Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 15, pp. 2613–2618, 1997

Printed in Great Britain
PII: S0957-4166(97)00277-2
0957-4166/97 $17.00 + 0.00

Two useful methods for the preparation of (*R*)- and (*S*)-*N*-methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine

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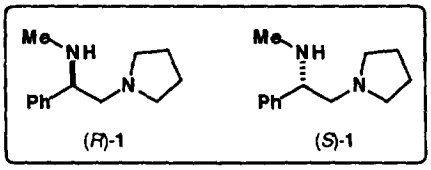
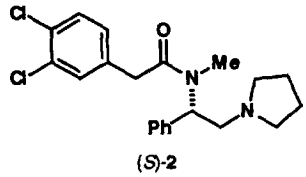
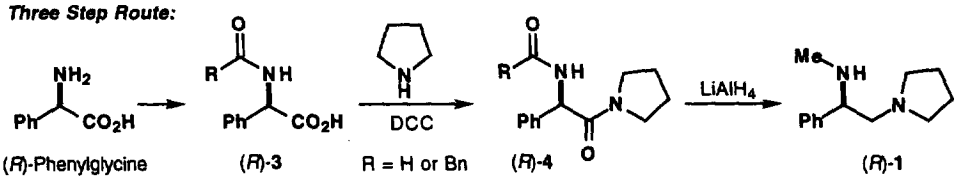
Abstract: Two methods for the efficient preparation of either enantiomer of the synthetically useful diamine *N*-methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine are reported. Each of the methods starts from readily available materials (styrene oxide or phenylglycinol) and is simple, high yielding and shorter than previous synthetic routes. © 1997 Elsevier Science Ltd

Introduction

N-Methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine **1** is a useful chiral diamine. For example, both Singh[1–3] and ourselves[4] have demonstrated that chiral lithium amide bases derived from diamines (*R*)- or (*S*)-**1** are particularly effective at converting cyclic epoxides into enantiomerically enriched allylic alcohols (≥75% ee).[5] In addition, diamine (*S*)-**1** is a valuable synthetic intermediate in its own right. Amides [e.g. (*S*)-**2**] prepared from (*S*)-**1** are potent κ agonists which possess associated analgesic properties.[6,7]







Although the synthesis of either enantiomer of diamine **1** has been reported a number of times before,[3,6,8] each one starts from phenylglycine and uses essentially the same three step approach [outlined above for the preparation of (*R*)-**1**]: (i) *N*-protection; (ii) amide formation and (iii) lithium aluminium hydride reduction. Full details of Singh's synthesis of (*R*)-**1** have been described[3] and the overall yield is 60–70% from (*R*)-phenylglycine which is very good for a three-step synthesis. However, the amide forming conditions must be carefully controlled in order to prevent racemisation[9,10] and each of the intermediates requires purification. This makes the overall synthetic route rather long and tedious.

In this paper, we report in full[11,12] two new methods for the synthesis of diamines (*R*)- or (*S*)-**1**. Both of these methods improve upon the previously published syntheses in terms of yield and convenience. The two routes are summarised below for the preparation of (*R*)-**1**. In each case, mesylation of amino alcohols [e.g. (*R*)-**5** and/or (*S*)-**6**] generates aziridinium ion (*S*)-**7** which undergoes regioselective and

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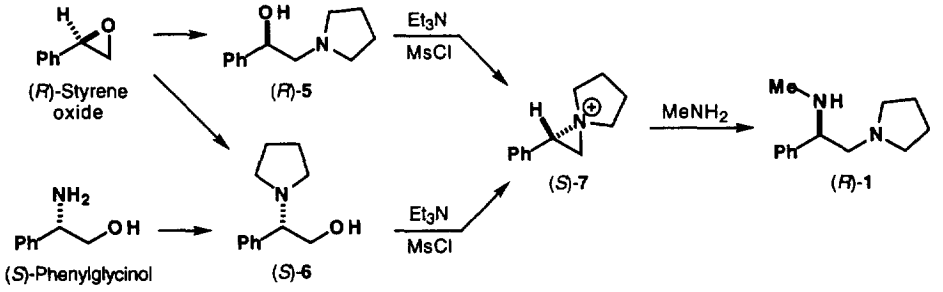
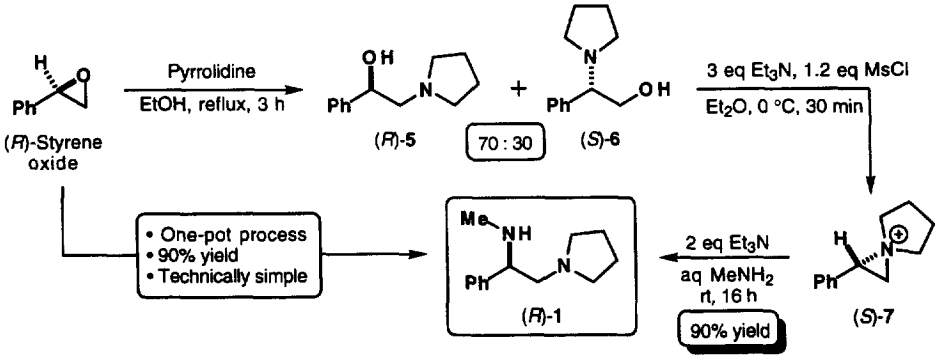
stereospecific reaction with methylamine. The two approaches differ only in the way in which the amino alcohols are prepared: in one case, they are prepared via ring opening of (*R*)-styrene oxide with pyrrolidine whilst in the other, *N,N*-dialkylation of (*S*)-phenylglycinol is used. The realisation of these synthetic routes owes much to the seminal contributions of Dieter[13] and Rossiter[8,14] who had prepared other diamines using related chemistry.



