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Synthesis of Optically Active N-Protected α-Aminoketones and α-Amino Alcohols

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ABSTRACT: *A series of optically active* N-*protected* α-*aminoketones were synthesized via the Grignard reaction of the Weinreb amides of the* N-tert-*butoxycarbonyl amino acids. Reduction of the* α-*aminoketones by sodium borohydride resulted in the corresponding 1,2-amino alcohols.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:603–606, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10195

INTRODUCTION

The preparation by synthetic method of chiral 1,2-amino alcohols and the isolation of their enantiomeric and/or diastereomeric forms, as well as the knowledge of their configuration were of great importance in pharmacological research on anaesthetics, analgesics, etc. It was well known that the receptorial centers were in many cases very stereoselective toward the above drugs. Moreover, 1,2-amino alcohols have been the important building blocks in the synthesis of various natural products [1] and bicyclic amidines and guanidines [2]. In addition, the enantiomers of chiral amino alcohols could be employed in the asymmetric synthesis of optically active compounds [3], mainly by the formation of complex hydrides [4–6], or in the presence of metal catalysts [7,8] in the asymmetric reaction of unsaturated molecules. Therefore, the synthesis of optically active 1,2-amino alcohols has attracted much attention of the organic chemists. Described herein is an efficient method for the synthesis of chiral N-protected α-aminoketones and the related 1,2-amino alcohols starting from the L-amino acids (Scheme 1).

The readily available L-amino acids were converted to the corresponding *N-tert*-butoxycarbonyl protected amino acids **1** and **5**. The condensation of **1** and **5** with *O*,*N*-dimethylhydroxylamine afforded the corresponding N-protected Weinreb amides **2** and **6**. Grignard reaction of the amides **2** and **6** with arylmagnesium bromide provided the pivotal α-aminoketone derivatives **3** and **7**. Reduction of the ketones **3** and **7** with sodium borohydride resulted in the exclusive formation of the corresponding 1,2-*syn*-amino alcohols **4** and **8**.

RESULTS AND DISCUSSION

Many methods were involved in the preparation of Weinreb amides. The original method [9] prepared the methyl *N*-methylhydroxamates by the reaction of simple acyl chlorides with *O*,*N*-dimethylhydroxylamine. However, this method was not applicable in the conversion of *N*-Boc amino acids **1** and **5** into Weinreb amides **2** and **6** because

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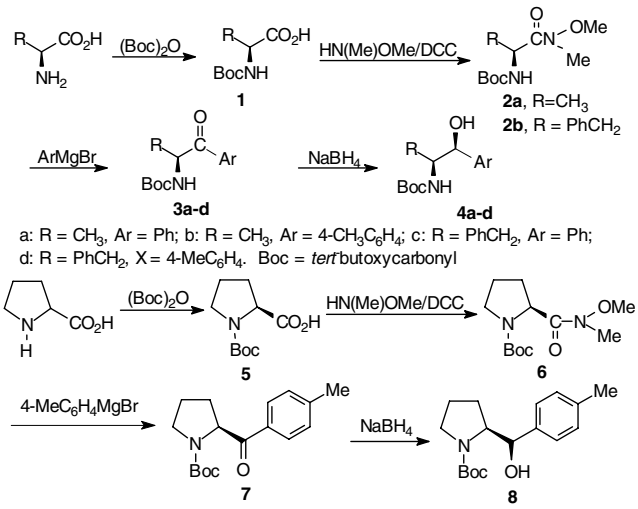

SCHEME 1

of the acid-sensitive character of the *N*-Boc amino acids. Castro [10] and Taylor [11] have reported using BOP [benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate] and NMM [*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride] as the coupling agents, respectively. It was found that the more readily available DCC (*N*,*N*′-dicyclohexylcarbodiimide) was also an efficient coupling agent for the formation of Weinreb amides of *N*-Boc amino acids. Under this condition, the corresponding Weinreb amides **2** and **6** were obtained in excellent yield.

