Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 1717–1720
Tetrahedron Letters

Efficient preparation of chiral diamines via Red-Al reduction of *N*-Boc-protected amino acid-derived secondary amides

Eric A. Voight,* Matthew S. Bodenstein, Norihiro Ikemoto and Michael H. Kress

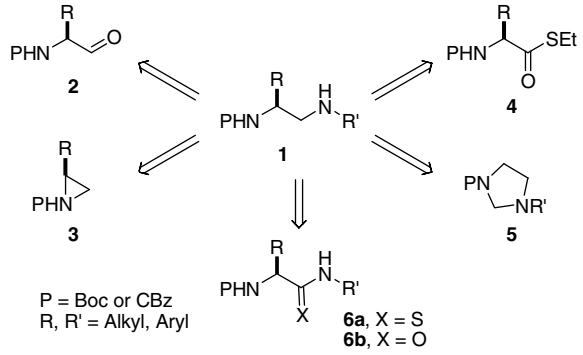
Merck Research Laboratories, Department of Process Research, Merck & Co., 466 Devon Park Drive, Wayne, PA 19087, USA

Received 1 December 2005; revised 11 January 2006; accepted 12 January 2006

Abstract—Conditions have been developed for the selective reduction of *N*-Boc-protected amino acid-derived secondary amides, avoiding the formation of overreduction and cyclic urea byproducts. The method is showcased by the efficient formal synthesis of NK-1 antagonist LY303870.

Vicinal diamines are commonly encountered as synthetic intermediates, drug targets, chiral auxiliaries, and ligands in asymmetric catalysis.[1] For this reason, the efficient preparation of chiral molecules containing a 1,2-diamino moiety is an important objective. Chiral vicinal diamines **1** (Scheme 1), containing a free dialkyl secondary amine and a carbamate protected primary amine, are attractive as peptide surrogates[2] and as precursors to a variety of heterocycles.[3] Several methods have been reported for their synthesis (Scheme 1).

Intermediates **2**–**6** have been reported as precursors to diamines **1** (Scheme 1). α-Aminoaldehydes **2** are commonly used to prepare diamines **1** via reductive amination with a primary amine.[4] Alternatively, aziridines **3** can be opened with primary amines.[5] Unfortunately, syntheses of **2** and **3** can be lengthy, and aldehyde **2** is prone to racemization. An alternative reductive amination approach involves the one-pot conversion of thioesters **4** to **1**.[6] Imidazolidines **5** can be deprotonated with *sec*-butyllithium/(−)-sparteine and reacted with alkyl halides enantioselectively, giving **1** after deprotection.[7] So far, this method remains substrate limited. Finally, thioamide[8] and amide reduction have been utilized to convert amides **6** to diamines **1**. This route appeared particularly attractive for our purposes.



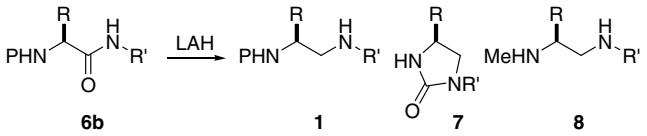
Scheme 1.

While conceptually superior to alternative methods, a general and high-yielding method for the direct reduction of readily available *tert*-butoxycarbonyl(Boc)-protected amino acid-derived secondary amides **6b** to Boc-diamines **1** has, to our knowledge, not been reported in the primary literature.[9] To this end, chemoselective borane reductions of aminoamides **6b** have been reported to give low to moderate yields of secondary amines, due to incomplete reactions and difficulty cleaving the B–N bond following reduction.[10] Notably, the use of lithium aluminum hydride (LAH) leads to significant amounts of cyclic urea **7** and overreduction product **8**, again resulting in low to moderate yields (Scheme 2).[11] These shortcomings are frequently avoided via deprotection prior to reduction, thus losing the differential functional group handle, or through the choice of less desirable amino acid protecting groups.[12]

To overcome these obstacles, a general and efficient reduction protocol to Boc-diamines **11** using inexpensive and widely available Boc-protected amino acids **9** was

* Corresponding author. Tel.: +1 215 652 1566; fax: +1 215 993 2100; e-mail: eric_voight@merck.com

0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.01.056



Scheme 2.

