ACYLATION OF SECONDARY AMINES IN ORGANIC SOLVENTS

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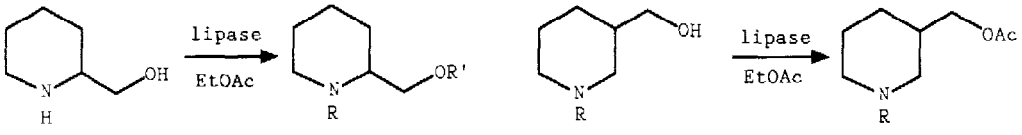
Abstract: Porcine pancreatic lipase (PPL) and lipase Amano P catalyze the enantioselective acylation of cyclic 1,2- and 1,3-aminoalcohol derivatives in organic solvents. The enantiomeric excesses (ee's) were shown to depend on the enzyme, reaction time, temperature and type of substrate.

The use of enzymes in organic synthesis has experimented a huge development in the last decade [1] Although the first applications were mainly concerned with transformations performed in aqueous media (ester hydrolyses, alcohol oxidations, etc), recent research has shown that enzymes can work as well in organic solvents, which prove even superior in terms of product solubility and enzyme stability [2] While ester hydrolysis constitute the main example of enzymatic reactions performed in water, transacylations are the most frequent reaction type among those carried out in organic media. Most of the published examples correspond, however, to O-acylations (transesterifications), N-acylations being comparatively much less frequent. From the latter type of reaction, many cases are concerned with peptide synthesis.[3] The enzymatic acylation leads here, however, to the mere creation of the peptide amide group, no enantioselection taking place during the process. Enzyme-mediated N-acylation of simple amines has been reported in a limited number of cases,[2,4] all of them being primary amines. Only some of these publications[2,4c] described enantioselective processes with formation of chiral amides. In the present communication, we wish to report our results in the enzymatic acylation of the cyclic secondary amines **1** and **2** Enantioselective reactions on these compounds are of interest because the resulting chiral derivatives may be useful for the synthesis of some types of alkaloids and amino acids.[5]



Racemic amino alcohol **1** was dissolved in EtOAc and stirred under the prescribed conditions (see Table 1) in the presence of PPL or lipase Amano P. Work-up and chromatographic separation yielded the hydroxy amide (−)-**3** and unreacted, optically enriched (−)-**1**. The ee's, estimated from the published optical rotation values,[5] were confirmed experimentally (NMR) and are higher than those observed in the same substrates by Jones *et al*[5a] with their enzymatic hydrolytic procedures (see Table 1, entries 1-5). The best ee's were found with PPL at low temperatures (0-5 °C) and short reaction times. Lipase Amano P required higher temperatures than PPL and gave also a certain amount of the N,O-diacylated product (−)-**4**.

Table 1. Lipase-mediated acylations of aminoalcohols 1, 2 and their N-acetyl derivatives.[a]

Entry	Comp.	Lipase	Temp. (°C)	Time (h)	Chiral reaction products, % yield[b] (% ee), config.[c]					
					1	3	4	5[d]	6[d]	7[d]
1	1	PPL	0-5	4	90 (10), R	9 (92), S	0	–	–	–
2	1	PPL	r.t.	4	74 (23), R	22 (70), S	0	–	–	–
3	1	PPL	40	4	80 (13), R	17 (59), S	0	–	–	–
4	1	PPL	0-5	30	59 (39), R	38 (51), S	0	–	–	–
5	1	Amano P	40	23	13 (81), R	75 (15), S	9 (85), S	–	–	–
6	2	PPL	0-5	45	–	–	–	47 (< 2)[e]	–	–
7	2	Amano P	40	5	–	–	–	7 (< 2)[e]	–	–
8	3	Amano P	40	24	–	73 (16), R	22 (52), S	–	–	–
9	6	Amano P	40	3	–	–	–	–	62 (42)	35 (65)

[a]Compounds **1** and **2** are commercially available. The starting material (8 mmol) was dissolved in EtOAc (40 mL) and stirred with PPL (2 g) or Amano lipase P (1.2 g) under the prescribed conditions of time and temp. The enzyme was then removed by filtration, the solvent evaporated *in vacuo* and the residue chromatographed on silica gel (elution with EtOAc-MeOH 10:1 and then EtOAc-MeOH-Et_2NH 100:10:1). [b]Yields are based on *total* starting product (R + S). [c] The ee's were determined by ^1H NMR in the presence of Eu(hfc)$_3$. The absolute configurations (R,S) of chiral **1**, **3** and **4** are known.[5] [d]Absolute configurations unknown: (−)-**5**, (−)-**6** and (+)-**7** were the isolated products. [e]Ee of the recovered **2** was also negligible.

In contrast to that observed in the vicinal amino alcohol **1**, compound **2** did not give any noticeable ee's (< 2) with either PPL or lipase Amano P (entries 6 and 7), a result which parallels that observed by Jones *et al*[5a] in the enzymatic hydrolysis of racemic amide ester **7**. The isolated product was the O-acyl derivative **5**, which underwent a slow, spontaneous isomerization to the N-acyl compound **6**. This finding suggested the possibility of (−)-**3** not being the primary acylation product of **1** but rather the result of a fast (N←O)acyl migration on an initially formed O-acyl derivative. We then tested the enzymatic acylation of *racemic* N-acetyl derivatives **3** and **6** (prepared by reaction of **1** and **2**, respectively, with isopropenyl acetate) under the same conditions as before. Interestingly, while comparable results are observed in the acylation of both (±)-**3** and (±)-**1** under similar conditions (entries 5 and 8), amide (±)-**6** displayed an appreciable enantioselectivity in the O-acylation to (+)-**7** (compare entries 7 and 9). It is also worth mentioning that unreacted R-(+)-**1** and R-(+)-**3** are recovered in the acylation of (±)-**1** and (±)-**3**, respectively. This means that the enzyme shows the same chiral preference towards either product (predominant selection of the S enantiomer) and therefore supports the idea that the primary process is actually the O-acylation.

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