A Short Synthetic Approach to Chiral Serine Azido Derivatives

Gautam Panda,*[1] N. Venugopal Rao

Steacie Institute for Molecular Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, K1A 0R6, Canada
E-mail: gautam_panda@lycos.com; E-mail: bapi@rocketmail.com

Received 26 December 2003

Abstract: We report a new synthetic methodology for the synthesis of chiral serine azido derivatives through a conversion of N-protected (Boc, Cbz and Fmoc) serine amino acid into its corresponding Weinreb amide. Thus, acidity of the α-proton of the serine is reduced and it allows nucleophilic addition reaction onto Weinreb amide to furnish chiral serine azido derivatives.

Key words: serine azido esters, Weinreb amide, Mitsunobu reaction, azido aldehyde, $LiOH–H_2O_2$, hydrolysis, Fmoc group

Biologically important and synthetically useful nonproteinogenic α-amino acids[2] have been found in natural products. They are important constituents in peptide-derived chemotherapeutics. α-Amino acids are versatile synthons and their unique structural motif has been found in several medicinally important entities like protein-tyrosine kinase inhibitors,[3] glycoprotein IIb/IIIa RGD receptor antagonists[4] and quisqualic acid analogues.[5] Thus, the development of new synthetic methodologies providing an expedient, general and novel approach for the synthesis of this class of compounds is as an active area of research.[6] A number of elegant approaches are available from the literature for the synthesis of various α-amino acids in their optically pure form.[7] Most of them involve the diastereoselective alkylation reactions of highly effective chiral glycine enolate synthons.[8]

Indirect homologation of the serine side chain is also reported. Another common route to prepare α,β-diamino acids involves azide displacement under Mitsunobu conditions of the hydroxy group of serine, followed by reduction of the azide.[9] But these strategies suffer from a lack of flexibility in terms of stereochemical control at the β-carbon of the amino acid. In this preliminary communication, we wish to report a simple and direct approach for the synthesis of novel chiral L-serine Weinreb amide[8] azido derivatives and illustrate the versatility of this amide for the synthesis of various α-amino and α,β-diamino acids and their derivatives.

Retrosynthetic analysis suggests that the compounds **2a**–**c** were expected to deliver serine azido ester **1a**–**c** through the displacement of the hydroxyl group in **2a**–**c** under Mitsunobu conditions (Figure 1). Attempted reaction between **2a**–**c** and the freshly prepared HN_3 solution in toluene in the presence of DEAD and PPh_3 furnished only the elimination product **3a**–**c**. There was no trace of the required product **1a**–**c** as indicated by electrospray MS. The hydroxyl group in **2a**–**c** was then converted to its mesylate derivative by reacting with MsCl and Et_3N. Subsequent reaction with sodium azide at 40 °C in DMF again yielded the elimination product **3a**–**c**, (Scheme 1).

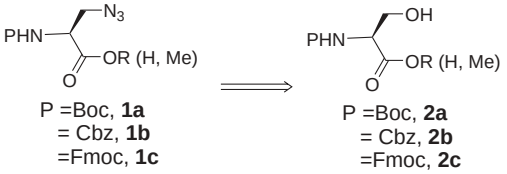
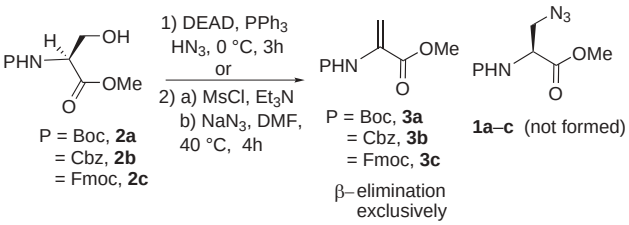


Figure 1

This is attributed to the fact that the relative acidity of the α proton of the serine methyl ester **2a**–**c** causes its easy removal under Mitsunobu conditions. The alkoxy phosphonium intermediate in Mitsunobu reaction is a good leaving group, which eliminates easily to form the β-elimination product **3a**–**c**. To overcome this problem, we have done a literature search.[9,10] Recently, Lajoie et. al[9] reported that by masking the carboxylic end of the serine to its cyclic base stable ortho ester derivative the acidity of the α-proton of L-serine could be substantially reduced.

