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# One Pot Synthesis Of (+-)/(S)-Atenolol And(+-)/(S)Propranolol By Employing Polymer Supported Reagent

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# ONE POT SYNTHESIS OF ( ± ) / ( S ) - ATENOLOL AND ( ± ) / ( S ) - PROPRANOLOL BY EMPLOYING POLYMER SUPPORTED REAGENT

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ABSTRACT: ( ± ) / ( S ) -Atenolol and ( ± ) / ( S ) - propranolol were synthesized by using reaction of ( ± ) /(S) -epichlorohydrin with polymer supported phenoxide anion followed by reaction with isopropylamine.

( ± ) - Atenolol and ( ± ) - propranolol are well known β -Adrenergic blockers, used for the treatment of hypertension and angina pectoris. These derivatives have been synthesized by various methods. [1-4] Aryloxypropanolamines are known to have hypotensive β - adrenergic blocking activity generally resides in the ( S ) - isomer [5]. Methods reported for the synthesis of ( S ) - propranolol involved the use of enzymes for resolution of intermediates [6], asymmetric

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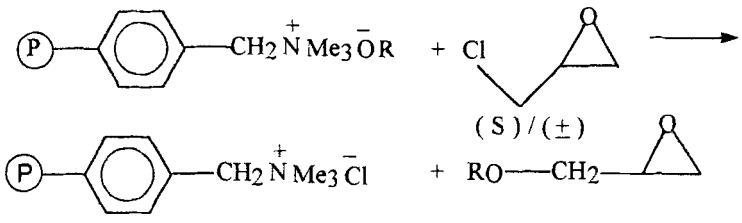
hydrogenation using chiral metal complex of the intermediate [7], asymmetric epoxidation of allyl-alcohol [8] and also from sorbitol [9] .The synthesis of ( S ) - atenolol involved use of chiral epichlorohydrin [10] , using stereoselective epoxidation [11] and also by using lipase [12].

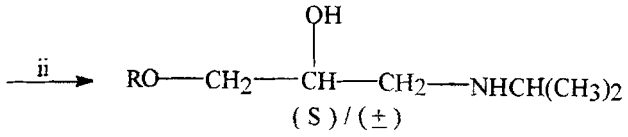
Polymeric reagents have proven useful for many chemical transformations in organic synthesis. The advantages of polymer supported reagents are easy work up, reuse of supported reagent after regeneration, adaptability to continuos flow process and reduced toxicity [13]. The importance of the titled drugs and advantages of polymeric reagents prompted us to investigate the methodology for the one pot synthesis of ( ± ) / ( S ) - atenolol and ( ± ) / ( S ) - propranolol using polymer supported phenoxide anion (SCHEME).

In the method described, the reaction is carried out in the absence of base which markedly reduced formation of the by-products. The products are obtained in good yields , high optical purity and considerably short reaction time, as compared to previous methods which may be attributed to the high nucleophilicity of supported phenoxide anion as compared to phenol.

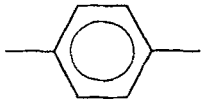
The treatment of sodium salt of phenol (sodium phenoxide) with Amberlite IRA-400 ($Cl^-$ form), a strong anion exchange resin containing quaternary ammonium groups, afforded the polymer supported phenoxide anion which on treatment with ( ± ) / ( S ) - epichlorohydrin , followed by addition of isoopropylamine to the same reaction vessel gave the product in good chemical yield / and optical purity. (**TABLE**).

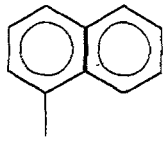
In summary, we have developed a simple method for the synthesis of ( ± ) / ( S ) - atenolol and ( ± ) / ( S ) - propranolol with high purity , high chemical yield and high optical yield. As other important β - blockers like practolol, oxprenolol, metaprolol, acebutolol, moprolol etc. are all closely related to propranolol, atenolol and are made by the same basic route [14], our present route should serve as a protocol for all these chiral drugs.





i ) MeOH, reflux/rt; ii) MeOH, isopropylamine (IPA), reflux/rt

R =  , Atenolol ;

R =  Propranolol.

**SCHEME** : Preparation of ( ± )/( S )-atenolol and ( ± )/( S )- propranolol.

## EXPERIMENTAL

$^1$H NMR spectra were recorded on (Perkin Elmer) 300 MHz spectrophotometer, using $CDCl_3$ and DMSO-$d_6$ as solvents. Optical rotation values were noted on JASCO-360 Polarimeter.