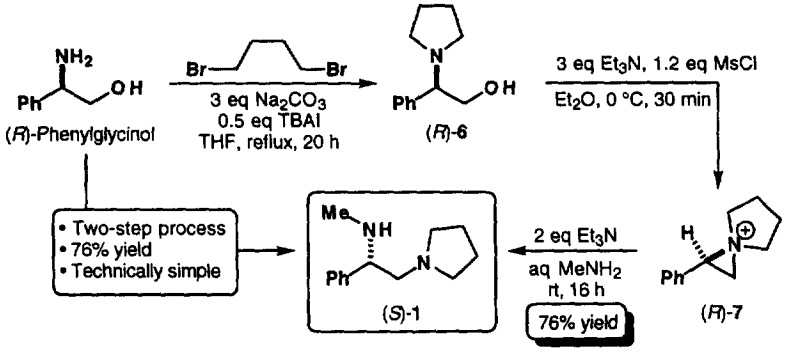
Results and discussion

We have developed a *one-pot process* for the conversion of commercially available[15] (*R*)-styrene oxide into diamine (*R*)-**1**. Thus, reaction of pyrrolidine with (*R*)-styrene oxide in refluxing EtOH followed by evaporation of the volatiles generated a crystalline mixture of regioisomeric amino alcohols (*R*)-**5** and (*S*)-**6**.[16] Then, *in the same flask*, this crude mixture was mesylated (triethylamine, mesyl chloride, Et_2O, 0°C) and reacted with an aqueous solution[17] of methylamine to afford a 90% yield of diamine (*R*)-**1** after work up and Kugelrohr distillation.



As expected,[8,13,14] the stereospecificity of the formation and ring opening of aziridinium ion (*S*)-**7** was complete: diamine (*R*)-**1** had $[\alpha]_D$ −65.4 (*c* 1.7 in EtOH) {lit.,[3] $[\alpha]_D$ −64.0 (*c* 1.4 in EtOH)} and an enantiomeric excess of ≥95% as shown by ^1H NMR spectroscopy in the presence of (*R*)-1-phenyl-2,2,2-trifluoroethanol.[18] In addition, (*R*)-**1** was the only regioisomer observed. It is important to note that this approach is successful for two reasons: (i) *both* amino alcohols (*R*)-**5** and (*S*)-**6** are converted into the *same* aziridinium ion (*S*)-**7** upon mesylation and (ii) aziridinium ion (*S*)-**7** is opened regio- and stereospecifically at the benzylic position.

Although we have used the one-pot method to prepare the enantiomeric diamine (*S*)-**1** {99% isolated yield; $[\alpha]_D^{20}$ +60.1 (*c* 1.4 in EtOH)} starting from (*S*)-styrene oxide, it is not a particularly convenient synthesis as (*S*)-styrene oxide is considerably more expensive than (*R*)-styrene oxide.[15] In order to address this limitation, we have devised a *sequential* two step synthetic route [outlined below for the preparation of (*S*)-**1**] in which it is equally easy to make *either* enantiomer of diamine **1**. This alternative approach utilises the fact that amino alcohol **6** can be prepared from *N,N*-dialkylation of phenylglycinol[19] which is readily available in both enantiomeric forms.[20]



The sequential two step method was carried out in the following way. First of all, reaction of (*R*)-phenylglycinol with 1,4-dibromobutane [0.5 equivalents of tetra-n-butylammonium iodide (TBAI), sodium carbonate, refluxing THF, 20 hours] afforded a reaction mixture which was filtered and subjected to an aqueous work up (to remove residual TBAI). The crude *N,N*-dialkylation product was then dissolved in Et_2O and treated sequentially with mesyl chloride and aqueous methylamine in the usual manner to give, after Kugelrohr distillation, a 76% yield of diamine (*S*)-**1** which had $[\alpha]_D$ +61.7 (*c* 1.2 in EtOH). In the same way, (*S*)-phenylglycinol was converted into diamine (*R*)-**1** {$[\alpha]_D$ −63.5 (*c* 1.6 in EtOH)} in 82% yield.