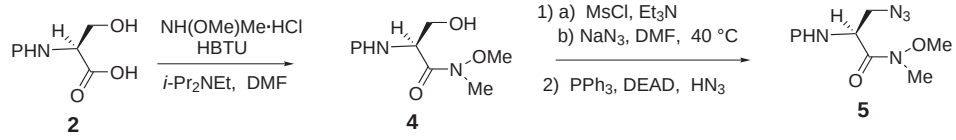


	DEAD/HN_3	MsCl, NaN_3
Boc	88 %	77 %
Cbz	90%	80 %
Fmoc	92 %	82 %

Scheme 1

We have taken three (Boc, Cbz and Fmoc) N-protected serine amino acids for our studies. All three amino acids were converted into their Weinreb amide esters by reacting with *N*,*O*-dimethyl hydroxylamine hydrochloride under standard DCC, HOBT, *i*-Pr_2NEt conditions (yield ca. 60%). The yields of the reaction were increased (yield 80%) by replacing DCC and HOBT by HBTU (**2** → **4**) (Scheme 2).

SYNLETT 2004, No. 4, pp 0714–0716
Advanced online publication: 17.02.2004
DOI: 10.1055/s-2004-817770; Art ID: G36503ST



2 **4** **5**

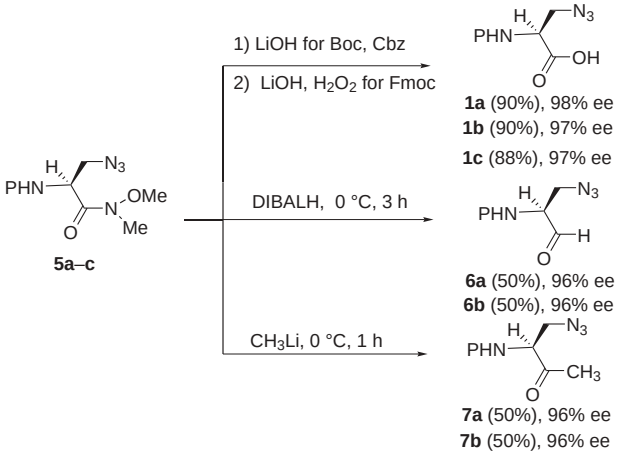
Boc (a), Cbz (b), Fmoc (c)

	HBTU	MsCl, NaN_3	DEAD/HN_3	%ee of **5a–c**
Boc	85 %	92 %	90 %	92
Cbz	81 %	90 %	88 %	94
Fmoc	80 %	88 %	90 %	97

Scheme 2

It was thought that Weinreb amide ester will substantially reduce the acidity of the α proton and thus transformation into its azide can be performed. All three esters **4a–c** were characterized by ^{1}H NMR and MS electrospray. The hydroxyl groups in **4a–c** were converted into their mesylate derivatives by reacting with mesyl chloride and Et_3N in CH_2Cl_2. The products were not separated at this stage and were directly used for the next step. The mesylate derivatives were heated at 40 °C with sodium azide in DMF. MS electrospray of the reaction mixtures showed the presence of the required products with absence of any elimination products. Column chromatography was performed for all the three reaction mixtures and the products were isolated in high yields. Mitsunobu transformation can also be performed directly on **4** by using HN_3 solution in toluene in presence of DEAD/PPh_3. Our method is very short and convenient to prepare the chiral serine azido esters from substituted serine derivatives. The compounds can be prepared in large scale as the two steps are very high yielding processes. Furthermore, the amide functionality in **5a–c** can be easily transformed into useful derivatives depending upon the requirements through nucleophilic addition reactions. Feasibility of this nucleophilic addition approach was not possible in previously reported literature procedures.[9]

