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A Simple and Efficient Method for the Preparation of Homochiral Amines: Application to the Synthesis of a New C_2 Symmetric Triamine

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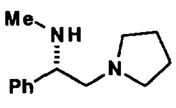
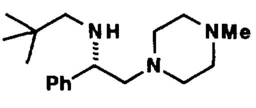
Abstract: Using a one-pot reaction, (*R*)-styrene oxide has been converted into a variety of novel diamines and a C_2 symmetric triamine. Yields range from 63-93%. The method is simple, efficient and is considerably shorter than other synthetic approaches. Copyright © 1996 Elsevier Science Ltd

Lithium amides derived from amines such as **1**, **2** and **3** have been used with much success as chiral bases and as ligands for copper in asymmetric conjugate addition reactions. For example, Singh used (*S*)- and (*R*)-**1** in epoxide rearrangement reactions,[1,2] Koga found that (*S*)-**2** gave the best results when he deprotonated some prochiral cycloketones[3] and Rossiter has added a lithium organo(amido)cuprate derived from (*S*)-**3** to cyclic enones to give products with up to 97% ee.[4] As well as being useful chiral reagents, these types of amines are also valuable synthetic intermediates: acylation of one such compound generated amide (*S*)-**4**, a κ agonist with potent naloxone-reversible analgesic effects.[5]



(*S*)-**1**



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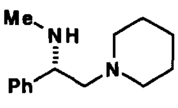

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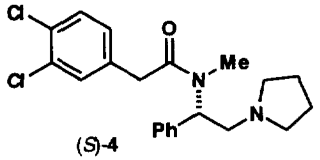


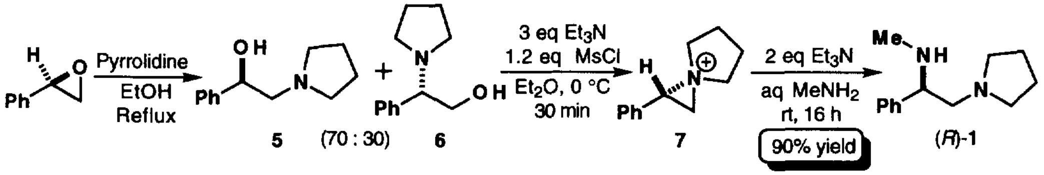
(*S*)-**4**

The most frequently employed synthetic route to amines **1-3** starts with phenylglycine and involves *N*-protection, amide formation and lithium aluminium hydride reduction. There is, however, a real problem with this three step approach: significant racemisation[6] can occur during amide formation and (*S*)-**1** of only 75% ee was obtained with either 1,3-dicyclohexylcarbodiimide (DCC)[2] or isobutyl chloroformate[4] coupling. Although carrying out the coupling reaction with DCC in the presence of 1-hydroxybenzotriazole[5,7] or with diethylphosphorocyanidate[8] solves this particular problem, the overall synthetic route is still rather long.

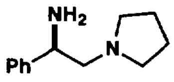
We now wish to report a one-pot method for the direct synthesis of amines such as **1-3** starting from styrene oxide and *not* phenylglycine. Our method is a much improved version of a synthetic route that

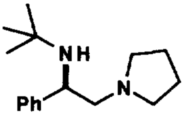
Dieter[9] used to make an ephedrine-derived triamine and Rossiter used to make (*R*)-**3**[4] and other amine analogues.[10] The usefulness of the method is demonstrated with the synthesis of a range of novel diamines as well as a C_2 symmetric triamine.

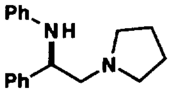
Because existing routes[2,4,5] to diamine **1** were inconveniently long, we decided to try making it using Rossiter's approach.[4] Thus, commercially available (*R*)-styrene oxide[11] was reacted with pyrrolidine (EtOH, reflux, 2-3 h) to give a quantitative yield of a crystalline mixture of regioisomeric alcohols **5** and **6** (70:30).[12] At this stage, we chose not to isolate the major alcohol **5** (unlike others[4,10]) as we reasoned that *both* **5** *and* **6** could be converted into the same aziridinium ion **7** upon treatment with triethylamine and mesyl chloride. This was indeed the case: mesylation of the *crude* mixture of alcohols **5** and **6** followed by reaction with excess methylamine (40% aqueous solution)[13] gave diamine (*R*)-**1** in an excellent 90% yield after distillation. Diamine (*R*)-**1** had $[\alpha]_D$ –65.4 (*c* 1.7 in EtOH) [lit.,[1] $[\alpha]_D$ –64.0 (*c* 1.4 in EtOH)]; it was the only regioisomer detected and there was no nucleophilic attack on **7** by water. As noted by others,[4,9,10] the reaction proceeds with overall retention via regio- and stereospecific opening of aziridinium ion **7** at the benzylic position.[14]

