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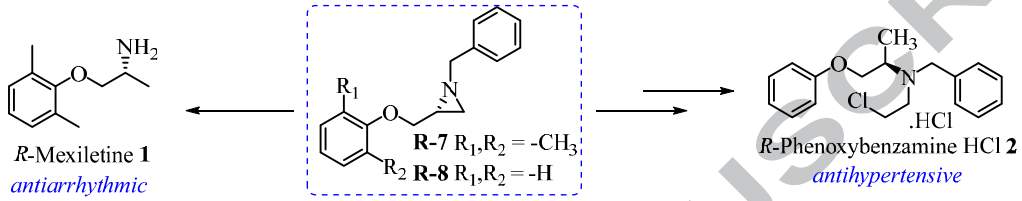

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# Chiral aziridine ring opening: Facile synthesis of (*R*)-mexiletine and (*R*)-phenoxybenzamine hydrochloride

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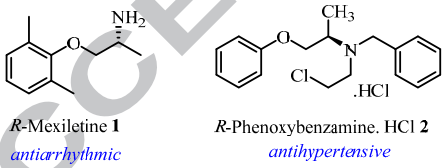
ABSTRACT

**Abstract**: A simple and efficient synthesis of chiral drugs (*R*)-mexiletine **1**, an anti-arrhythmic drug and (*R*)-phenoxybenzamine hydrochloride **2**, an anti-hypertensive drug has been described *via* controlled reductive ring opening of chiral aziridine as a key step. The target compounds **1** and **2** were obtained in overall yields of 34% and 10.5% respectively



Synthesis of compounds in their enantio-enriched form became very important in the market place, especially in the pharmaceutical sector. This is mainly because; the enantiomers of chiral drugs often exhibit significantly different pharmacological, toxicological, pharmacodynamic and pharmacokinetic properties. Hence the development of newer methods aiming the synthesis of active enantiomer or both enantiomers (for careful evaluation of individual enantiomers) of chiral drugs is a main focus of research in many academic and industrial laboratories.[1]