To illustrate the outcome of nucleophilic addition, we have treated all three Weinreb amide esters **5a–c** with base to transform them into their acids. Boc and Cbz derivatives of **5a**,**b** reacted with LiOH in THF. The corresponding acids were obtained in high yields (ca. 90%). There was no indication of β elimination as the Weinreb amide esters substantially reduced the acidity of the α proton in **5a**,**b**. LiOH was replaced by LiOH–H_2O_2[10,11] in case of **5c** as it contains the base sensitive Fmoc group. Compound **5c** was hydrolyzed to its acid derivative **1c** by its treatment with 2 equivalents of LiOH and 8 equivalents of H_2O_2 in THF–H_2O (yield 88%). The amide functionality in **5a**,**b** reacted with DIBAL-H and CH_3Li to give their aldehyde and ketone derivatives respectively (**6a**,**b**, **7a**,**b**).



Scheme 3

DIBAL-H and CH_3Li reaction of **5c** resulted in uncharacterized products with deprotection of Fmoc group. Boc and Cbz derivatives of chiral serine azido derivatives (**6a**,**b**, **7a**,**b**) were obtained in moderate yields (ca. 50%),[12] (Scheme 3).

In conclusion, we have described a new strategy for the synthesis of chiral serine azido derivatives by converting the carboxyl functional group of serine into its Weinreb amide ester using three common reaction steps, i.e. amide bond formation, Mitsunobu reaction and hydrolysis of Weinrab amide (overall yields, Boc: 70.38%, Cbz: 64.15%, Fmoc: 63.36%). Nucleophilic addition was performed on Weinreb amide esters to furnish chiral serine azido aldehyde. Utilization of this short reaction sequence for the synthesis of various α,β-diamino acids and subsequent construction of conformationally constrained cyclic peptides is currently underway.

Acknowledgement

We thank Dr. Prabhat Arya, National Research Council, Ottawa, Canada for providing his laboratory to carry out this work and financial assistance to both of us in the form of NRC/NSERC visiting postdoctoral fellowship.

References

(1) Present Address: Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226001, UP, India, e-mail: gautam_panda@lycos.com.

(2) (a) *Chemistry and Biochemistry of the Amino Acids*; Barett, G. C., Ed.; Chapman and Hall: London, **1985**. (b) Wagner, I.; Musso, H. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 816. (c) Evans, C. S.; Qureshi, M. Y.; Bell, E. A. *Phytochemistry* **1977**, *16*, 565. (d) Arya, P.; Rao, N. V.; Singkhonrat, J.; Alper, H.; Bourque, S. C.; Manzer, L. E. *J. Org. Chem.* **2000**, *65*, 1881. (e) Arya, P.; Panda, G.; Rao, N. V.; Alper, H.; Bourque, S. C.; Manzer, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 2889.

(3) Lee, E. S.; Jurayj, J.; Cushman, M. *Tetrahedron* **1994**, *50*, 9873.

(4) Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Emmett, G.; Sze, J. Y.; Liu, J.; Tobin, A.; Wang, S.; Jiang, B.; Ma, P.; Mousa, S. A.; Wexler, R. R.; Olson, R. E. *J. Med. Chem.* **1997**, *40*, 50.

(5) (a) Subasinghe, N.; Schute, M.; Roon, R. J.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1992**, *35*, 4602. (b) Dugenet, P.; Yaounc, J. J.; Sturtz, G. *Synthesis* **1982**, 781. (c) Sinclair, P. J.; Zhai, D.; Reibenspier, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103. (d) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc*. **1983**, *105*, 5390. (e) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106. (f) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis, Construction of Chiral Molecules Using Amino Acids*; John Wiley & Sons: Toronto, **1987**.

(6) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Toronto, **1989**, ; and references cited therein.

(7) Schollkopf, U. *Top. Curr. Chem.* **1983**, *109*, 66.

(8) (a) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377; and references cited therein. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3818. (c) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15.