The methods that we have described for the preparation of either enantiomer of diamine **1** are concise, technically simple, high yielding and improvements on previous three step approaches. The one-pot method from (*R*)-styrene oxide is our preferred method for the preparation of diamine (*R*)-**1** whereas (*S*)-**1** is most economically prepared from (*R*)-phenylglycinol using the sequential two step method.

Experimental section

General

Et_2O and THF were freshly distilled from sodium-benzophenone ketyl. Triethylamine was stored over potassium hydroxide pellets. All non-aqueous reactions were carried out under oxygen-free nitrogen using oven-dried glassware. Thin layer chromatography was carried out on commercially available Merck 5554 aluminium-backed silica plates. Proton and carbon NMR spectra were recorded on a Jeol EX-270 (270 MHz) instrument using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield of tetramethylsilane. Carbon NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT experiments. Infra-red spectra were recorded on an ATI Mattson Genesis FT IR spectrometer. Chemical ionisation and high resolution mass spectra were recorded on a Fisons Analytical (VG) Autospec spectrometer. Optical rotations were recorded on a Jasco DIP-370 polarimeter (using the sodium D line; 589 nm) and $[\alpha]_D^{20}$ are given in units of 10^{-1} deg cm^2 g^{-1}.

(R)-N-*Methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine 1*

(*R*)-Styrene oxide (0.5 cm^3, 4.4 mmol) was added to a stirred solution of pyrrolidine (0.6 cm^3, 7.2 mmol) in EtOH (15 cm^3) and the resulting mixture was heated under reflux for 3 h. After cooling, the solvent was evaporated under reduced pressure to give the crude product which was thoroughly dried for at least 1 h under high vacuum (during which time the product slowly crystallised). Under nitrogen, this crude product was dissolved in Et_2O (20 cm^3), triethylamine (1.85 cm^3, 13.2 mmol) was added and the solution was cooled to 0°C. Then, methanesulfonyl chloride (0.7 cm^3, 8.8 mmol) was added dropwise. A white precipitate formed which made stirring difficult and after 30 minutes, triethylamine (1.25 cm^3, 8.8 mmol) was added. After being allowed to warm to room temperature, methylamine (5.55 cm^3 of a 40% aqueous solution, 74.8 mmol) was added and the resulting two

phase reaction mixture was vigorously stirred for 16 h. The layers were separated and the light brown aqueous layer was extracted with Et_2O (3×30 cm^3). The combined organic extracts were washed with 5% sodium hydrogencarbonate solution (30 cm^3) and water (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which was purified by Kugelrohr distillation to give diamine (*R*)-**1** (807 mg, 90%) as a colourless oil, b.p. 170–180°C/1 mmHg; R_f(10:1 CH_2Cl_2–MeOH) 0.4; $[\alpha]_D^{20}$ −65.4 (*c* 1.7 in EtOH)[lit.,[3] $[\alpha]_D$ −64.0 (*c* 1.4 in EtOH)]; ν_{max}(film)/cm^{-1} 3325 (NH), 2966, 2783, 1603 (Ph), 1350, 758 and 702; δ_H (270 MHz; $CDCl_3$) 7.35–7.24 (5 H, m, Ph), 3.59 (1 H, dd, *J* 3.4 and 10.9, PhC*H*NH), 2.84 (1 H, dd, *J* 10.9 and 12.1, CH_AH_BN), 2.64–2.59 (2 H, m, CH_2N), 2.50–2.45 (3 H, m, CH_2N and NH), 2.30 (3 H, s, NH*Me*), 2.28 (1 H, dd, *J* 3.4 and 12.1, CH_AH_BN) and 1.80–1.75 (4 H, m, CH_2CH_2); δ_C(67.5 MHz; $CDCl_3$) 142.6 (*ipso*-Ph), 128.3 (Ph), 127.4 (Ph), 127.1 (Ph), 64.3 (Ph*C*HN), 63.8 (*C*HCH_2N), 54.2 (CH_2NCH_2), 34.8 (NHMe) and 23.6 (CH_2CH_2); *m/z* 205 (75%, M^+ +1), 174 (20, M–NHMe) and 84 (60, $CH_2NC_4H_8$)(Found: M^+ +1, 205.1698. $C_{13}H_{20}N_2$ requires M +1 205.1705).

