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Synthesis of Chiral β -Amino Sulfides and β -Amino Thiols from α -Amino Acids

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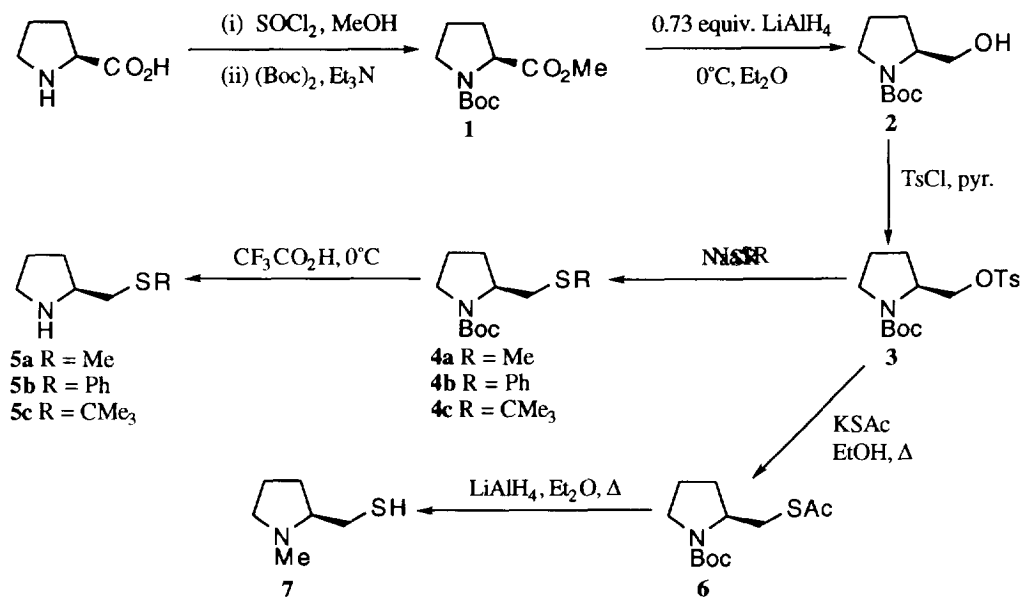
Abstract: Bifurcated routes to two series of chiral secondary β -amino sulfides **5a - c** and **11a - c** have been developed from L-proline and (*S*)-phenylglycine, respectively. The developed methodology has also led to the synthesis of the tertiary β -amino thiol **7** and the primary β -amino sulfide **12** from L-proline and (*S*)-phenylglycine, respectively.

The enantioselective formation of carbon-carbon bonds through the asymmetric dialkylzinc addition to prochiral ketones¹ and conjugate addition of organocuprates to enones² continue to be very important areas in current enantioselective methodology development. In this context, amino sulfur containing ligands and catalysts are beginning to show promise in these asymmetric bond forming processes. Thus, β -amino sulfides and their corresponding disulfides have been shown to be particularly effective catalysts for the enantioselective addition of dialkylzinc reagents to prochiral carbonyl compounds.³ Catalytic quantities of γ -amino thiols have also been used in the asymmetric addition of diethylzinc to aldehydes,⁴ while β -amino sulfides⁵ and γ -amino thiols⁶ have been shown to be effective ligands and catalysts in enantioselective conjugate addition of organocuprates to enones. In addition, Donner has recently reported the use of N-Boc protected β -amino ethyl sulfides in the synthesis of enantiomerically pure α -methylamines.⁷

As part of our continuing interest in the use of bidentate sulfur containing compounds as ligands and catalysts in transition metal mediated asymmetric carbon-carbon bond processes we have been developing novel routes to various sulfur containing amino compounds. In this communication we report a general divergent synthetic route to chiral β -amino sulfides and thiols in which the stereogenic centre is derived from α -amino acids.⁸ Two series of bidentate sulfur containing amines have been prepared: β -amino sulfides **5a - c** and β -amino thiol **7** derived from L-proline (Scheme 1), and β -amino sulfides **11a - c** (Scheme 2) and **12** (Scheme 3) obtained from (*S*)-phenylglycine.

