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Aziridinium Ions from Phenylglycinol – A New Approach to the Synthesis of Chiral Diamines

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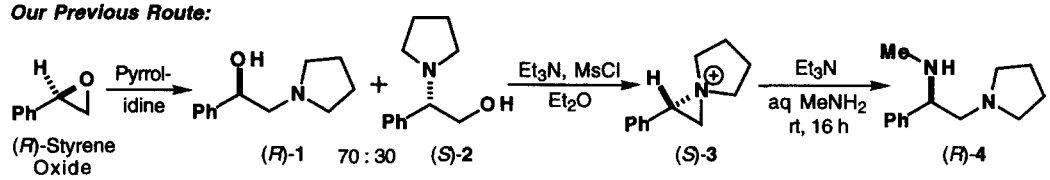
Abstract: A new two-step method [(i) *N,N*-dialkylation; (ii) aziridinium ion formation followed by amine attack] for the synthesis of chiral diamines from phenylglycinol is described. The two steps can be carried out sequentially without isolation of the intermediate amino alcohols to give diamines in good yields (62-76%). An improved protocol for the *N,N*-dialkylation of phenylglycinol is also reported. © 1997 Elsevier Science Ltd.

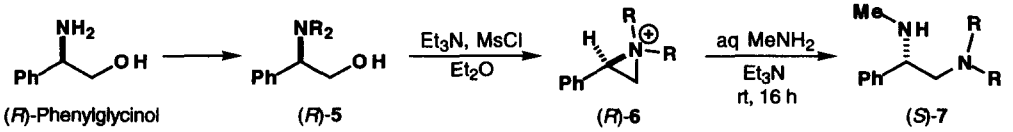
Recently,[1] we reported a convenient one-pot method for the preparation of homochiral diamines such as (*R*)-**4** starting from commercially available (*R*)-styrene oxide. Crucial to the success of this approach was the conversion of a *mixture* of amino alcohols (*R*)-**1** and (*S*)-**2** [generated by non-selective ring opening (*R*)-styrene oxide with pyrrolidine] into the *same* aziridinium ion (*S*)-**3** and the regiospecific opening of (*S*)-**3** at the benzylic position.

Our Previous Route:



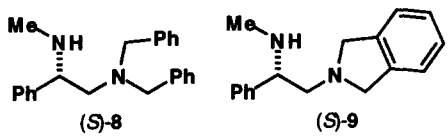
Although this method for the preparation of diamines is simple to carry out, high yielding and an improvement on the originally reported[2-4] three step syntheses, two issues remained. First of all, the synthesis of (*S*)-diamines necessitates the use of expensive[5] (*S*)-styrene oxide. Secondly, we[6] have shown that the one-pot method is only successful when reactive amines such as pyrrolidine and piperidine are used in the first step; ideally, we wanted to prepare diamines which contained other substituents. In this paper, both of these limitations are addressed and we report a new and useful method for the preparation of chiral diamines.

Our Proposed New Route:

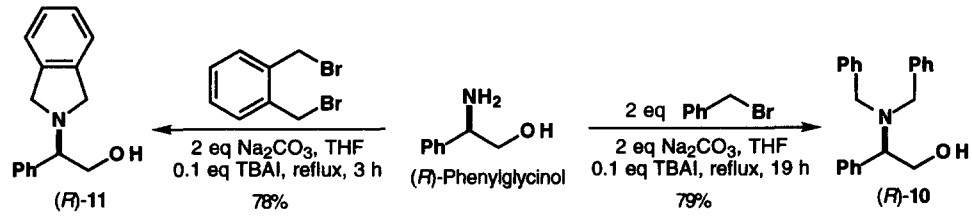


As with our previous method, the new approach [outlined above for the preparation of (*S*)-diamines] relies on the efficient conversion of amino alcohols **5** into diamines **7** (*via* aziridinium ions **6**) upon mesylation and reaction with methylamine. However, a completely different approach is used for the preparation of amino alcohols **5** – we now prepare them *via N,N*-dialkylation of phenylglycinol, a starting material that is

cheap and readily available in both enantiomeric forms.[7] Implementation of the new strategy is exemplified by the efficient conversion of (*R*)-phenylglycinol into the known[2-4] diamine (*S*)-**4** and two new chiral diamines (*S*)-**8** and (*S*)-**9**. Two independent reports[8,9] of the use of a related *N,N*-dialkylation strategy for the synthesis of a β-amino thioacetate, a β-amino disulfide and some pyrrolidinyl hydroxamic acid analgesics have recently been described; this has prompted us to reveal our own results.