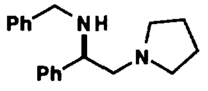


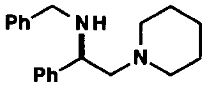
Next, we repeated the synthesis of diamine (*R*)-**3** using our improved one-pot procedure. Combining piperidine with (*R*)-styrene oxide again gave a quantitative yield of a mixture of regioisomeric alcohols and sequential reaction with mesyl chloride and then methylamine gave diamine (*R*)-**3** in 89% yield after chromatography. This is a significant improvement on the 47% yield obtained previously using the two step method.[4]

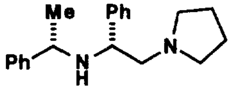

(*R*)-**8**

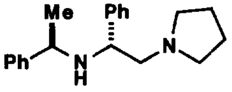

(*R*)-**9**


(*R*)-**10**


(*R*)-**11**

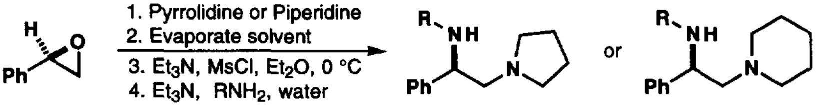

(*R*)-**12**

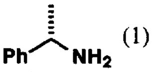
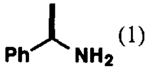

(*S*,*R*)-**13**


(*R*,*R*)-**13**

To our delight, amines other than methylamine also reacted with aziridinium ion **7** and we have completed syntheses of the diamines **8-13** depicted above; of these, only (*S*)-**12** has been made before (and that was by a different route[4]). Our one-pot method appears to be fairly general: sterically hindered amines (e.g. t-butylamine) and less nucleophilic amines (e.g. aniline) work just as well as methylamine. The actual conditions and yields are summarised in the Table. In cases where neat amine was used (entries 4-9), it was necessary to add a reasonable amount of water just after addition of the amine. With volatile methylamine, ammonia and t-butylamine (entries 1-4), a large excess of the amine was required in order to obtain acceptable yields. In contrast, the use of only one equivalent of the less volatile aniline, benzylamine and *α*-methylbenzylamine (entries 5-9) meant that the diamine products were easier to purify (by chromatography). We believe that all of the reactions presented in the Table proceed stereospecifically with retention of configuration. When aziridinium ion **7** was opened with (*S*)-*α*-methylbenzylamine, only one diastereoisomer of diamine **13** was formed (entry 8) – any loss of stereospecificity in the reaction would have been detected by the formation of the other diastereoisomer (which was, of course, identified by a separate synthesis – see entry 9). Furthermore, for the known diamines (*R*)-**1**, (*R*)-**3** and (*S*)-**12**, our optical rotations are in agreement with the literature values.

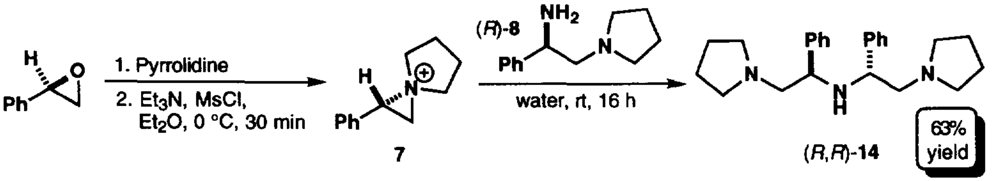
Table: One-pot Transformation of (*R*)-Styrene Oxide into Diamines **1**, **3** and **8**-**13**