In the first series, L-proline was chosen as the starting amino acid because alcohols and ether derivatives of this template have been shown to be valuable ligands in asymmetric conjugate additions.^{2,5c} In our approach, we required a nitrogen protecting group that could be removed in the presence of sulfur containing compounds and that could afford both the free amine and the corresponding N-methyl derivatives. Thus, L-proline was protected as its N-Boc methyl ester derivative **1** (74%) by a two step, one-pot procedure involving treatment with thionyl chloride in methanol followed by reaction with di-*tert*-butyl dicarbonate (1 equivalent) and

triethylamine. Reduction of the N-Boc methyl ester derivative **1** with 0.73 equivalents of lithium aluminium hydride in ether at 0°C afforded the alcohol **2** (86%).⁹ Treatment of the alcohol **2** with 2 equivalents of 4-toluenesulfonyl chloride in pyridine at 0°C provided the tosylate **3** (90%). Displacement of the 4-toluenesulfonate group in tosylate **3** with either sodium methanethiolate (1.63 equivalents) in N-methyl pyrrolidinone or thiophenol and sodium hydride (2 equivalents) in THF or sodium 2-methyl-2-propanethiolate (2 equivalents) in N-methyl pyrrolidinone afforded the corresponding sulfides **4a** (58%), **4b** (52%) and **4c** (66%), respectively.¹⁰ The conversion of the protected β -amino sulfides **4a - c** into the corresponding free amines was achieved by treatment with trifluoroacetic acid at 0°C, followed by basification which afforded the β -amino sulfides **5a** (79%), **5b** (82%) and **5c** (83%), respectively.

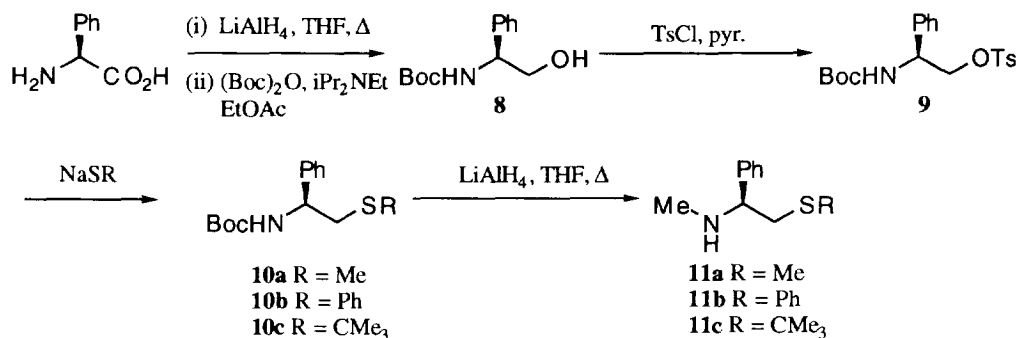


Scheme 1

In the case of the synthesis of β -amino thiols we were conscious of the fact that any synthesis should leave the unmasking of the thiol group until the last step. This follows since β -amino thiols are known to undergo facile air oxidation to disulfides.³ Furthermore, attempted direct displacement of the 4-toluenesulfonate group in tosylate **3** with sodium hydrosulfide hydrate was unsuccessful. Thus, treatment of the tosylate **3** with 5 equivalents of potassium thioacetate in ethanol at reflux smoothly furnished the protected thiol acetate **6** (88%). Subsequent deprotection with concomitant conversion of the N-Boc moiety into the required N-methyl functionality was achieved by treatment of the thiol acetate **6** with excess lithium aluminium hydride in ether at reflux. Work up under oxygen free conditions and kugelrohr distillation (70°C @ 1.5 mm Hg) afforded the oxygen sensitive β -amino thiol in 41% yield (Scheme 1).

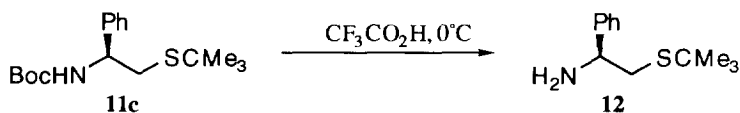
The application of the above methodology to acyclic amino acids was important for the development of a wide range of bidentate amino sulfur containing ligands. In order to test fully the applicability of the above approach we chose to investigate a second series, based on (*S*)-phenylglycine as the starting material. In this case, the stereogenic centre is benzylic and, therefore, would be an important test in systems where racemisation

is a potential problem. Indeed, direct application of the above methodology to (*S*)-phenylglycine resulted in racemisation problems in large scale preparations and required a modified approach (Scheme 2). Thus, reduction of (*S*)-phenylglycine with excess lithium aluminium hydride in THF followed by *N*-Boc protection with di-*tert*-butyl dicarbonate ((*t*BuOCO)₂O, *i*Pr₂NEt, EtOAc)¹¹ afforded the *N*-Boc phenylglycinol **8** in 66% overall yield. Conversion of *N*-Boc phenylglycinol **8** into the corresponding tosylate **9** was achieved by reaction with 4-toluenesulfonyl chloride (2 equivalents) in pyridine (78%). Displacement of the 4-toluenesulfonate moiety in tosylate **9** with either sodium methanethiolate (2 equivalents) in *N*-methyl pyrrolidinone or thiophenol and sodium hydride (2 equivalents) in THF or sodium 2-methyl-2-propanethiolate (2 equivalents) in *N*-methyl pyrrolidinone afforded the corresponding *N*-Boc protected sulfides **10a** (47%), **10b** (87%) and **10c** (90%), respectively. Reductive conversion of the *N*-Boc protecting group in the protected sulfides **10a - c** was achieved by treatment with excess lithium aluminium hydride in THF at reflux and provided the corresponding *N*-methyl sulfides **11a** (78%), **11b** (48%) and **11c** (53%), respectively.



