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Lipase Catalyzed Resolution of Chiral Acids using their Mixed Carboxylic Carbonic Anhydrides

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Abstract: Mixed carboxylic-carbonic anhydrides are efficient irreversible acyl transfer reagents for lipase-catalyzed esterification in organic media , and can be used for the resolution of chiral carboxylic acids.

Many enzymatic methods of resolution of racemic alcohols have been reported, which are based on irreversible or quasi-irreversible acyl tranfer processes[1a,b]. Only a few of these, however, can be applied to the resolution of racemic acids[2a-c]. We describe here a new and convenient enzymatic method for the resolution of α-substituted carboxylic acids based on an acyl transfer reaction between their mixed carboxylic-carbonic anhydrides and alcohols (eq. 1).

$$R_1R_2CHCOOCOOiPr + R_3OH \xrightarrow[\text{Lipozyme, rt}]{CO_2} R_1R_2CHCOOR_3 + iPrOH \qquad \text{eq 1}$$

1 R_1 = phenyl, R_2 = methyl
2 R_1 = p-^{t}bu-phenyl, R2 = methyl
3 R_1 = phenyl, R_2 = methoxy
4 R_1 = propyl, R_2 = methyl

R_3 = n-C_3H_7, n-C_4H_9, nC_8H_{17}

Carboxylic-carbonic anhydrides (which are widely used in peptide synthesis)[3] are known to be resistant towards racemisation. Therefore, in our method, the non esterified enantiomers retain their configuration.The enzymatic acyl transfers from these mixed anhydrides are fast (reaction time 20min to 2hrs): due to evolution of CO_2, this reaction is completely shifted towards the products. The by-products of the reaction, CO_2 and isopropanol are inert and neither cause side-reactions nor induce enzyme modifications.

The mixed anhydrides are readily prepared in high yields by condensation of carboxylic acids with isopropyl chlorocarbonate in the presence of N-methylmorpholine.[4] After their separation from N-methylmorpholine hydrochloride, they can be stored in solution in ether at -10° C for several months and used without further purification. They are good substrates for several lipases such as Lipozyme, Pseudomonas sp; lipase (LP) (see also in note 5), or Novozym[5] (see also p.2 last §). Lipozyme mediated resolution of the mixed carboxylic-carbonic anhydrides 1-4 in the presence of various primary alcohols were studied. The results obtained in terms of reaction time, substrate conversion, enantiomeric excess of the residual substrate or product (ee) and enantiomeric ratio of the reactions (E) are reported in Table 1.

TABLE 1: esters from 1 to 4

ESTER	ALCOHOL R_3	SOLVENT	TIME (Min)	CONVERSION (%)	Ee (%)	E
1	n-Propyl	Et_2O	120	49	66 [a]	11
1	n-Propyl	^tBuOMe	60	55	90 [a]	20
1	n-Octyl	^tBuOMe	40	50	79 [a]	20
2	n-Octyl	^tBuOMe	60	47	74 [a]	24
3	n-Butyl	^tBuOMe	15	28	33 [a]	17
4	n-propyl	Et_2O	60	29	67 [b]	7
4	n-octyl	Et_2O	20	47	80 [b]	19

Lipozyme (Novo) 500mg, anhydride (1 mmol), alcohol (2 mmol), solvent (20ml).
a) Ee of residual substrate were determined by GC of the corresponding S-methyl benzylamides, which is prepared within a few minutes by reacting the anhydrides and the amine in diethylether at 0°C.
b) Ee of products determined by NMR.

Reactions were monitored by GC and stopped at 50% conversion by filtering off the enzyme. The filtrate was then stirred with water at pH 9 (using a pH stat), in the presence of 0.1 equivalent of DMAP for 30 min. The esters from the enzymatic transformation and the acids from hydrolysis of the remaining mixed anhydride were finally obtained through conventional work up with yields > 90%.

The observed enantioselectivity and the enantiomeric ratio of the reactions was of the same order as those reported elsewhere[6]. However the reaction rates, using mixed anhydride showed to be significantly higher, comparing to other enzyme catalysed resolution of acids or their corresponding esters.

Mixed carboxylic-carbonic anhydrides may also be used for the resolution of chiral alcohols. For instance, the resolution of racemic 1-phenethyl alcohol was carried out through Novozym or LP catalyzed acylation with propionic- or octanoic-isopropyloxycarbonic anhydride. These procedures led to enantiomeric excesses comparable to those obtained by Bianchi and al[7], using the symmetric anhydride of propionic acid and lipase LP.

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