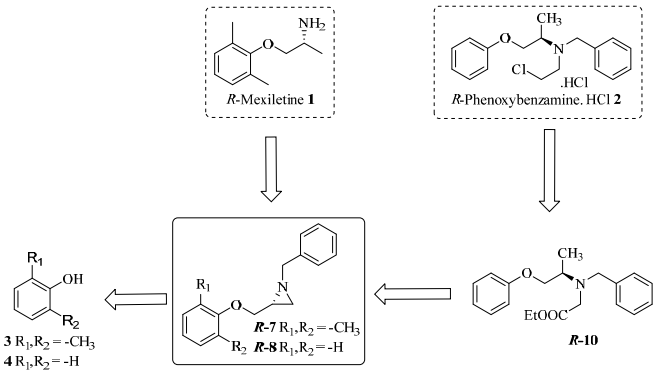

*R*-Mexiletine **1** *antiarrhythmic*

*R*-Phenoxybenzamine. HCl **2** *antihypertensive*

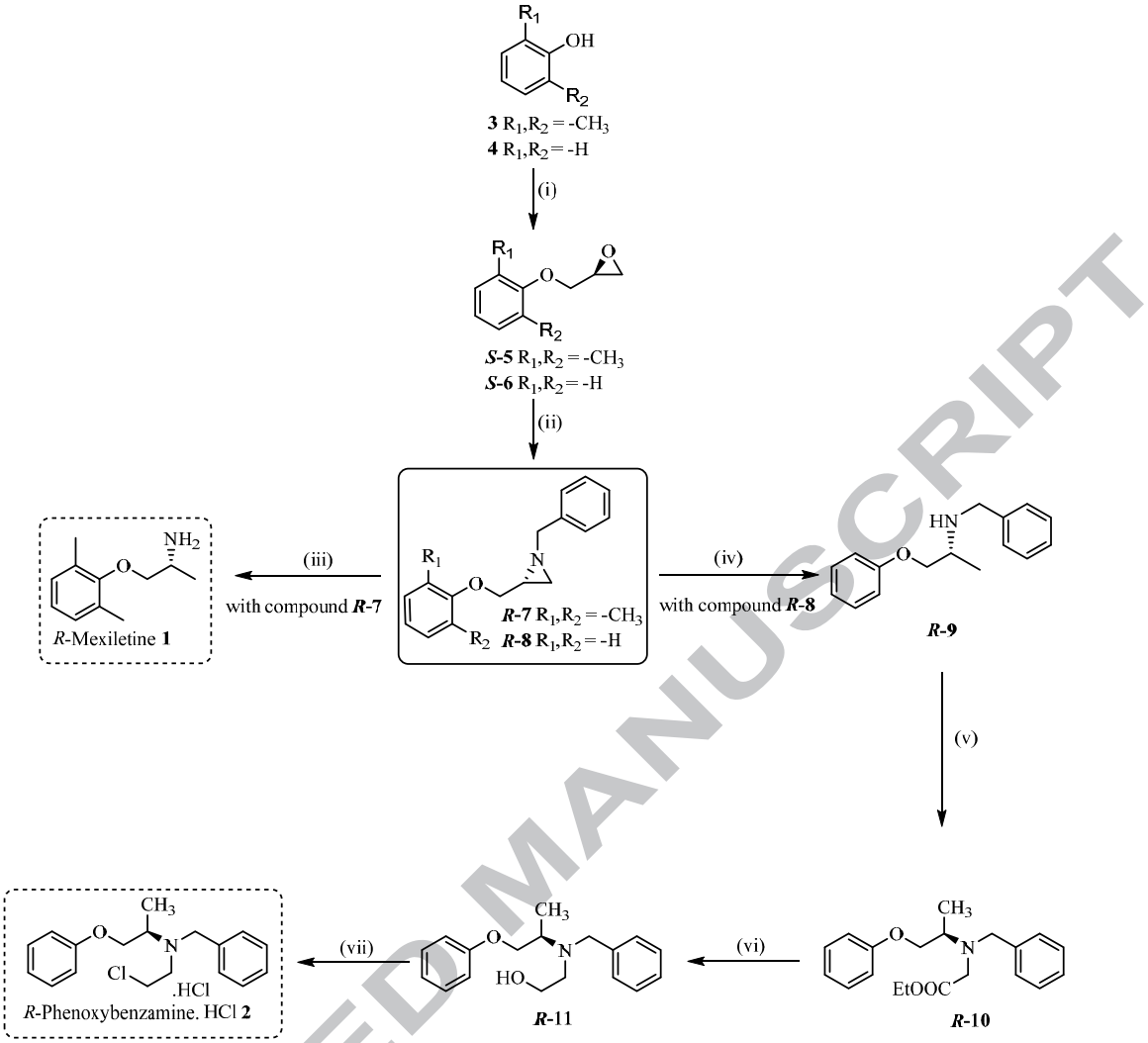
**Figure 1** Structure of (*R*)-mexiletine and (*R*)-phenoxybenzamine hydrochloride

Mexiletine is an important β-amino aryl ether class of drug used in the treatment of arrhythmia, allodynia and myotonic syndromes, etc. and its racemic form of mexiletine is available in the market with the trade name Mexitil®.[2] However, the (*R*)-isomer of mexiletine (**1**) is more potent than the (*S*)-isomer in experimental arrhythmias and in binding studies on cardiac sodium channels.[3] Similarly, phenoxybenzamine hydrochloride (**2**, PB; Commercial name Dibenzyline®) is an important β-chloroethylamine class of drug in the α-blocker series, widely used in the treatment of hypertension.[4] It has also found application in treating benign prostatic hyperplasia (BPH) and hypoplastic left heart syndrome, etc. However, the (*R*)-isomer of phenoxybenzamine hydrochloride (**2**) is 14.5 times more potent than its (*S*)-isomer.[5] Approaches that have been used so far to prepare enantiopure mexiletine and PB includes chiral pool, chemo/enzymatic resolution strategy or using stereoselective protocols.[6,7]

As part of our ongoing program on developing a new and improved process for the preparation of various pharmaceutically important compounds for industrial applications,[8,9] sometime ago we reported the preparation of **1** and **2** employing hydrolytic kinetic resolution strategy.[9a,b] Importantly, the potential utility of compounds **1** and **2** in new therapeutic areas inspired us to develop a robust method for their synthesis preferably from a




**Scheme 1**: Retrosynthetic analysis




**Scheme 2.** *Reagents and conditions*: (i) (*R*)-epichlorohydrin, $K_2CO_3$, dry acetone, reflux, 16-20 h, ***S*-5** (73%), ***S*-6** (82%); (ii) (a) benzylamine, LiBr (neat), 6-9 h (b) $PPh_3$, DIAD, dry toluene, 0 $^oC$ to reflux, 12-16 h, ***R*-7** (64%), ***R*-8** (67%) (two steps); (iii) $H_2$ (50 psi), 10% Pd/C, MeOH, rt, 6 h, 73%; (iv) $H_2$ (50 psi), 10% Pd/C, MeOH, rt, 45 min, 72%; (v) $BrCH_2COOEt$, $K_2CO_3$, DMF, 80 $^oC$, 12 h, 66%; (vi) $LiAlH_4$, THF, 0 $^oC$ to rt, 3h, 72%; (vii) $SOCl_2$, benzene, reflux, 8 h, 56%.