Scheme 2

In the phenylglycine system, an alternative method of deprotection of the *N*-Boc β -amino sulfide **10c** was carried out by reaction with trifluoroacetic acid at 0°C followed by aqueous basic work up which afforded the primary β -amino sulfide **12** in 65% yield (Scheme 3).



Scheme 3

In conclusion, a series of chiral β -amino sulfides **5a - c** as well as the optically active β -amino thiol **7** have been prepared from *L*-proline in 6 steps *via* the tosylate **3**, which serves as a common intermediate. A modification of this procedure to avoid racemisation problems has been applied to (*S*)-phenylglycine and has provided the chiral β -amino sulfides **11a - c** and **12** in 5 steps overall *via* the tosylate **9**. We are currently investigating the use of the above chiral β -amino sulfides and thiol as ligands and catalysts in transition metal mediated asymmetric carbon-carbon bond forming processes.

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 - All new compounds gave satisfactory IR, ^1H NMR, ^{13}C NMR and elemental analysis and/or HRMS. Known compounds gave specific rotations in accord, or better than the literature values. The quoted yields are for homogeneous ($\geq 95\%$) materials isolated by chromatography or kugelrohr distillation or recrystallization. Selected data: (*S*)-**5a** B.p. 60°C @ 1.5 mm Hg (kugelrohr); $[\alpha]_{\text{D}}^{20} +17.3$ ($c=1$, CHCl_3). (*S*)-**5b** B.p. 100°C @ 0.1 mm Hg (kugelrohr); $[\alpha]_{\text{D}}^{20} +20$ ($c=0.56$, CHCl_3) lit.^{5c} $[\alpha]_{\text{D}}^{20} +16.8$ ($c=0.56$, CHCl_3). (*S*)-**5c** B.p. 70°C @ 1.1 mm Hg (kugelrohr); $[\alpha]_{\text{D}}^{20} -4.6$ ($c=1$, CHCl_3). (*S*)-**7** B.p. 70°C @ 1.5 mm Hg (kugelrohr); $[\alpha]_{\text{D}}^{20} -85.76$ ($c=0.85$, CHCl_3). (*S*)-**11a** B.p. 80°C @ 0.1 mm Hg (kugelrohr); $[\alpha]_{\text{D}}^{20} +94.2$ ($c=1$, CHCl_3). (*S*)-**11b** B.p. 130°C @ 0.05 mm Hg (kugelrohr); $[\alpha]_{\text{D}}^{20} -6.5$ ($c=1$, CHCl_3). (*S*)-**11c** B.p. 85°C @ 0.1 mm Hg (kugelrohr); found C, 69.81, H, 9.55, N, 6.59 S, 14.36, MH^+ 224.1400 $\text{C}_{13}\text{H}_{21}\text{NS}$ requires C, 69.9, H, 9.5, N, 6.3 S, 14.35, MH^+ 224.1466; $[\alpha]_{\text{D}}^{20} +79.5$ ($c=1$, CHCl_3); δ_{H} (250 MHz, CDCl_3) 7.42-7.24 (m, 5H, ArH), 3.61 (dd, $J = 9.5, 4.3$ Hz, 1H, H-1), 2.84 (dd, $J = 12.4, 4.3$ Hz, 1H, H-2a), 2.72 (dd, $J = 12.4, 9.5$ Hz, 1H, H-2b), 2.29 (s, 3H, NCH_3), 1.95 (s, 1H, NH), 1.33 (s, 9H, $\text{C}(\text{CH}_3)_3$); δ_{C} (62 MHz, CDCl_3) 143.3, 128.7, 127.6, 127.3 (all ArC), 65.1 (C-1), 42.6 (C-2) 37.0 (CMe_3), 34.8 (NCH), 31.2 ($(\text{CH}_3)_3$); ν_{max} (CCl_4) 3314, 3087, 3068, 2961, 2904, 2867, 2798, 608. (*S*)-**12** B.p. 105°C @ 0.3 mm Hg (kugelrohr); $[\alpha]_{\text{D}}^{20} +28.9$ ($c=1$, CHCl_3).
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