Stereospecific arylation of *N*-Boc amino acids to form the aryl ketones **3** and **7** may be the key step in achieving an asymmetric synthesis of 1,2-amino alcohols **4** and **8**. Although arylation of amino acids has been reported [12], the yield was very low and the admired ketone was hard to separate from the reaction mixture. Moreover, Friedel–Crafts reaction of the acid chloride was very sluggish and the product was not isolable because of contamination of impurities [13]. However, the Grignard reaction of the Weinreb amides **2** and **6** has overcome these problems associated with the aforementioned two methods. The corresponding α-aminoketones were obtained in high yield.

The reduction of the aminoketones **3** and **7** with sodium borohydride ($NaBH_4$) resulted in the exclusive formation of the corresponding *syn*-1,2-amino alcohols **4** and **8** except for **4a**, which had a ratio of *syn*/*anti* as 85:15. Pure *syn*-**4a** was obtained by column chromatography or recrystallization from 10:1 petroleum ether/ethyl acetate (the stereochemistry of the 1,2-amino alcohols **4** and **8** was determined according to the literature [14]).

In the ^{1}H NMR of compounds **3d** and **4d**, the signal of the methyl group on the benzene ring was split into two peaks with a ratio of 2:1. However, the similar phenomenon was not observed in the ^{1}H NMR of compounds **3b** and **4b**, which also have a methyl group on the benzene ring. It was also found that the carbonyl group attached to the pyrrolidine ring has a dramatic influence on the ^{1}H NMR of the compounds **6** and **7**, whose ^{1}H NMR of the *tert*-butyl group was split into two peaks with a ratio of 4:5. However, only a single signal of *tert*-butyl was observed in the ^{1}H NMR spectroscopy when transformation of the carbonyl group in compound **7** into a hydroxyl group (compound **8**) via reduction took place.

EXPERIMENTAL

^{1}H NMR data were recorded in $CDCl_3$ on a Bruker AC-P200 instrument using TMS as an internal standard. Elemental analyses were conducted on a Yanaco CHN Corder MT-3 automatic analyzer. Melting points are determined on a MP-500 melting point apparatus. All temperatures are uncorrected. *N-tert*-Butoxycarbonyl amino acids were prepared according to the literature method [15].

Preparation of the Weinreb Amides **2** *and* **6** *(General Procedure)*

To an ice-cold mixture of *N-tert*-butoxycarbonyl-L-amino acids (10 mmol), *O*,*N*-dimethylhydroxylamine (0.61 g, 10 mmol), and 20 ml alcohol-free chloroform was added *N*,*N*′-dicyclohexylcarbodiimide (DCC, 10 mmol) at intervals. The resulting mixture was stirred at the same temperature till the N-protected amino acid disappeared (monitored by TLC). The reaction mixture was filtered, and the residual solid (*N*,*N*′-dicyclohexylurea, DCU) was washed with cold chloroform. The combined filtrate was concentrated and the crude product was purified by column chromatography (silica gel 200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to afford the pure Weinreb amides.

N$^{\alpha}$*-(tert-Butoxycarbonyl)-L-alanine N-Methoxy-N-methylamide (***2a***).* Thick liquid, 94.3% yield, $[\alpha]^{20}_{D}$; +5.0 (*c* 1.1, $CHCl_3$). ^{1}H NMR (δ, $CDCl_3$): 1.32 (d, 3H, CH_3, $^3J_{HH}$ = 7.12 Hz), 1.43 (s, 9H, *t*-Bu), 3.05 (s, 3H, NCH_3), 3.62 (s, 3H, OCH_3), 4.73 (q, 1H, CH, $^3J_{HH}$ = 7.12 Hz), 5.32 (br, 1H, NH).