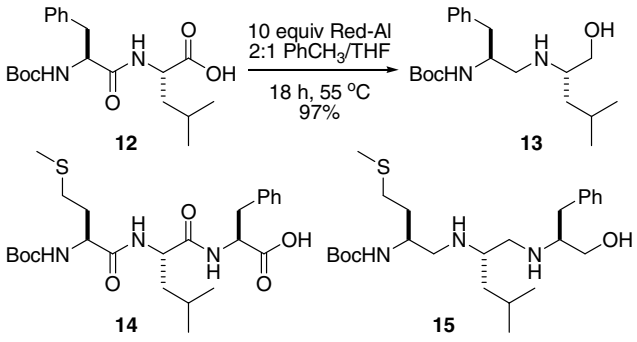
sought. Our experience with borane and LAH reductions of amides **10** gave no improvement over previously reported results in terms of impurity profile or conversion. In contrast, we have found the use of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), to be remarkably effective for this transformation.[13] Routinely provided as an inexpensive 65 wt % solution in toluene, this reagent was found to reduce secondary amides **10** in good to excellent yields with good volume efficiency, reasonable reaction times and temperatures, and minimal amounts of overreduction and cyclic urea byproducts. The results of our studies are shown in Table 1.

Starting from commercially available Boc-protected amino acids **9** (a–g), mixed anhydride formation using *N*-methylmorpholine (NMM), and *iso*-butylchloroformate was followed by the addition of a primary amine ($R'NH_2$).[14,15] Aqueous workup gave crude amides **10** (a–g) which, without further purification, were reduced with Red-Al in 2:1 toluene/THF between 35 and 65 °C.[15] In all cases, good to excellent yields of isolated Boc-diamines **11** (a–g)[16] were observed after aqueous workup and column chromatography. Amino acid R groups from alanine (entries a–c), phenylalanine (entries d–f), and valine (entry g) performed well. Aryl (entries a and g), benzylic (entries b and f), and alkyl (entries c–e) amides were all tolerated in the reaction. Entries e and f, with more sterically hindered amides, required higher temperatures and gave slightly lower yields than other examples.[17]

A particularly noteworthy extension of this methodology was observed in the selective reduction of dipeptide Boc-Phe-Leu-OH (**12**, Scheme 3) to the corresponding Boc-aminoalcohol **13**[16] in 97% isolated yield. Of the three carbonyls in **12**, only the amide and carboxylic acid were reduced, with no evidence of carbamate reduction. Furthermore, tripeptide Boc-Met-Leu-Phe-OH (**14**) was reduced to diaminoalcohol **15**[16] in 79% yield under the same conditions. Using this method, a large variety of chiral aminoalcohols should be easily accessible starting from readily available Boc-polypeptides.[18]

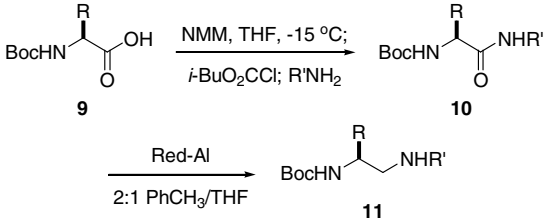
To further demonstrate the utility of this procedure, we carried out a formal synthesis of Eli Lilly NK-1 antagonist LY303870 (Scheme 4).[12] In the published route to this drug target, the authors encountered typical amide reduction problems with Boc-protected secondary amide **17**. For this reason, the triphenylmethyl (trityl) amine protecting group was employed, requiring the use of a noncommercially available tryptophan derivative.

For our formal synthesis, commercially available Boc-D-tryptophan (**16**) underwent amide bond formation with *ortho*-methoxybenzylamine, giving **17**. Amide **17** was then cleanly reduced using 5 equiv Red-Al at 35 °C. Acetylation of the crude Boc-diamine gave acetylamine **18** in 75% overall yield over three steps. To determine