common precursor there as to make a diverse range of chiral analogues of **1**[10] and **2** in a simple manner to test their biological activities. We herein report a simple and efficient approach towards the preparation of **1** and **2** via the reductive ring opening reaction of the enantiopure aziridine as a key step.

A retrosynthetic analysis of (*R*)-mexiletine (**1**) and (*R*)-phenoxybenzamine. HCl (**2**) is outlined in Scheme 1. As shown in scheme 1, we envisaged that chiral aziridines ***R*-7** & ***R*-8** would be an ideal key intermediate for the synthesis of both (*R*)-mexiletine (**1**) and (*R*)-phenoxybenzamine HCl (**2**), respectively. These intermediates ***R*-7** & ***R*-8** can be converted to the target molecules via reductive ring opening followed by simple synthetic sequences. The chiral aziridines ***R*-7** & ***R*-8** in turn, can be prepared from commercially available phenols via *O*-alkylation, regioselective ring opening followed by intramolecular ring closure sequences.

As illustrated in Scheme 2, synthesis of, (*R*)-mexiletine (**1**) began with the commercially available 2,6-dimethyl phenol **3** which on *O*-alkylation with (*R*)-epichlorohydrin in anhydrous acetone in the presence of potassium carbonate at reflux for 20 h to give epoxide ***S*-5** in 73 % yield. Subsequently, the epoxide ***S*-5** was converted into the desired aziridine ***R*-7** in 64 % yield (two steps) by successive regioselective ring opening of epoxide with benzylamine[11] followed by intramolecular cyclization employing Mitsunobu reaction. Finally, compound ***R*-7** was subjected to palladium carbon catalyzed reductive ring opening [$H_2$ (50 psi), 10 % Pd/C, MeOH, 6 h] to give the (*R*)-mexiletine (**1**) in 73 % yield (overall yield 34 %; ee >97%). The structure of (*R*)-mexiletine (**1**) was confirmed by means of IR, $^1H$ NMR, $^{13}C$ NMR and mass spectroscopic analysis. Similarly, the synthesis of (*R*)-Phenoxybenzamine HCl (**2**) started with the simple phenol **4** as a starting material which on *O*-alkylation with (*R*)-epichlorohydrin in anhydrous acetone in the presence of potassium carbonate at reflux for 16 h gave epoxide ***S*-6** in 82 % yield. Epoxide ***S*-6** was converted into the desired aziridine ***R*-8**

in 67% yield (two steps) by employing the same two step sequences used for the preparation of (*R*)-mexiletine (**1**). Subsequently, palladium carbon catalyzed controlled reductive ring opening of ***R*-8** [$H_2$ (50 psi), 10 % Pd/C, MeOH, 45 min.] afforded the amine derivative ***R*-9** in 72 % yield. To introduce, chloroethyl moiety on nitrogen, we first alkylated the secondary amine ***R*-9** with ethylbromoacetate in the presence of potassium carbonate as a base to obtain a tertiary amine product ***R*-10** in 66% yield. Finally, compound ***R*-10** was reduced using lithium aluminiumhydride to give amino alcohol ***R*-11** in which the hydroxyl group was replaced by a chloride using thionyl chloride to afford (*R*)-Phenoxybenzamine. HCl (**2**) in over all yield 10.5% (ee >99%)**.** The structure of (*R*)-phenoxybenzamine. HCl (**2**) was confirmed by means of IR, $^{1}$H NMR, $^{13}$C NMR and mass spectroscopic analysis.

**Conclusion:**

In conclusion, we have developed a concise and efficient route for the synthesis of active enantiomer of antiarrhythmic drug (*R*)-mexiletine (**1**) and an antihypertensive agent (*R*)-phenoxybenzamine. HCl (**2**) *via* controlled reductive ring opening of chiral aziridine intermediate as a key step. Simple procedures, ready availability of the starting materials and good overall yields are some of the salient features of this approach. Further, this strategy is being exploited for the preparation of other optically active mexiletine and phenoxybenzamine analogues, in our laboratory.

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**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at

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