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LIPASE-CATALYZED RESOLUTION: ENANTIOSELECTIVE ESTERIFICATION OF 2-PROPANOL AMINES

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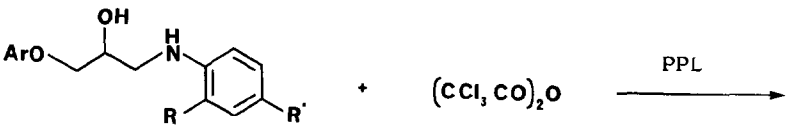
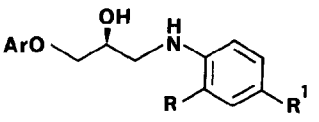
Abstract: Porcine pancreatic lipase catalyzes the specific hydroxyl acylation of 2-propanol amines with enantioselectivity employing trichloroacetic anhydride in organic solvents.

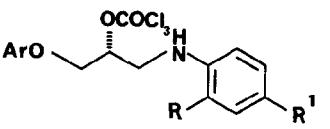
Asymmetric synthesis and kinetic resolution employing enzymes, are an attractive alternative to the classical techniques.[1] The use of organic solvents instead of water as a reaction medium for enzymatic reactions further generated interest in this methodology.[2] The recent finding about the substrate specificity and enantioselectivity of enzymes can be regulated by the reaction medium creates new perspectives in synthetic organic chemistry.[3] Recently, lipases have successfully been used for the regioselective acylation and deacylation of a number of compounds.[4] In most of the reported examples, enzymes exhibit a predominant preference towards a primary hydroxyl group in both acylation and deacylation reactions.[5] As a part of our continuing studies on the utility of enzymes as biocatalysts,[6] we report here a regiospecific and stereoselective acylation of 2-propanol amines by porcine pancreatic lipase (PPL) and trichloroacetic anhydride in organic solvents. Resolution of 2-propanol amines is of interest as the biological activity resides mainly in one of the enantiomers as in the case of β-adrenergic blocking agents.[7]



(R,S)-1



(S)-1



(R)-2

(R)-1

Table. Enantioselective Esterification of racemic 2-propanol amines

Substrate	R	R^1	Ar	Reaction temp.(°C); time (h)	(S)-1		(R)-1[a]	
					Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]
1a	$COCH_3$	H	Ph	70; 15	28	96	26	68
1b	$COCH_3$	Cl	4-$AcNHC_6H_4$	75; 24	40	60	29	72
1c	$COCH_3$	H	4-ClC_6H_4	75; 18	49	71	33	66
1d	$COCH_3$	H	2-$CH_3COC_6H_4$	75; 15	44	75	41	86
1e	$COCH_3$	Cl	2-$CH_3COC_6H_4$	75; 24	43	67	37	89
1f	$COCH_3$	H	2-$CH_3COC_6H_4$	75; 24	50	28	31	78
1g	COC_6H_5	H	Ph	85; 18	38	33	28	73
1h	COC_6H_5	Cl	4-$AcNHC_6H_4$	85; 48	36	51	34	76
1i	COC_6H_5	Cl	4-$CH_3COC_6H_4$	85; 20	46	82	35	88
1j	COC_6H_5	Cl	2-$PhCOC_6H_4$	85; 24	39	78	38	82
1k	COC_6H_5	Cl	α-naphthyl	85; 24	47	31	33	85

a) This enantiomer was obtained by alkaline hydrolysis of the corresponding compound **2**.

b) Referred to the racemic compound 1.

c) HPLC employing LKB EnantioPac α_1-AGP 10 μm column (4.0x100 mm), 0.1 M phosphate buffer (pH 7.2) containing 0.5% (v/v) of acetonitrile at 0.7 ml/min and 220 nm wave length, on derivatization of 1 to their diacetates.

This enzyme-catalyzed reaction provides a convenient method for the enantioselective acylation of secondary hydroxyl in the presence of an amino group. Conventional methods even for regioselective protection employing acetylchloride or acetic anhydride-pyridine in THF afford mainly diacylated and as well as mixtures of monoacylated products. At room temperature and lower temperatures the reaction fails to proceed. Attempts to drive these reactions to completion by increased temperature and addition of excess acetic anhydride result in increased yields of the diacylated product. Other lipase catalyzed esterification methods[4] employing ethyl acetate,[4d] vinyl acetate,[4e] O-acetylcyclohexanone oxime,[4f] acetic anhydride[5a] as esterification agents failed or gave low yields.

In a typical procedure, PPL[8] (100 mg per mmol of the substrate) was added to a stirred solution of 1 eq of 2-propanol amine[9] and 1.3 eq of trichloroacetic anhydride in dioxane (1 M solution). The reaction was stirred at indicated temperature and time (Table), after which the PPL was removed by filtration. The organic phase was diluted with dioxane and excess anhydride was removed by washing with aqueous 1 M NaOH solution. The product was isolated by column chromatography.[10]

In conclusion, the method described here illustrates the potential of PPL as a biocatalyst not only in the specific hydroxyl protection but as well for the enantioselective acylation and ultimately for the resolution of biologically important 2-propanol amines. Further work on the enzymatic resolution by hydrolases is currently in progress in our laboratory.

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8. The porcine pancreatic lipase used was purchased from Sigma, Type II crude.
9. These precursors were prepared by the reaction of 1-aryloxy-2,3-epoxypropane with substituted arylamines in refluxing ethanol.[11]
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