Tetrahedron Letters, Vol. 33, No. 28, pp. 4077-4080, 1992
Printed in Great Britain

0040-4039/92 $ 5.00 + .00
Pergamon Press Ltd

STEREOSELECTIVE SYNTHESIS OF (S)-PROPANOL AMINES: LIVER MICROSOMES MEDIATED OPENING OF EPOXIDES WITH ARYLAMINES

Ahmed Kamal,* Adari B. Rao and Maddamsetty V. Rao

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

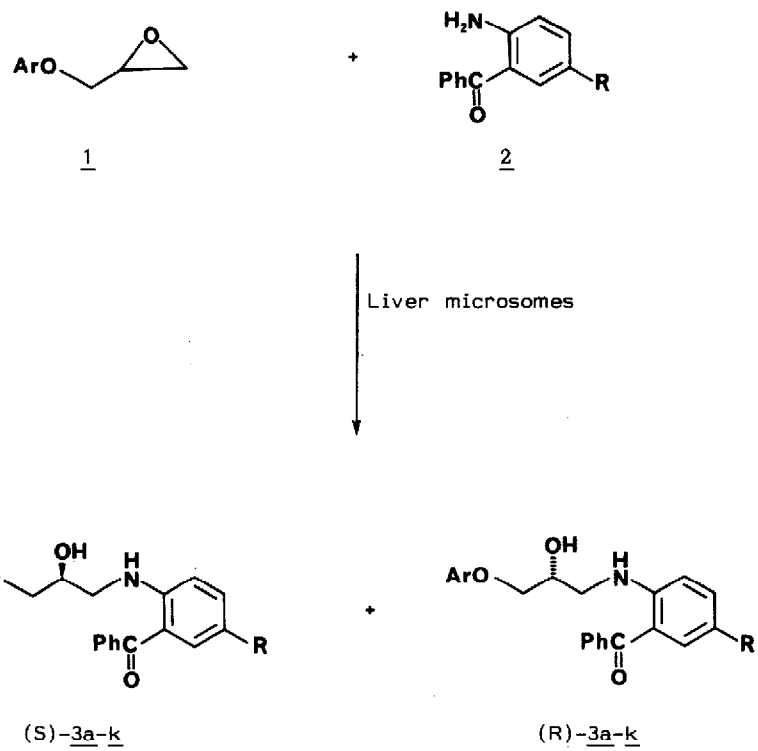
Key words: (S)-propanol amines; liver microsomes; stereoselective synthesis

Abstract: Stereoselective synthesis of 2-(S)-propanol amines by the ring-opening of racemic epoxides with arylamines in presence of rat liver microsomes.

The ring-opening reaction of epoxides with amines is of significance particularly from the stereoselectivity point of view. Most of the biologically important compounds such as in the beta-adrenergic blocking agents[1,2] the activity usually resides mainly in the (S)-enantiomer[3] and are often synthesized by the opening of epoxides with corresponding amines. It is well established that liver microsomes produce biotransformations with remarkable selectivity.[4] This feature can also be correlated to the *in vitro* metabolism studies of various compounds, wherein regio- and stereoselective phenomena are often experienced.[5]

The stereoselective opening of the epoxides to diols by liver microsomes has been extensively studied.[6] To our knowledge, there are no reports on the opening of epoxides with amines in presence of liver microsomes. In continuation of our efforts on the application of enzymes as biocatalysts[7,8] in stereoselective synthesis, the present investigation describes the enantioselective ring-opening reaction of 1-aryloxy-2,3-epoxypropanes with arylamines in presence of rat liver microsomes.

In a typical reaction, to 1a (150 mg) and half a molar equivalent amount of 2a in ethanol (3 ml) as well as 0.1 M phosphate buffer (30 ml, pH 9.5) solution was added freshly prepared rat liver microsomal preparation[7] (4 ml) of protein content 4.8 mg/ml. The mixture was incubated at 37°C for 24 h and was extracted thrice with chloroform (occasionally appearing emulsions were broken by centrifugation at 2000-4000 g). The organic phase was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was subjected to column chromatography, chloroform-methanol (97:3) to give 3a, m.p. 93-95°C.