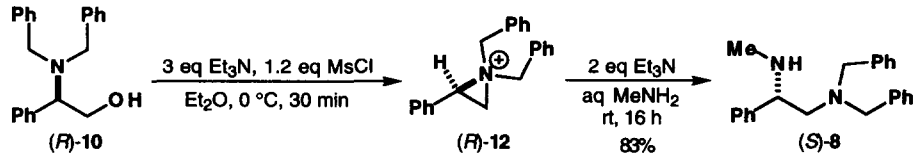


We began our study by investigating the conversion of (*R*)-phenylglycinol[7] into amino alcohol (*R*)-**11** *via* alkylation with α,α'-dibromo-*ortho*-xylene. Brown and Touet have reported an efficient procedure for the *N,N*-dialkylation of (*R*)-2-aminobutan-1-ol using α,α'-dichloro-*ortho*-xylene[10] and a related low yielding synthesis of (*R*)-**11** itself.[11] By modifying their conditions slightly, we have devised a useful method for *N,N*-dialkylation of amino alcohols which improves upon previous attempts.[10-12]



Our method involves refluxing the amino alcohol with the appropriate alkyl bromide in THF containing sodium carbonate and a catalytic amount of tetra-n-butylammonium iodide (TBAI). In this way, dialkylation of (*R*)-phenylglycinol with α,α'-dibromo-*ortho*-xylene was complete after just 3 hours[13] and, after a simple aqueous work up, the crude product (quantitative yield) was essentially pure and could be used in subsequent reactions. Recrystallisation afforded pure amino alcohol (*R*)-**11** in 78% yield {m.p. 92-93 °C; lit.,[10] 78 °C; $[\alpha]_D$ –19.2 (*c* 1.4 in MeOH); lit.,[10] $[\alpha]_D$ –20.5 (*c* 5 in MeOH)}. Similarly, alkylation with 2 equivalents of benzyl bromide (refluxing THF, 19 hours) gave amino alcohol (*R*)-**10** {$[\alpha]_D$ –118.2 (*c* 5.5 in $CHCl_3$)} in 79% yield after chromatography.

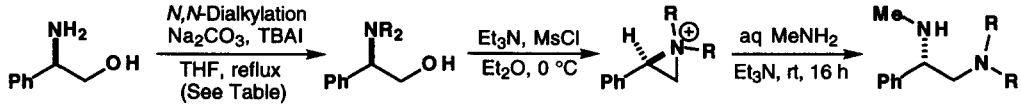
Both of these amino alcohols can be converted into the corresponding diamines. As an example, treatment of amino alcohol (*R*)-**10** sequentially with mesyl chloride and then methylamine in the usual manner[1] gave the novel[14] diamine (*S*)-**8** {$[\alpha]_D$ +74.1 (*c* 1.0 in $CHCl_3$)} in a typically good 83% yield after purification by chromatography.

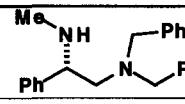
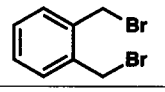
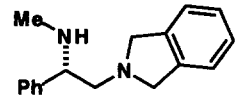
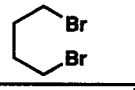
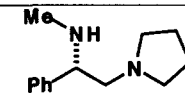


With this simple two step synthesis completed, we embarked on developing a two step preparation of chiral diamines *without* recourse to purification of the intermediate amino alcohols. Our optimised and preferred protocol is a *sequential* two step synthesis of diamines and the results are summarised in the Table. Initially, *N,N*-dialkylation of (*R*)-phenylglycinol is performed in refluxing THF containing the appropriate

alkyl bromide, sodium carbonate and TBAI. After removal of the solids by filtration and an aqueous work up, the crude product is then dissolved in dry Et_2O and subjected to the normal diamine forming conditions to give good isolated yields of the (*S*)-diamines. In line with our earlier work,[1] only one regioisomeric diamine was detected (by ^1H NMR spectroscopy) and we now have further proof of the stereospecificity of the overall process: diamine (*S*)-**4** had $[\alpha]_D$ +61.7 (*c* 1.2 in EtOH) {lit.,[1] $[\alpha]_D$ –65.4 (*c* 1.4 in EtOH) for (*R*)-**4**} and an enantiomeric excess of ≥95% as shown by ^1H NMR spectroscopy in the presence of (*R*)-1-phenyl-2,2,2-trifluoroethanol.[15] This contrasts with episelenium[16] and episulfonium[17] ions derived from (*R*)-styrene oxide which partially racemise (presumably *via* the open chain carbocation) during Ritter-type substitution reactions.

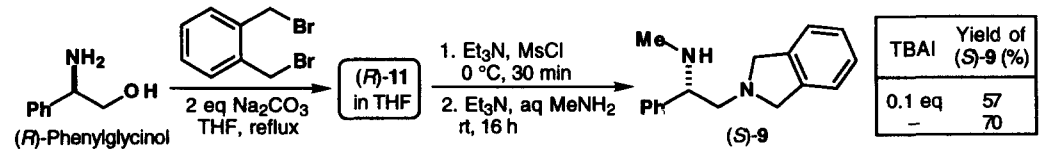
Table: Sequential two-step synthesis of (*S*)-diamines from (*R*)-phenylglycinol



Entry	Alkylating Agent	TBAI[a]	Time (h)[a]	Diamine	Yield (%)[b]
1	2 eq 	0.1 eq[c]	19	 (*S*)-**8**	62[e]
2	1 eq 	0.1 eq[c]	3	 (*S*)-**9**	69[e]
3	1 eq 	0.5 eq[d]	20	 (*S*)-**4**	76[f]

[a] For the *N,N*-dialkylation step; [b] Yield from (*R*)-phenylglycinol; [c] 2 equiv of Na_2CO_3 was used; [d] 3 equiv of Na_2CO_3 was used; [e] Purified by chromatography; [f] Purified by Kugelrohr distillation.