N$^{\alpha}$*-(tert-Butoxycarbonyl)-L-phenylalanine N-Methoxy-N-methylamide (***2b***).* Thick liquid, 94.8% yield, $[\alpha]^{20}_{D}$ +29.0 (*c* 1.23, $CHCl_3$). ^{1}H NMR (δ, $CDCl_3$): 1.26 (s, 9H, *t*-Bu), 3.02 (s, 3H, NCH_3), 3.51

(s, 3H, CH_3O), 3.98 (m, 2H, CH_2), 4.86 (br, 1H, NH), 5.21 (m, 1H, CH), 7.07–7.10 (m, $5H_{arom}$).

*N^{α}-(tert-Butoxycarbonyl)-L-proline N-Methoxy-N-methylamide (**6**).* Thick liquid, 98.2% yield, $[\alpha]^{20}_D$ +15.6 (*c* 1.55, $CHCl_3$). ^1H NMR (δ, $CDCl_3$): 1.31 (s, 5H, five protons of *t*-Bu), 1.35 (s, 4H, four protons of *t*-Bu), 1.69 (m, 2H, CH_2), 2.01 (m, 2H, CH_2), 3.09 (s, 3H, NCH_3), 3.48 (m, 2H, NCH_2), 3.65 (s, 3H, CH_3O), 4.58 (m, 1H, CH).

Preparation of the α*-Aminoketones* **3** *(General Procedure)*

To an ice-cold solution of the Weinreb amides (4 mmol) in 10 ml anhydrous THF was added dropwise a solution of arylmagnesium bromide [10 mmol, prepared from Mg (4.48 g, 20 mmol) and aryl bromide (10 mmol) in THF] . The resulting mixture was stirred at the same temperature for 4 h. The reaction was quenched by addition of aqueous 10% HCl solution (10 ml) and stirred for 5 min. The resulting solution was extracted with ethyl acetate (3 × 25 ml). The combined extract was washed sequentially with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent the crude product was purified by column chromatography [silica gel 200–300 mesh, petroleum ether/ethyl acetate (1:10) as the eluent] to afford the pure α-aminoketones **3**.

3a: Thick liquid, 47.5% yield, $[\alpha]^{20}_D$ 0 (*c* 0.9, $CHCl_3$). ^1H NMR (δ, $CDCl_3$): 1.37 (d, 3H, CH_3, $^3J_{HH}$ = 6.98 Hz), 1.44 (s, 9H, *t*-Bu), 5.21 (q, 1H, CH, $^3J_{HH}$ = 6.98 Hz), 5.56 (br, 1H, NH), 7.20–7.48 (m, $5H_{arom}$). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.36; H, 7.65; N, 5.57.

3b: White solid, m.p. 99–100°C, 59.6% yield, $[\alpha]^{20}_D$ −66.0 (*c* 0.94, $CHCl_3$). ^1H NMR (δ, $CDCl_3$): 1.36 (d, 3H, CH_3, $^3J_{HH}$ = 7.10 Hz), 1.43 (s, 9H, *t*-Bu), 2.39 (s, 3H, CH_3), 5.16 (q, 1H, CH, $^3J_{HH}$ = 7.10 Hz), 5.60 (br, 1H, NH), 7.25 (d, $2H_{arom}$, J_{AB} = 16.1 Hz), 7.83 (d, $2H_{arom}$, J_{AB} = 16.1 Hz). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.27; H, 8.01; N, 5.38.

3c: White solid, m.p. 94–96°C, 58.1% yield, $[\alpha]^{20}_D$ +52.3 (*c* 1, $CHCl_3$). ^1H NMR (δ, $CDCl_3$): 1.41 (s, 9H, *t*-Bu), 2.96 (m, 1H, NH), 3.16 (m, 1H, CH), 5.45 (m, 2H, CH_2), 7.18–7.94 (m, $10H_{arom}$). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.62; H, 7.24; N, 4.35.

