Conversion of Chiral Amino Acids to Enantiomerically Pure α-Methylamines

B. G. Donner
Aging and Degenerative Diseases Research Division, Department 47B,
Abbott Laboratories, Abbott Park, IL 60064-3500

Abstract: Enantiomerically enriched α-methylamines are obtained in high yield by Raney nickel reduction of N-Boc-protected, amino acid-derived thioethers.

α-Methylamines, particularly those which might be derived from enantiomerically pure α-amino acids, are important targets in the synthesis of biologically active compounds. The use of α-amino acids as starting materials in the synthesis of these amines, however, is precluded by the rigorous reaction conditions typically employed for the conversion of carboxyl groups to methyl groups. With few exceptions, these conditions provide only modest yields or are incompatible with amino acids bearing acid or base-sensitive functionality. This report describes an efficient preparation of enantiomerically pure (>98% ee) N-Boc-α-methylamines from the corresponding chiral amino acids.

Raney nickel is a commonly used reagent for the desulfurization of thioethers. Woo has also demonstrated the utility of this reaction in the synthesis of chiral, N-Boc-protected statine. A similar use was envisioned for reduction of N-Boc-protected thioethers 4a-g, prepared from chiral amino acids 1a-g, via a modification of the optically active taurine synthesis described by Ienaga and coworkers. An illustrative synthesis of N-Boc-(R)-(+)amphetamine is shown in Scheme 1.

Scheme 1

\[ \begin{align*}
1a & \xrightarrow{a} 2a \xrightarrow{b} 3a \\
4a & \xrightarrow{d} 5a
\end{align*} \]

Reagents and conditions: a) BH₃ THF, 0°C, 2.5h; b) CH₃SO₂Cl, TEA, CH₂Cl₂, 0°C, 1h; c) NaH, THF, CH₃CH₂SH, 67°C, 2h; d) Ra-Ni, EtOH/H₂O, 70°C, 24h.
The results are summarized in Table 1. Commercially available N-Boc-α-amino acids 1a-g were converted to the corresponding amino alcohols 2a-g by treatment with 2.5 equivalents of diborane in THF.\textsuperscript{8} The yields of this conversion ranged from 90 to 100%, depending on the nature of the amino acid side chain present. Entries 1d-g provided the lower range yields, presumably due to irreversible ligation of the heteroatom-containing side chains with the reducing agent. Treatment of 2a-g with 1.1 equivalents of methane sulfonyl chloride in the presence of base provided the mesylates 3a-g.\textsuperscript{9} These yields (88-97%) were notably dependent on the reaction conditions used but were optimized using triethylamine, dry (4Å sieves) CH\textsubscript{2}Cl\textsubscript{2} and temperatures between -5 and 0°C. The conversion of 3a-g to thioethers 4a-g was effected with 3 equivalents of sodium thioethoxide in refluxing THF.\textsuperscript{10} Formation of thioether 4e was accompanied by deprotection of the imidazoyl side chain of 3e. Raney nickel reduction of 4a-g in refluxing ethanol/water gave the title N-Boc-α-methylamines 5a-g in quantitative yields\textsuperscript{11} with ee’s ≥98%.
The enantiomeric purities of 5a-g were confirmed by 300 MHz 1H NMR analysis of the Mosher amide derivatives in CDCl₃. (R)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid adducts of racemic α-methylamines, prepared under standard coupling conditions (1-ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride, 1-hydroxybenzotriazole), display well-separated α-methoxy proton absorbances. These diastereomeric proton signals were not observed for Mosher amides prepared from 5a-g in over 90% yield. Thus the sequence described herein proceeds with retention of optical purity.

Scheme 1 represents a widely applicable means through which chiral amino acids are converted to enantiomerically pure α-methylamines. The deprotection of amino acid side chains of mesylate 3e and thioether 4f are noted as limitations of this method. Mild reaction conditions, suitable for milligram or multigram scale, allow a powerful alternative choice of routes to these ubiquitous structural intermediates.

Acknowledgements: The author wishes to thank Brian S. Macri for expert technical assistance and David M. Stout and Steven J. O’Connor for helpful discussions during the course of this work.

References and notes:

1. Preliminary results of this work were presented at the 205th National American Chemical Society Meeting in Denver, CO, March 28-April 2, 1993. Abstract Number 258.


7. Proton NMR, mass spectral and combustion analyses were consistent with the assigned structures for all bulk final products for which yields are reported.

8. A mechanically stirred solution of Boc-Tyr, 1d, (30.0 g, 101 mmol) in THF (337 mL) at 0°C was treated over 1h with 1M BH₃-THF (254 mL). Upon complete addition, the ice bath was removed and the solution was allowed to room temperature until the starting material was consumed as indicated by TLC (CHCl₃,CH₂OH,H₂O, 9:2:1). The reaction was cooled to 0°C and quenched over 1h by the dropwise addition of brine. The layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried (MgSO₄), filtered and concentrated to provide 28.4 g (100%) of 2d. Alcohols 2a (100%), 2b (99%), 2c (100%), 2e (93%), 2f (97%) and 2g (90%) were likewise obtained using this procedure.

9. A solution of 2d (28.0 g, 99.5 mmol) and triethylamine (28 mL, 199 mmol) in CH₂Cl₂ (330 mL) at -3°C was treated over 2.5h with methane sulfonyl chloride (8.5 mL) in CH₂Cl₂ (8.5 mL). The resulting brown slurry was stirred for an additional 2.5h. All volatiles were removed under high vacuum (0.1 mm Hg) at 25°C. The residue was taken up in ethyl acetate and washed successively with 0.1N HCl, 5% NaHCO₃ and brine. The organic layer was dried (MgSO₄), filtered and reduced to provide a brown oil. Chromatography of the oil on silica gel with ethyl acetate/hexane provided 34.7 g (97%) mesyl ester 3d. Esters 3a (95%), 3b (95%), 3e (88%), 3f (99%) and 3g (88%) were likewise obtained using this procedure.

10. A solution of 3d (34.0 g, 94.6 mmol) in THF (95 mL) was added to a mechanically stirred suspension of sodium thioethoxide (31.8 g, 378 mmol, prepared in situ from NaH and CH₃CH₂SH) in THF (500 mL) at room
temperature. The mixture was warmed to reflux for 2h, cooled and quenched with brine. The layers were separated, and the aqueous layer was washed twice with ethyl acetate. The combined organic extracts were dried (MgSO₄), filtered through a pad of silica gel and reduced to provide 30.8 g (100%) of thioether 4d. Thioethers 4a (100%), 4b (100%), 4c (100%), 4e (100%) and 4g (96%) were likewise obtained using this procedure. **CAUTION:** ethanethiol is volatile and has an obnoxious odor! It should be used in an efficient fume hood.

11. To Raney nickel (54.1 g, 922 mmol) in water (54.1 mL) was added a solution of 4d in ethanol (184 mL). The mixture was refluxed for 18h, cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated to approximately one half of its original volume, saturated with NaCl, and extracted twice with ethyl acetate. The combined organic layers were dried (MgSO₄), filtered through a pad of silica gel and concentrated to provide 24.5 g (100%) of α-methyl amine 5d. 5a (100%), 5b (100%), 5c (100%), 5e (100%), 5f (100%) and 5g (100%) were likewise obtained using this procedure.


*(Received in USA 28 July 1994; revised 15 November 1994; accepted 19 December 1994)*