In the sequential two step method described above, we reasoned that an aqueous work up was necessary to remove the TBAI catalyst prior to the diamine forming step. However, we wondered whether it would be possible to omit this step and carry out the whole process in THF, thereby establishing another one-pot method for diamine synthesis. With this in mind, amino alcohol (*R*)-**11** was prepared *via N,N*-dialkylation in the usual manner with and without TBAI as a catalyst[13] and then the solids were removed by filtration. Having established that diamine formation was successful with THF in place of Et_2O[1] as the solvent,[18] the THF solution of the crude *N,N*-dialkylation product (*R*)-**11** was treated with mesyl chloride and then methylamine to give diamine (*S*)-**9** in a one-pot process from (*R*)-phenylglycinol.



Although the dialkylation step takes longer in the absence of TBAI (refluxing THF, 19 hours), the overall yield of diamine (*S*)-**9** is higher (70% yield) than that obtained when TBAI is present (57% yield).

This suggests that TBAI does have a detrimental effect on the diamine forming step. Clearly, the one-pot method with no added TBAI is the most useful way of preparing diamine (*S*)-**9**. However, it is not suitable for the synthesis of diamines (*S*)-**4** and (*S*)-**8** as *N,N*-dialkylation with less reactive 1,4-dibromobutane and benzyl bromide takes several days in the absence of TBAI.

In summary, we have developed a new sequential two-step method for the synthesis of chiral diamines. The method is technically easy to perform and has allowed us to prepare the known[2-4] diamine (*S*)-**4** {$[\alpha]_D$ +61.7 (*c* 1.2 in EtOH); lit.,[1] $[\alpha]_D$ –65.4 (*c* 1.4 in EtOH) for (*R*)-**4**} and the novel[14] diamines (*S*)-**8** {$[\alpha]_D$ +80.8 (*c* 1.05 in $CHCl_3$)} and (*S*)-**9** {$[\alpha]_D$ –6.2 (*c* 1.8 in $CHCl_3$)} in good yields from (*R*)-phenylglycinol.[7] Additionally, diamine (*S*)-**9** has been prepared *via* an efficient one-pot process. As both (*R*) and (*S*)-phenylglycinol are readily available and cheap,[7] our new methods are suitable for the synthesis of either enantiomer[19] of diamines like **4**, **8** and **9**.

Acknowledgements

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5. Current Aldrich Chemical Company Ltd prices: (*R*)-styrene oxide £32.50 per 5 g; (*S*)-styrene oxide £20.00 per 1 g.
6. Less reactive diamines require the use of a Lewis acid catalyst to promote epoxide ring opening. For example, lithium perchlorate-mediated ring opening of styrene oxide with diethylamine has been reported. In our hands, use of these conditions with styrene oxide and diethylamine, dimethylamine or dibenzylamine failed to generate high yields of the amino alcohol mixtures; our crude products were always contaminated with unreacted starting materials. See: Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.*, **1990**, *31*, 4661-4664; Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.*, **1991**, *56*, 5939-5942; Augé, J.; Leroy, F. *Tetrahedron Lett.*, **1996**, *37*, 7715-7716; Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2597-2601.
7. (*R*)- and (*S*)-Phenylglycinol are commercially available from Lancaster Synthesis Ltd: (*R*)-phenylglycinol £32.80 per 5 g; (*S*)-phenylglycinol £40.80 per 5 g. Alternatively, they can be prepared by reduction of (*R*)- and (*S*)-phenylglycine; we prefer Meyers' method ($NaBH_4/BF_3{\cdot}Et_2O$) for the reduction: Tschantz, M. A.; Burgess, L. E.; Meyers, A. I. *Org. Synth.*, **1996**, *73*, 221-230.
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13. In the absence of TBAI the reaction must be refluxed for 19 hours to reach completion.
14. All new compounds were characterised by ^1H and ^{13}C NMR spectroscopy and high resolution mass spectrometry.
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17. Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Tetrahedron*, **1994**, *50*, 8997-9008.
18. Treatment of a THF mixture of amino alcohols **1** and **2** (obtained by opening *racemic* styrene oxide with pyrrolidine) with mesyl chloride and then methylamine in the usual manner gave diamine *rac*-**4** in 89% yield after distillation. A 90% yield of diamine *rac*-**4** was obtained using Et_2O as the solvent.
19. Starting from (*S*)-phenylglycinol and using the conditions described in the Table (entry 3), an 82% yield of diamine (*R*)-**4** {$[\alpha]_D$ –63.5 (*c* 1.6 in EtOH)} was obtained after Kugelrohr distillation.

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