(9) (a) Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y.; Lajoie, G. A. *J. Org. Chem.* **1998**, *63*, 3631. (b) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021. (c) Luo, Y.; Blaskovich, M. A.; Lajoie, G. A. *J. Org. Chem.* **1999**, *64*, 6106. (d) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237. (e) Otsuka, M.; Kittaka, A.; Iimorei, T.; Amashita, H.; Kobayashi, S.; Ohno, S. *Chem. Pharm. Bull.* **1985**, *33*, 509.

(10) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(11) Typical Procedure for Mitsunobu Reaction: A mixture of Fmoc-Ser-Weinreb amide ester **4c** (2.01 g, 5.4 mmol) and Ph_3P (2.13 g, 8.1mmol) in anhyd THF (120 mL) was cooled in an ice bath. A solution of DEAD (1.46 g, 8.1 mmol) in THF (18 mL) was added dropwise. After mixing of the solution for 5 min, a HN_3–toluene solution (8.7 mL, 16.2 mmol) was slowly added. The mixture was allowed to warm to r.t. and stirred for 8 h. The solvent was removed in vacuo. The oily residue was purified by column chromatography (hexane–EtOAc, 1:1) to provide product **5c** (2.0 g, 93%). $[\alpha]_D^{25}$ = +12.50 (*c* = 1.0, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.7 (d, *J* = 8 Hz, 2 H), 7.5 (d, *J* = 8 Hz, 2 H), 7.4 (d, *J* = 8 Hz, 2 H), 7.2 (d, *J* = 7.8 Hz, 2 H), 6.1 (br s, 1 H), 5.0 (br s, 1 H), 4.4 (m, 3 H), 4.2 (m, 2 H), 3.8 (s, 3 H), 3.6 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 156.2, 151.3, 144.1, 144.0, 141.9, 130.5, 128.6, 128.1, 127.5, 127.4, 125.5, 120.5, 120.3, 108.3, 68.0, 67.7, 62.8, 62.4, 52.6, 51.6, 47.4. MS: *m*/*z* = 395 [M$^+$]. Anal. Calcd: C, 60.75; H, 5.35; N, 17.71. Found: C, 61.01; H, 5.21; N, 17.88. Typical Procedure for Hydrolysis of **5c**: To a solution of azide **5c** (75 mg, 0.189 mmol) in THF (3mL) and H_2O (1 mL) were added LiOH (7 mg, 0.283 mmol) and H_2O_2 (0.1 mL, 1.51 mmol) and the reaction mixture was stirred at 0 °C for 8 h. The mixture was quenched by sat. solution of Na_2SO_3 at 0 °C and THF was removed in vacuo. CH_2Cl_2 was added to remove any unchanged starting material. The aqueous phase was acidified with NH_4Cl and extracted twice with EtOAc. The crude acid **1c** was obtained which was purified through column chromatography (58 mg, 88%).

