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A SIMPLE PROCEDURE FOR THE PREPARATION OF CHIRAL AMIDES

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Summary: Yeast lipase (Candida cylindracea) catalysed the reaction between ethyl (±)-2-chloropropionate and different aliphatic and aromatic amines yielding optically active amides.

The use of lipases to generate amide bonds in organic solvents[1] has been described in the preparative synthesis of peptides.[2] However the utility of these enzymes in the preparation of simple chiral amides has not been exploited.

In this communication, we report that yeast Candida cylindracea lipase (CCL) catalizes the amynolisis of ethyl (±)-2-chloropropionate with several aliphatic and aromatic amines.[3] Moreover, we have found that yeast lipase can be used as a catalyst below room temperature.

A representative example for this biocatalytic amide formation is as follows: to a solution of 10 mM of (1) and 5 mM of (2) in 30 ml of hexane or tetrachloromethane was added 4 g of (CCL). The reaction mixture was stirred and then filtered off, the organic solvents and the excess of ester were evaporated under reduced pressure. The chiral amides (3) were obtained with moderated yields and high enantiomeric excesses (see Table). Unlike the case of N-acylation of aminoalcohols,[4] PPL displayed very low catalytic activity in the preparation of (3). For example, the formation of amide (3d) ocurred in 24 % of chemical yield and only 5 % e.e. even when 7 g of PPL in 40 ml of hexane were used.

As shown in the Table, yeast lipase can act over a wide range of temperatures. In the case of aliphatic amides, the reaction was carried out at 2° because the racemic amide is slowly formed at room temperature in the absence of the enzyme. However, the use of aromatic amides required more vigorous reaction conditions. On the other hand, non polar organic solvents, such as hexane or tetrachloromethane, are more suitable for the preparation of the corresponding chiral amides, which is consistent with the data reported in the literature.[5]

$$CH_3\text{-}CHCl\text{-}CO_2C_2H_5 + RNH_2 \xrightarrow{(CCL)} CH_3\text{-}CHCl\text{-}CONHR$$

(1) (2) (3)

(±) (e.e.s. 40-95 %)

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Table. Optically active amides (3) from (1) and amines (2) with yeast lipase[a] in organic solvents.[b]

Entry	R	Reaction time, h	(T,°C)	Yield,%	mp.°C	$[\alpha]_D^{25}$, deg (EtOH)	Isomer[c]	ee, %[c]
(3a)	n-butyl[d]	3	(2)	62	32-34	-16.6(c 1.47)	S	95
(3a)	n-butyl[e]	3	(2)	38	32-34	-7.0(c 0.14)	S	40
(3b)	i-propyl[d]	22	(25)	85	102-104	-26.0(c 0.20)	S	95
(3c)	ciclohexyl[d]	3.5	(2)	48	140-142	-2.2(c 0.67)	S	30
(3d)	bencyl[d]	21	(25)	56	64-66	-4.3(c 0.35)	S	74
(3d)	bencyl[e]	21	(25)	47	64-66	-3.6(c 0.75)	S	62
(3e)	allyl[d]	7	(2)	60	oil	-5.2(c 1.08)	S	92
(3f)	phenyl[d]	48	(60)	26	81-83	-34.0(c 0.22)	S	56
(3f)	phenyl[e]	48	(60)	52	81-83	-48.7(c 0.95)	S	80
(3g)	p-tolyl[e]	31	(60)	81	114-116	-41.7(c 0.48)	S	65
(3h)	p-chlorophenyl[e]	62	(60)	46	106-108	-38.5(c 0.26)	S	62

a) The yeast Candida cylindracea lipase (E.C.3.1.1.3) used is the purchased from Sigma, Type VII crude. b) The use of hexane as solvent in the case of aromatic amides resulted in poored yields because the lower solubility of the amine. c) The e.e.s. were determined by ^{1}H-NMR spectroscopy (300 MHz) in the presence of tris-[3-(trifluormethyl-hydroxymethylen)--(+)-camphorato]-europium (III). Eu(Tfc)$_3$. The configuration was determinated by analogy with the optically active amide obtained from the (S)-(-)-ester and the corresponding amine. d) Solvent hexane. e) Solvent tetrachloromethane.

References and Notes

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