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STEREOSELECTIVE SYNTHESIS OF (S)-PROPANOL AMINES : LIPASE CATALYZED OPENING OF EPOXIDES WITH 2-PROPYLAMINE

Ahmed Kamal*, Yalamati Damayanthi and Maddamsetty V. Rao

Division of Organic Chemistry
Indian Institute of Chemical Technology, Hyderabad 500 007, India

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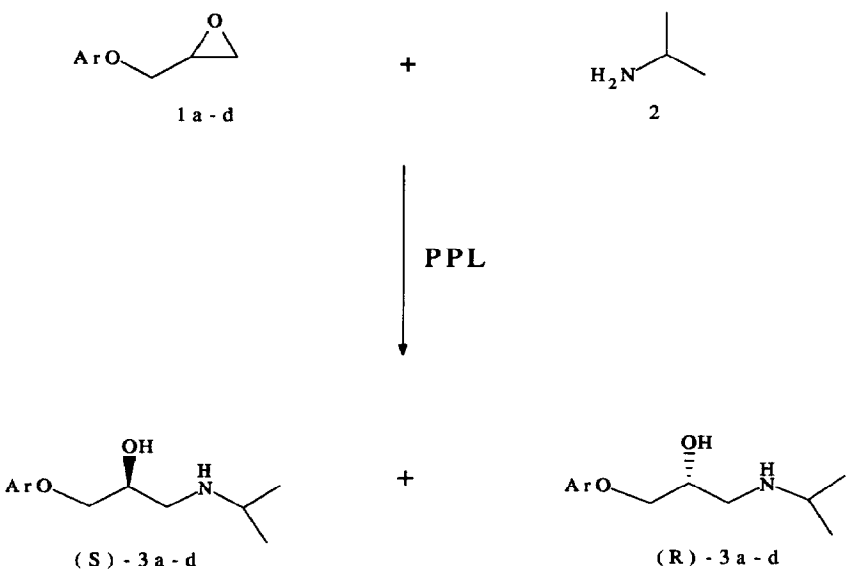
Abstract: The ring opening of epoxides with 2-propylamine in presence of lipase in organic solvents affords selectively (S)-propanol amines. The effect of solvents towards selectivity has also been examined.

It is well established that in the beta-adrenergic blocking agents the biological activity resides mainly in the (S)-enantiomer[1-3]. On the contratry the opposite (R)-enatiomer may be responsible for the side-effects[4]. As a result, in the recent years, there have been considerable efforts in the preparation of the enantiomerically pure form of (S)-propanolamines by asymmetric synthesis[5] or bioconversions[6]. The conventional method for the synthesis of these compounds is by the opening of epoxides with corresponding amines. Based on our previous interest on the application of enzymes as biocatalysts[7], we recently studied the stereoselective opening of epoxides by arylamines in presence of liver microsomes[8]. In continuation of this approach it was considered worthwhile to open the epoxides by an amine in presence of a lipase. This could offer an advantage of carrying out the reactions in organic media and thus enhancing the suitability of this reaction for the water-susceptible or insoluble substrates. However, lipases have been extensively employed in the enantio- or regioselective transformations[9] involving acylations, transesterifications, hydrolyses, lactonization, hydrazinolysis, aminolysis and transamidation.

This report describes for the first time the enantioselective opening of epoxides (**1**) by 2-propylamine (**2**) in presence of porcine pancreatic lipase (PPL)[10] in organic solvents. Furthermore, the effect of solvents on the selectivity of propanol amines (**3**) has been studied. In a typical reaction; to **1a** (50 mg) and PPL (100mg) in hexane (40 ml) was added slightly more than half a molar equivalent amount of **2a**. After being stirred at room temperature for 12h, the lipase is filtered and the resulting solution is

evaporated to give the residue. This was immediately subjected to column chromatography, chloroform-methanol (9.8:0.2) to recover the unreacted epoxide **1a**. After the complete recovery of **1a** the eluent was changed to chloroform-methanol (9.5:0.5) for obtaining the propanol amine (**3a**). The reactions were monitored by TLC.



The comparative analysis of the results in Table 1 clearly reflects the considerable influence of the solvents on the enantioselectivities of **3**. With the exeception of the reaction of **1c** in hexane the ring opening to (S)-form seems to be preferential in presence of lipase, particularly employing toluene as the solvent. The absolute configuration was obtained by the correlation of the reaction of 3-(1-napthyloxy)-1,2-epoxypropane with isopropyl amine to give propranolol, which was then compared with chirally pure (R)- and (S)-propranolol.

The strategy descibed here provides a facile synthesis of (S)-propanol amines by ring-opening of epoxides in presence of lipase. Thus, this methodology is noteworthy as it offers the preparation as well as resolution of propanol amines in one-pot.

Table 1. Lipase-catalyzed opening of epoxides with 2-propylamine

Entry	Ar	Reaction medium	Conversion (%)	Enantiomeric ratio (%) [a] (R)	(S)
1a	C_6H_5	hexane	48	39	61
		toluene	42	0	>99
		ethyl acetate	36	40	60
1b	4-ClC_6H_4	hexane	41	48	52
		toluene	45	7	93
		ethyl acetate	39	19	81
1c	2-$OCH_3C_6H_4$	hexane	35	62	38
		toluene	39	35	65
		ethyl acetate	43	20	80
1d	4-$NHCOCH_3C_6H_4$	hexane	b	-	-
		toluene	47	0	>99
		ethyl acetate	40	20	80

[a]Compounds **3** were derivatized to oxazolidones[11] and enantiomeric ratio was determined by HPLC employing LKB enantiopac, α-AGP 10 μm cartridge column (4.0 x 100 mm), 2-propanol (10% for 3a; 15% for 3c; 20% for 3b and 3d) in 8mM sodium dihydrogen phosphate / sodium hydrogen phosphate buffer with 0.1M sodium chloride pH 6.9 at 0.25 ml / min flow and 230 nm wavelength; calibrated by the authentic racemic forms of **3**.
[b]Substrate almost insoluble in hexane.

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