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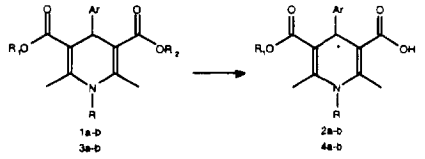
Influence of the N-MOM group in the enantioselective lipase catalyzed methanolysis of racemic 1,4-dihydropyridine dicarboxylates

Mª Soledad de Castro, Loreto Salazar and José V. Sinisterra *
Dpto. Química Orgánica y Farmacéutica, Facultad de Farmacia, U.C.M. 28040 Madrid, Spain

Abstract: The hydrolysis of (*RS*)-acetoxymethyl-ethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylates, N-methoxymethylated and N-unsubstituted has been carried out using lipases AK and PS from *Pseudomonas*. The presence of N-MOM changed the enantiopreference of lipase AK but not of lipase PS. The observed enantiopreference of the lipases is not changed by the nature of the organic solvent or the temperature.

Recently, hydrolytic enzymes have being explored as a promising tool for the preparation of chiral 4-aryl-1,4-dihydropyridines, widely used as calcium channel drugs. In particular, lipases from *Pseudomonas* have succesfully performed the enantiotopically selective hydrolysis/alcoholysis of prochiral (bisacyloxymethyl)-4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates.[1]

An important topic on biocatalysis is the prediction of enzymatic stereoselectivity. Recently, the change of enantiopreference of lipase AK (*Pseudomonas* sp.) towards prochiral 1,4-dihydropyridines by introduction of a protecting group on the heterocyclic nitrogen has been reported. The hydrolysis of prochiral diacetoxymethyl esters **1b** led to the (*S*)-**2b** enantiomers, while the N-unsubstituted derivatives **1a** lead to the (*R*)-**2a** enantiomers.[2]



1a R = H; $R_1 = R_2$ = -CH $_2$OAc; Ar = Ph, *m*-C $_6$H $_4$-NO $_2$
1b R = MOM; $R_1 = R_2$ = -CH $_2$OAc; Ar = Ph, *m*-C $_6$H $_4$-NO $_2$
3a R = H; R_1 = Et; R_2 = -CH $_2$OAc; Ar = Ph
3b R = MOM; R_1 = Et; R_2 = -CH $_2$OAc; Ar = Ph

In order to explore if this fact could also be generalized to asymmetric racemic compounds, we have synthesized racemic compounds **3a–b**[3] and studied their resolutions with lipases from *Pseudomonas*.

Both compounds were treated with lipases AK and PS (Table 1). As was expected, the enantiopreference of lipase AK changed drastically. Whereas resolution of the N-substituted **3b** was preferential towards the (*R*)-enantiomer, the opposite *S* preference was observed for the N-unprotected derivative **3a**. On the other hand, the stereochemical behaviour of lipase PS toward both substrates was similar, showing the best resolution for the unsubstituted compound. These results are in accordance with the results previously reported for the prochiral compounds.[2]

Then, the influence of different organic solvents on selectivity of lipase AK towards N-protected compound **3b** was explored (Table 2). Although the enantiomeric preference was not modified by changing the solvent, the enantiomeric purity and reaction rate were strongly influenced by organic media. Ethers have been shown to be suitable solvents for this resolution. Variations of temperature into a range of 15–35°C (data not shown) did not affect the enantioselectivity of lipase AK.

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* Corresponding author.

Table 1. Methanolysis of **3a** and **3b** catalyzed by lipases AK and PS.[4] [a]Isolated compound

SUBSTRATE	LIPASE	TIME (h)	(%) YIELD[a] **3**	(%) YIELD[a] **4**	ee (%) **3**	ee (%) **4**
3a	AK	26.5	50	30	15 (R)	20 (R)
3a	PS	24.0	51	39	70 (R)	70 (R)
3b	AK	7.0	42	51	95 (S)	63 (S)
3b	PS	11.0	39	39	18 (R)	24 (R)

Table 2. Methanolysis of **3b** catalyzed by lipase AK.[4] [a]Isolated compound

SOLVENT (Log P)	TIME (h)	(%) YIELD[a] **3b**	(%) YIELD[a] **4b**	ee (%) **3b**	ee(%) **4b**
Isooctane (4.5)	23.5	33	51	18 (S)	10 (S)
Toluene (2.5)	48.0	37	55	80 (S)	51 (S)
MTBE (1.35)	7.0	42	51	95 (S)	63 (S)
IPE (0.9)	6.5	30	61	95 (S)	38 (S)
EtOEt (0.85)	10.5	55	33	54 (S)	70 (S)

References

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2. Salazar, L.; Sih, C. J. *Tetrahedron: Asymmetry*, **1995**, *6*, 2917–2920.
3. Compounds **3a–b** were synthesized by known methods: a) Murakami, M.; Takahashi, K.; Osaza, T.; Tamazawa, K.; Kawai, R.; Takanaza, T. Japanese Patent (kokai), **1973**, 85574; b) Ogawa, T.; Nakazato, A.; Tsuchida, K.; Hatayama, K. *Chem. Pharm. Bull.*, **1993**, *41*, 108–116.
4. The reaction was carried out with 25 mg of substrate in 10 ml MTBE at 25°C and 0.24 mmol of methanol. Compounds **4** were methylated with diazomethane, and the ees of the mixed esters were determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$. The absolute configuration was determined by analogy with known optically active compounds (Ref. 3).

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