**Preparation of Polymer Supported Phenoxide Anion :**

Commercially available Amberlite IRA-400 ($Cl^-$ form) placed in a column was washed by 0.25N aqueous sodium salt of phenol (prepared by dissolving 25 mmol

**TABLE**

| Product | Reaction condition | Time( h ) | Yield ( % ) | m.p. ( $^0$C ) | ee ( % ) |
|---|---|---|---|---|---|
| (S)-atenolol[a] | R.T. | 20 | 80 | 148-151 Lit.[12] =148-152 | 100 |
| (S)-atenolol[b] | Reflux | 2 | 82 | 148-151 Lit.[12] =148-152 | 88 |
| (S)-proranolol[c] | R.T. | 20 | 83 | 70-71 Lit.[6b] =70-71 | 100 |
| (S)-propranolol[d] | Reflux | 3 | 85 | 70-71 Lit .[6b] =70-71 | 94 |
| (± ) - atenolol* | Reflux | 2 | 82 | 146-148 Lit.[3] =146-148 | – |
| (±)-propranolol** | Reflux | 3 | 85 | 96 Lit.[2] =96 | – |

a. $[\alpha]_D$ = -16.0 (c =1.0,MeOH) ; Lit.[12] $[\alpha]_D$ = -16.0 (c =1.0, 1N HCl).

b. $[\alpha]_D$ = -14.0 (c =0.5, MeOH); Lit.[12] $[\alpha]_D$ = -16.0 (c =1.0, 1N HCl).

c. $[\alpha]_D$ = -10.2 (c =0.5, EtOH); Lit.[6a] $[\alpha]_D$ = -10.2 (c =1.02, EtOH).

d. $[\alpha]_D$ = -9.0 (c =0.5, EtOH); Lit.[6a] $[\alpha]_D$ = -10.2 (c =1.02, EtOH).

* $^1$H NMR (DMSO-d6 ) δ 1.1 (d, 6H), 2.5 (m,1H), 2.6-2.8 (m,2H), 3.4 (s,2H), 3.8 (s,2H), 3.9 (m,1H), 5.0 (s,4H), 6.8(d,2H), 7.2 (d,2H).

** $^1$H NMR ($CDCl_3$ ) : δ 1.1-1.2 (d, 6H ), 2.8-3.1 ( m, 3H), 4.1-4.3 (d,3H), 6.8-8.3 (m,7H).

of phenol *viz.* α - naphthol or p -hydroxyphenyl acetamide) until complete removal of $Cl^-$ ions (confirmed by $AgNO_3$ test).The resin was then successively washed with water, methanol and ether until the excess of phenoxide anion was removed, which was tested by alcoholic $FeCl_3$ test. The resin was finally dried over anhydrous phosphorous pentaoxide for 10 h under vacuum at 50 $^0$C. The exchange capacity was determined by passing 1M aqueous sodium chloride (100 ml) through the resin (0.3g) placed in a column. The amount of phenoxide anion in the eluent was determined by titrating against (0.01N) hydrochloric acid using methyl orange as an indicator. The exchange capacity of polymer supported phenoxide anion reagent was found to be in the range of 1.3-1.4 mmol/g of dry resin.(capacity of α-naphthol was found to be 1.4 mmol/g ; capacity of p-hydroxyphenyl acetamide was found be 1.3 mmol/g).

**Preparation of ( ± ) / ( S ) - atenolol and ( ± ) / ( S ) - propranolol :**

The amberlite IRA-400 phenoxide anion (of p-hydroxyphenylacetamide / α - naphthol ) , resin (5 mmol),epichlorohydrin (5 mmol) and methanol (25 ml) were stirred at room-temperature for 10 h or refluxed for 1 h. After the formation of arylepoxyether, isopropylamine ( 24 mmol / 5 mmol) was added to the same vessel and stirred at room-temperature /refluxed, as per conditions indicated in TABLE. After completion of reaction, ( monitored by tlc ), the resin was filtered and washed with methanol (2 x 5 ml). Evaporation of solvent and isopropylamine afforded the crude ( ± ) / ( S ) - atenolol / ( ± ) / ( S ) - propranolol. It was further purified by column chromatography (silica gel 60-120 mesh ).

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