(12) Typical Procedure for DIBAL-H Reduction: To a solution of **5a**,**b** (Boc dervative; 110 mg, 0.402 mmol, Cbz dervative 155 mg, 504 mmol) in anhyd THF (5 mL) at –78 °C was added DIBAL-H (0.68 mL for Boc, 0.85 mL for Cbz) and the reaction micture was stirred for 1 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc. Column chromatography over silica gel furnished **6a** (50 mg, 50%) and **6b** (72 mg, 50%). Spectral data: **4a**: ^{1}H NMR: δ = 5.8 (br s, 1 H), 4.8 (br s, 1 H), 3.8 (m, 1 H), 3.7 (br s, 2 H), 3.3 (s, 3 H), 2.9 (s, 3 H), 1.4 (s, 9 H). MS: *m*/*z* = 248 [M$^+$]. Anal. Calcd; C, 48.38; H, 8.12; N, 11.28. Found: C, 49.00; H, 9.00; N, 10.28. **5a**: $[\alpha]_D^{25}$ = +2.9 (*c* = 1.0, EtOAc). ^{1}H NMR: δ = 5.1 (br s, 1 H), 4.9 (br s, 1 H), 3.9 (m, 1 H), 3.1 (m, 2 H), 3.2 (s, 3 H), 3.0 (s, 3 H), 1.4 (s, 9 H). ^{13}C NMR: δ = 169.9, 155.5, 80.5, 61.2, 61.0, 52.7, 51.0, 32.5, 28.6 MS: *m*/*z* = 273 [M$^+$]. Anal. Calcd for C, 43.95; H, 7.01; N, 25.63. Found: C, 44.00; H, 7.89; N, 24.96. **6a**: $[\alpha]_D^{25}$ = +12.0 (*c* = 1.0, EtOAc). ^{1}H NMR: δ = 9.0 (s, 1 H), 6.2 (m, 1 H), 5.2 (s, 2 H), 1.4 (s, 9 H). MS: *m*/*z* = 214 [M$^+$]. **9b**: ^{1}H NMR: δ = 8.0 (s, 1 H), 7.4–7.2 (m, 5 H), 5.1 (br s, 2 H), 3.8 (m, 1 H), 3.7 (s, 2 H), 3.2 (s, 3 H), 3.0 (s, 3 H). MS: *m*/*z* = 282 [M$^+$]. Anal. Calcd: C, 44.85; H, 6.59; N, 26.15. Found: C, 44.0; H, 7.00; N, 26.10. **5b**: $[\alpha]_D^{25}$ = +0.3 (*c* = 1.0, EtOAc). ^{1}H NMR: δ = 7.4–7.2 (m, 5 H), 6.0 (br s, 1 H), 5.1 (br s, 2 H), 4.9 (m, 1 H), 3.8 (s, 3 H), 3.5 (d, J_1 = 6 Hz, J_2 = 2 Hz, 2 H), 3.1 (s, 3 H). ^{13}C NMR: δ = 169.9, 156.2, 136.54, 128.9, 128.5, 128.4, 67.4, 62.7, 62.5, 52.5, 51.5, 32.5. MS: *m*/*z* = 307 [M$^+$]. Anal. Calcd: C, 50.81; H, 5.58; N, 22.79. Found: C, 51.01; H, 5.68; N, 22.99. **1b**: $[\alpha]_D^{25}$ = +9.0 (*c* = 1.0, EtOAc). ^{1}H NMR: δ = 7.4–7.2 (m, 5 H), 6.9 (br s, 1 H), 5.1 (m, 2 H), 4.0 (br s, 1 H), 3.8 (m, 2 H). MS: *m*/*z* = 264 [M$^+$]. Anal. Calcd: C, 50.00; H, 4.58; N, 21.20. Found: C, 50.89; H, 4.78; N, 21.55. **6b**: $[\alpha]_D^{25}$ = +8.8 (*c* = 1.0, EtOAc). ^{1}H NMR: δ = 9.0 (s, 1 H), 7.4–7.2 (m, 5 H), 7.1 (m, 1 H), 6.4 (s, 1 H), 5.6 (s, 1 H), 5.1 (s, 2 H). MS: *m*/*z* = 248 [M$^+$]. Anal. Calcd: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.99; H, 4.99; N, 23.99. **4c**: ^{1}H NMR: δ = 7.7 (d, *J* = 8 Hz, 2 H), 7.5 (d, *J* = 8 Hz, 2 H), 7.4 (d, *J* = 8 Hz, 2 H), 7.2 (d, *J* = 7.8 Hz, 2 H), 6.1 (br s, 1 H), 5.8 (br s, 1 H), 4.3 (s, 2 H), 4.2 (m, 1 H), 3.8 (m, 1 H), 3.7 (m, 2 H), 3.2 (s, 3 H), 2.9 (s, 3 H). ^{13}C NMR: δ = 163.1, 156.9, 144.2, 144.1, 141.6, 141.5, 128.8, 128.1, 127.4, 125.5, 125.2, 120.3, 67.5, 63.5, 62.0, 53.3, 47.5, 39.0, 36.9, 34.2, 32.5, 31.8. MS: *m*/*z* = 370 [M$^+$]. Anal. Calcd: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.00; H, 6.99; N, 8.89.