Besides epoxide 1a, the selective ring-opening reaction for several epoxides with arylamines was carried out successfully employing the present method. The results are illustrated in Table 1. These reactions were monitored by HPLC.[9] Analytical and spectroscopic data were satisfactory.[10] A control incubation with boiled microsomal fraction did not produce 3.

The absolute configuration of 3k obtained from 1k was established by recovering unreacted 1k and further reacting with isopropylamine to give propranolol which was then compared with chirally pure (R)-propranolol.[11] The unambiguous assignment of the predominant configuration of 3 as (S) and recovered 1 as (R) was thus possible.

Earlier, we synthesized compounds 3 in the racemic form with an interest to explore their biological potential by the well established method of the ring-opening of epoxides with arylamines in protic solvents under reflux conditions.[12] As such, this study enables now to derive a correlation between the stereochemistry and biological activity.

Table. Liver microsomes mediated ring-opening of racemic epoxides with arylamines

	R	Ar	% Yield	% e.e.[a]
a	Cl	Ph	40	86
b	H	4-AcNHC$_6$H$_4$	43	77
c	Cl	4-AcNHC$_6$H$_4$	37	51
d	H	4-ClC$_6$H$_4$	42	57
e	Cl	4-MeOC$_7$H$_4$	38	61
f	H	2-MeCOC$_6$H$_4$	46	52
g	Cl	2-MeCOC$_6$H$_4$	48	88
h	H	2-PhCOC$_6$H$_4$	27	65
i	Cl	2-PhCOC$_6$H$_4$	33	68
j	H	α-naphthyl	46	75
k	Cl	α-naphthyl	41	85

[a] Compounds 3 were derivatized to diacetates and e.e. was determined by HPLC employing LKB enantiopac, α-AGP 10 μm column (4.0x100 mm), 0.01 M phosphate buffer containing 0.50% (v/v) of acetonitrile at 0.7 ml/min and 220 nm wavelength and were calibrated by the authentic racemic forms of 3.

In conclusion, the present investigation employing liver microsomes provides a mild and stereoselective procedure for the synthesis of 2-(S)-propanol amines. Further studies to determine the full scope of this methodology by the addition of cosolvents and cofactors are in progress.

REFERENCES AND NOTES

1 Main, B.G.; Tucker, H. in "Medicinal Chemistry: The Role of Organic Chemistry in Drug Research of Beta Blockers"; eds. Roberts, S.M.; Price, B.J.; Academic Press, London, 1985; pp 69-91.

2 Jamali, F.; Mehvar, R.; Pasutto, F.M.; **J. Pharm. Sci.**, **1989**, **78**, 695.

3 Scott, A.K.; **Drug News & Perspectives**, **1991**, **4**, 476.

4 Shetty, H.U.; Nelson, W.L.; **J. Med. Chem.**, **1986**, **29**, 2004.

5 In "Handbook of Stereoisomers: Therapeutic Drugs", ed. Smith, D.F.; CRC Press, Florida, 1989.

6 Belluci, G.; Chiappe, C.; Marioni, F.; **J. Chem. Soc., Perkin Trans. 1**, **1989**, 2369.

7 Kamal, A.; **J. Org. Chem.**, **1991**, **56**, 2237.

8 Kamal, A.; Rao, M.V.; **Tetrahedron: Asymmet.**, **1991**, **2**, 751.

9 Employing TSK Si-150, 5 μm column (4.6x250 mm), chloroform-butanol (90:10) at 0.7 ml/min flow rate and 254 nm wavelength.

10 Selected spectral data for **3a:** I.R. ν_{max}(KBr) 3430, 3210, 1600, 1580 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$+D_6-DMSO) δ 8.7 (1H, br s), 6.7-7.1 (13H, m), 4.0-4.4 (3H, m), 3.6 (2H, m), 2.9 (1H, br d, J=6.5 Hz).

11 Klunder, J.M.; Ko, S.Y.; Sharpless, B.; **J. Org. Chem.**, **1986**, **51**, 3710.

12 Reddy, A.V.N.; Kamal, A.; Rao, A.B.; Diwan, P.V.; Sattur, P.B.; Indian Pat. No. 165911, 25 April 1986.

IICT Communication No. 2701

(Received in UK 22 April 1992)