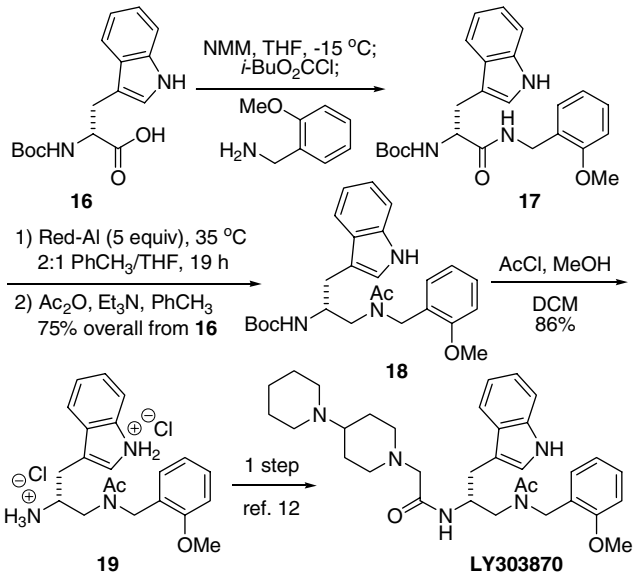
Scheme 3.

Table 1. Results of Red-Al reduction



Entry	R=	R′=	Reduction time (h)	Reduction temperature (°C)	Red-Al (equiv)	Yield[a] (%) (**9**→**11**)
a	Me	Ph	40	35	3	82
b	Me	Bn	24	35	5	75
c	Me	Et	17	35	3	93
d	Bn	Et	36	35	5	76
e	Bn	*t*-Bu	27	65	5	57
f	Bn		16	65	5	68
g	*i*-Pr	Ph	14	40	5	87

[a] Isolated yields after flash column chromatography.



Scheme 4.

whether any epimerization had taken place in the reduction step, the enantiomer of **18** was prepared, and each compound was found to have >99% ee by chiral SFC.[19] Deprotection of **18** was accomplished with methanolic HCl, giving bis-HCl salt **19** with characterization data identical to that in the literature.[12]

In conclusion, a general and high-yielding procedure has been reported using Red-Al for the reduction of a variety of chiral amino acid-derived Boc-protected secondary amides. Extension of this methodology to Boc-polypeptide reduction has also been accomplished. Finally, using this procedure, an efficient formal synthesis of an NK-1 antagonist has been carried out, demonstrating the utility of the method. This protocol should provide an attractive alternative to previously reported methods for chiral Boc-diamine synthesis.