3d: White solid, m.p. 89–91°C, 47.3% yield, $[\alpha]^{20}_D$ +51.2 (*c* 0.5, $CHCl_3$). ^1H NMR (δ, $CDCl_3$): 1.31 (s, 9H, *t*-Bu), 2.35 (s, 1H, one proton of CH_3), 2.41 (s, 2H, two protons of CH_3), 4.08 (m, 1H, CH), 4.65 (br, 1H, NH), 5.52 (m, 2H, CH_2), 6.68 (d, $2H_{arom}$, J_{AB} = 15.6 Hz), 6.99–7.23 (m, $5H_{arom}$), 7.81 (d, $2H_{arom}$, J_{AB} = 15.6 Hz). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.32; H, 7.37; N, 4.13. Found: C, 74.37; H, 7.46; N, 4.23.

7: White solid, m.p. 85–86°C, 63.3% yield, $[\alpha]^{20}_D$ −22.9 (*c* 0.96, $CHCl_3$). ^1H NMR (δ, $CDCl_3$): 1.24 (s, 5H, five protons of *t*-Bu), 1.43 (s, 4H, four protons of *t*-Bu), 1.90 (m, 4H, $2CH_2$), 2.39 (s, 3H, CH_3), 3.64 (m, 2H, NCH_2), 5.18 (m, 1H, CH), 7.24 (d, $2H_{arom}$, J_{AB} = 7.84 Hz), 7.83 (d, $2H_{arom}$, J_{AB} = 7.84 Hz). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.64; H, 8.02; N, 5.00.

Preparation of the 1,2-Amino Alcohols **4** *and* **8** *(General Procedure)*

To a stirred solution of the aminoketones **3** (2 mmol) in dry methanol (25 ml) at −20°C was added sodium borohydride (0.15 g, 4 mmol) in one lot and stirring was continued at the same temperature for 5 h. The reaction was then quenched by addition of water (5 ml). The resulting mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (50 ml) and washed successively with water and brine. After drying over anhydrous Na_2SO_4 and removal of the solvent the crude product was purified by column chromatography [silica gel 200–300 mesh, petroleum ether/ethyl acetate (1:5) as the eluent] to provide the *syn*-amino alcohols **4**.

4a: White solid, m.p. 86–87°C, 82.3% yield, $[\alpha]^{20}_D$ +9.8 (*c* 1, $CHCl_3$). ^1H NMR (δ, $CDCl_3$): 1.37 (d, 3H, CH_3, $^3J_{HH}$ = 6.98 Hz), 1.44 (s, 9H, *t*-Bu), 3.09 (br, 1H, OH), 3.96 (m, 1H, $\underline{CH}CH_3$), 4.61 (br, 1H, NH), 4.82 (d, 1H, $\underline{CH}OH$, $^3J_{HH}$ = 2.76 Hz), 7.28–7.32 (m, $5H_{arom}$). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.84; N, 5.57. Found: C, 66.81; H, 9.02; N, 5.55.

4b: White solid, m.p. 128–129°C, 97.6% yield, $[\alpha]^{20}_D$ −70.4 (*c* 1.02, $CHCl_3$). ^1H NMR (δ, $CDCl_3$): 0.96 (d, 3H, CH_3, $^3J_{HH}$ = 6.74 Hz), 1.44 (s, 9H, *t*-Bu), 2.32 (s, 3H, CH_3), 3.92 (m, 1H, $\underline{CH}CH_3$), 4.86 (d, 1H, $\underline{CH}OH$, $^3J_{HH}$ = 2.92 Hz), 7.15–7.23 (m, $9H_{arom}$). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 67.71; H, 8.84; N, 5.20.

4c: White solid, m.p. 136–137°C, 77.1% yield, $[\alpha]^{20}_D$ −24.8 (*c* 0.71, $CHCl_3$). ^1H NMR (δ, $CDCl_3$): 1.31 (s, 9H, *t*-Bu), 2.68–2.94 (m, 2H, $\underline{CH}OH$ and $\underline{CH}NH$), 3.16 (br, 1H, OH), 4.05 (br, 1H, NH), 4.91 (m, 2H, CH_2), 7.11–7.38 (m, $10H_{arom}$). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.26; H, 7.74; N, 4.35.