(S)-N-Methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine **1**

In the same way, (*S*)-styrene oxide (0.3 cm^3, 2.6 mmol) and pyrrolidine (0.3 cm^3, 3.6 mmol) in EtOH (7.5 cm^3) gave the crude product which was dissolved in Et_2O (20 cm^3) and treated sequentially with triethylamine (0.9 cm^3, 6.4 mmol), methanesulfonyl chloride (0.3 cm^3, 3.8 mmol), triethylamine (0.6 cm^3, 4.3 mmol) and methylamine (3 cm^3 of a 40% aqueous solution, 40.4 mmol). Purification by Kugelrohr distillation gave diamine (*S*)-**1** (537 mg, 99%) as a colourless oil identical spectroscopically to that obtained previously; $[\alpha]_D^{20}$ +60.1 (*c* 1.4 in EtOH) [lit.,[3] $[\alpha]_D$ −64.0 (*c* 1.4 in EtOH) for (*R*)-**1**].

(S)-N-Methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine **1**

Sodium carbonate (770 mg, 7.2 mmol), tetra-n-butylammonium iodide (450 mg, 1.2 mmol), 1,4-dibromobutane (0.29 cm^3, 2.4 mmol) were added successively to a stirred solution of (*R*)-phenylglycinol (330 mg, 2.4 mmol) in THF (10 cm^3) at room temperature under nitrogen. The resulting suspension was heated at reflux for 20 h. After cooling to room temperature, the solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (20 cm^3), washed with water (3×20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Under nitrogen, this crude product was dissolved in Et_2O (1 cm^3), triethylamine (1.0 cm^3, 7.0 mmol) was added and the solution was cooled to 0°C. Then, methanesulfonyl chloride (0.28 cm^3, 3.5 mmol) was added dropwise. A white precipitate formed which made stirring difficult and after 30 minutes, triethylamine (0.7 cm^3, 4.9 mmol) was added. After warming to room temperature, methylamine (3.0 cm^3 of a 40% aqueous solution, 40.4 mmol) was added and the resulting two phase reaction mixture was vigorously stirred for 16 h. The layers were separated and the light brown aqueous layer was extracted with Et_2O (3×20 cm^3). The combined organic extracts were washed with 5% sodium hydrogencarbonate solution (20 cm^3) and water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which was purified by Kugelrohr distillation to give diamine (*S*)-**1** (370 mg, 76%) as a colourless oil identical spectroscopically to that obtained previously; $[\alpha]_D^{20}$ +61.7 (*c* 1.2 in EtOH)[lit.,[3] $[\alpha]_D$ −64.0 (*c* 1.4 in EtOH) for (*R*)-**1**].

(R)-N-Methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine **1**

In the same way, sodium carbonate (1.14 g, 10.8 mmol), tetra-n-butylammonium iodide (450 mg, 1.2 mmol), 1,4-dibromobutane (0.43 cm^3, 3.6 mmol) and (*S*)-phenylglycinol (500 mg, 3.6 mmol) in THF (15 cm^3) gave the crude product which was dissolved in Et_2O (15 cm^3) and treated sequentially with triethylamine (1.5 cm^3, 10.8 mmol), methanesulfonyl chloride (0.42 cm^3, 5.4 mmol), triethylamine (1.0 cm^3, 7.2 mmol) and methylamine (4.5 cm^3 of a 40% aqueous solution, 58.1 mmol). Purification by Kugelrohr distillation gave diamine (*R*)-**1** (600 mg, 82%) as a colourless oil identical spectroscopically to that obtained previously; $[\alpha]_D^{20}$ -3.5 (*c* 1.6 in EtOH) [lit.,[3] $[\alpha]_D$ −64.0 (*c* 1.4 in EtOH)].

Acknowledgements

The Royal Commission for the Exhibition of 1851 are acknowledged and thanked for the award of a Fellowship (to PO'B). We also thank the EU for funding (of PP) under the ERASMUS scheme, EPSRC for the award of a grant (to SEdS), Parke-Davis Neuroscience Research Centre for additional support and Professor R. J. K. Taylor for many useful discussions.

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16. Alcohols (*R*)-**5** and (*S*)-**6** were obtained in a 70:30 ratio as judged by ^{1}H NMR spectroscopy: For (*R*)-**5**, δ_H (270 MHz, $CDCl_3$) 4.76 (1 H, dd, *J* 3.2 and 10.4, PhC*H*OH); for (*S*)-**6**, δ_H (270 MHz, $CDCl_3$) 3.92 (1 H, dd, *J* 5.8 and 10.7, CH_AH_BOH), 3.84 (1 H, dd, *J* 5.3 and 10.7, CH_AH_BOH) and 3.54 (1 H, t, *J* 5.8, PhC*H*N).
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(*Received in UK 11 June 1997*)