Entry	Cyclic Amine	RNH_2 (eq)	Diamine	Yield (%)	$[\alpha]_D$ (*c* in $CHCl_3$)
1	Pyrrolidine	$MeNH_2$[a] (17)	(*R*)-**1**	90	–65.4 (1.4)[b,c]
2	Piperidine	$MeNH_2$[a] (17)	(*R*)-**3**	89	–94.4 (1.9)[d]
3	Pyrrolidine	NH_3[e] (50)	(*R*)-**8**	79	–42.6 (1.7)
4	Pyrrolidine	t-$BuNH_2$ (11)	(*R*)-**9**	90	–78.7 (1.6)
5	Pyrrolidine	Ph–NH_2 (1)	(*R*)-**10**	79	+13.4 (1.8)
6	Pyrrolidine		(*R*)-**11**	81	–92.2 (1.8)
7	Piperidine		(*R*)-**12**	93	–108.6 (2.0)[f]
8	Pyrrolidine		(*S*,*R*)-**13**	74	–131.4 (2.3)
9	Pyrrolidine		(*R*,*R*)-**13**	80	–29.7 (2.1)

[a] 40% aqueous solution; [b] *c* in EtOH; [c] lit.,[1] $[\alpha]_D$ –64.0 (*c* 1.4 in EtOH); [d] lit.,[4] $[\alpha]_D$ –107 (*c* 1.23 in $CHCl_3$); [e] 30% aqueous solution; [f] lit.,[4] $[\alpha]_D$ +107 (*c* 1.98 in $CHCl_3$) for (*S*)-**12**.

Finally, we recognised that reaction of aziridinium ion **7** with one of the new diamines, (*R*)-**8**, could be used to synthesise a novel and particularly attractive C_2 symmetric triamine (*R*,*R*)-**14**. Using our one-pot reaction with (*R*)-**8**, triamine (*R*,*R*)-**14** [$[\alpha]_D$ –125.2 (*c* 1.8 in $CHCl_3$)] was obtained in a good 63% yield after distillation.



In summary, our one-pot transformation of (*R*)-styrene oxide into a variety of diamines and a C_2 symmetric triamine is not only simple to carry out but is also high yielding. This approach is considerably shorter than alternative synthetic routes and, since both enantiomers of styrene oxide are commercially available, our method can be used to prepare either enantiomer of a range of useful chiral amines.

Typical Experimental Procedure: Commercially available (*R*)-styrene oxide[11] (4.4 mmol) was added to a stirred solution of pyrrolidine (7.2 mmol) in EtOH (15 cm^3) and the resulting mixture was heated under reflux for 2-3 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 (13.2 mmol; 3 eq) was added and the solution was cooled to 0 °C. Then, methanesulfonyl chloride (5.3 mmol; 1.2 eq) was added dropwise. A white precipitate formed which made stirring difficult and after 30 minutes, triethylamine (8.8 mmol; 2 eq) was added. After being allowed to warm to room temperature, the amine (1-50 eq)[†] and then water[‡] (5 cm^3) were added and the resuting 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 x 30 cm^3). The combined organics were washed with 5% sodium bicarbonate solution (20 cm^3) and water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as an oil. Purification by Kugelrohr distillation or flash chromatography on silica eluting with 40:1 → 10:1 CH_2Cl_2-MeOH gave the pure amine. Amines **1**, **8**, **9** and **14** were best purified by distillation; the rest by flash chromatography.

[†] For molar equivalents of amines used, see Table; [‡] With methylamine (40% aq) and ammonia (30% aq), water was not added.

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6. For example, footnote 8 in: Denis, J-N.; Correa, A.; Greene, A. E. *J. Org. Chem.*, **1991**, *56*, 6939-6942.
7. The details of the modified synthetic route are described in footnote 15 (see reference 1).
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11. (*R*)- and (*S*)-Styrene oxide are available from Aldrich Chemical Company Ltd.
12. Alcohols **5** and **6** were identified by ^1H NMR spectroscopy: For **5**, δ_H (270 MHz, $CDCl_3$) 4.76 (1 H, dd, *J* 3.2 and 10.4, PhC*H*OH); for **6**, δ_H (270 MHz, $CDCl_3$) 3.92 (1 H, dd, *J* 5.8 and 10.7, CH_AH_BOH with *H*$_A$), 3.84 (1 H, dd, *J* 5.3 and 10.7, CH_AH_BOH with *H*$_B$) and 3.54 (1 H, t, *J* 5.8, PhC*H*N).
13. This is a vigorously stirred two phase reaction which requires 16 hours to reach completion.
14. For leading references on the use of other aziridinium ions in synthesis, see: Richardson, P. F.; Nelson, L. T. J.; Sharpless, K. B. *Tetrahedron Lett.*, **1995**, *36*, 9241-9244; Liu, Q.; Simms, M. J.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1363-1365.

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