4d: White solid, m.p. 131–134, 92.3% yield, $[\alpha]^{20}_D$ −25.3 (*c* 0.3, $CHCl_3$). ^1H NMR (δ, $CDCl_3$): 1.31 (s, 9H, *t*-Bu), 2.31 (s, 1H, one proton of CH_3), 2.35 (s, 2H, two protons of CH_3), 2.71–2.98 (m, 2H, $\underline{CH}OH$ and $\underline{CH}NH$), 3.56 (br, 1H, OH), 4.01 (br, 1H, NH), 4.86 (m, 2H, CH_2), 7.13–7.24 (m, $9H_{arom}$). Anal. Calcd

for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.65; H, 7.80; N, 4.02.

8: Thick liquid, 92.3% yield, $[\alpha]^{20}_D$ −25.8 (*c* 1, $CHCl_3$). ^{1}H NMR (δ, $CDCl_3$): 1.49 (s, 9H, *t*-Bu), 1.68 (m, 4H, $2CH_2$), 2.30 (s, 3H, CH_3), 3.31 (m, 2H, NCH_2), 4.48 (d, 1H, CHOH, $^3J_{HH} = 8.40$ Hz), 5.28 (s, 1H, OH), 7.12 (d, $2H_{arom}$, $J_{AB} = 8.73$ Hz), 7.21 (d, $2H_{arom}$, $J_{AB} = 8.73$ Hz). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.93; H, 8.58; N, 4.78.

REFERENCES

[1] Ager, D. J.; Prakash, I.; Schaad, D. R. Chem Rev 1996, 96, 835; Cooke, J. W. B.; Davies, S. G.; Naylor, A. Tetrahedron 1993, 49, 7955; Donnelly, D. M. X.; Fitzpatrick, B. M.; O'Reilly, B. A.; Finet, J.-P. Tetrahedron 1993, 49, 7967; Enders, D.; Reinhold, U. Angew Chem, Int Ed Engl 1995, 34, 1219; Deng, J.; Hamada, Y.; Shioiri, T. J Am Chem Soc 1995, 117, 7824; Gennari, C.; Pain, G.; Moresca, D. J Org Chem 1995, 60, 6248.

[2] Boyle, P. H.; Davis, A. P.; Dempsey, K. J.; Hosken, G. D. Tetrahedron: Asymmetry 1995, 6, 2819; Davis, A. P.; Dempsey, K. J. Tetrahedron: Asymmetry 1995, 6, 2829.

[3] Meyers, A. I.; Brich, Z.; Erickson, G. W. J Chem Soc, Chem Commun 1979, 566.

[4] Morrison, J. D.; Mosher, H. S. Asymmetric Organic Reactions; Prentice-Hall: Englewood Cliffs, N.J., 1971; p. 204.

[5] Yamaguchi, S.; Mosher, H. S.; Pohland, A. J Am Chem Soc 1972, 94, 9254; Yamaguchi, S.; Mosher, H. S. J Org Chem 1973, 38, 1870.

[6] Vigheron, J. P.; Jacquet, I. Tetrahedron 1976, 32, 939.

[7] Izumi, Y. Angew Chem, Int Ed Engl 1971, 12, 871.

[8] Yoshida, T.; Harada, K. Bull Chem Soc Jpn 1971, 44, 1062.

[9] Nahm, S.; Weinreb, S. Tetrahedron Lett 1981, 22, 3815.

[10] Fehrentz, J. A.; Castro, B. Synthesis 1983, 676.

[11] Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. Synthesis 1998, 1707.

[12] Buckley, T. F., III; Rapoport, H. J Am Chem Soc 1981, 103, 6157.

[13] McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. J Org Chem 1983, 48, 2675.

[14] Soai, K.; Ookawa, A. J Chem Soc, Chem Commun 1986, 412; Datta, A.; Kumar, J. S. R.; Roy, S. Tetrahedron 2001, 57, 1169.

[15] Keller, O.; Keller, W. E.; Wersin, G.; Wersin, G. Org Synth 1985, 63, 160.