References and notes

1. For a review, see: Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.
2. For examples, see: (a) Thierry, J.; Servajean, V. *Tetrahedron Lett.* **2004**, *45*, 821; (b) Guziec, F. S.; Wasmund, L. M. *Tetrahedron Lett.* **1990**, *31*, 23; (c) Oyamada, H.; Ueki, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 267, and references cited therein.
3. For example, see: Lewis, R. T.; Macleod, A. M.; Merchant, K. J.; Kelleher, F.; Sanderson, I.; Herbert, R. H.; Cascieri, M. A.; Sadowski, S.; Ball, R. G.; Hoogsteen, K. *J. Med. Chem.* **1995**, *38*, 923.
4. For examples, see Refs. 3 and (a) Dinsmore, C. J.; Bergman, J. M.; Bogusky, M. J.; Culberson, J. C.; Hamilton, K. A.; Graham, S. L. *Org. Lett.* **2001**, *3*, 865; (b) Harre, M.; Nickisch, K.; Schulz, C.; Weinmann, H. *Tetrahedron Lett.* **1998**, *39*, 2555.
5. See Refs. 2a and (a) Fukushi, H.; Mabuchi, H.; Terashita, Z.; Nishikawa, K.; Sugihara, H. *Chem. Pharm. Bull.* **1994**, *42*, 551; Tosylate or mesylate displacement has also been reported, potentially also going through an aziridine intermediate: (b) Hu, X. E.; Kim, N. K.; Leoussal, B. *Org. Lett.* **2002**, *4*, 4499; (c) Salituro, F. G.; Baker, C. T.; Court, J. J.; Deininger, D. D.; Kim, E. E.; Li, B.; Novak, P. M.; Rao, B. G.; Pazhanisamy, S.; Porter, M. D.; Schairer, W. C.; Tung, R. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3637; (d) Sajiki, H.; Ong, K. Y.; Nadler, S. T.; Wages, H. E.; McMurry, T. J. *Synth. Commun.* **1996**, *26*, 2511.
6. Han, Y.; Chorev, M. *J. Org. Chem.* **1999**, *64*, 1972.
7. (a) Ashweek, N. J.; Coldham, I.; Haxell, T. F. N.; Howard, S. *Org. Biomol. Chem.* **2003**, *1*, 1532; (b) Coldham, I.; Copley, R. C. B.; Haxell, T. F. N.; Howard, S. *Org. Lett.* **2001**, *3*, 3799.
8. For example, see Ref. 2b.
9. During the preparation of this manuscript, an isolated example of the Red-Al reduction of a chiral Boc-protected amino acid-derived secondary amide was found in the recent patent literature: Liebeschuetz, J. W.; Sheehan, S. M.; Watson, B. M. WO 2004/60872 A1, 22 July 2004.
10. For examples, see Refs. 2c and (a) Manku, S.; Laplante, C.; Kopac, D.; Chan, T.; Hall, D. G. *J. Org. Chem.* **2001**, *66*, 874; (b) Jacobsen, E. J.; Stelzer, L. S.; TenBrink, R. E.; Belonga, K. L.; Carter, D. B.; Im, H. K.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D.; Zhong, W.; Mickelson, J. W. *J. Med. Chem.* **1999**, *42*, 1123.
11. For example, see: He, X.; Raymon, L. P.; Mattson, M. V.; Eldefrawi, M. E.; de Costa, B. R. *J. Med. Chem.* **1993**, *36*, 4075.
12. For example, see: Hipskind, P. A.; Howbert, J. J.; Cho, S.; Cronin, J. S.; Fort, S. L.; Ginah, F. O.; Hansen, G. J.; Huff, B. E.; Lobb, K. L.; Martinelli, M. J.; Murray, A. R.; Nixon, J. A.; Staszak, M. A.; Copp, J. D. *J. Org. Chem.* **1995**, *60*, 7033.
13. An achiral Boc-glycine derivative has been reduced with Red-Al previously: Beylin, V. G.; Colbry, N. L.; Giordani, A. B.; Goel, O. P.; Johnson, D. R.; Leeds, R. L.; Leja, B.; Lewis, E. P.; Lustgarten, D. M.; Showalter, H. D. H.; Secrcel, A. D.; Reily, M. D.; Uhlendorf, S. E.; Zisek, K. A. *J. Heterocycl. Chem.* **1991**, *28*, 517.
14. Shendage, D. M.; Frohlich, R.; Haufe, G. *Org. Lett.* **2004**, *6*, 3675.
15. For example, entry g: Boc-Val-OH (1.0 g, 4.60 mmol) was dissolved in THF (10.0 mL) and cooled to −20 °C under N_2. *N*-Methylmorpholine (0.531 mL, 4.83 mmol) was added and the mixture was allowed to stir for 10 min. Then, *iso*-butylchloroformate (0.635 mL, 4.83 mmol) was added dropwise over 5 min, keeping the temperature ⩽−14 °C. The reaction was allowed to stir for 20 min. Aniline (0.462 mL, 5.06 mmol) was added dropwise over 5 min, maintaining the temperature between −20 and −30 °C. The reaction was kept at −20 °C, then allowed to warm to room temperature over 30 min. Toluene (10 mL) and 1 N HCl (10 mL) were added and the layers were separated. The organic layer was washed with water (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated, giving a glassy solid. THF (1.5 mL) and toluene (3.1 mL) were added with stirring, and the mixture was cooled to <5 °C. Red-Al (6.90 mL, 23.0 mmol) was added dropwise, keeping the temperature ⩽20 °C. The clear solution was heated to 40 °C. After 14 h, the solution was cooled to <5 °C and 5 N NaOH (10 mL) was added carefully, keeping the temperature <25 °C. After stirring for 20 min at room temperature, toluene (30 mL) was added, the layers were separated, and the organic layer was washed with 5 N NaOH (2 × 10 mL) and concentrated. Purification by flash column chromatography (10–30% MTBE/hexanes) gave **11g** (R = *i*-Pr, R′ = Ph, 1.11 g, 3.99 mmol, 87% yield).

16. Selected characterization data: **11a**: ^{1}H NMR ($CDCl_3$): δ 7.3–7.1 (m, 2H), 6.8–6.6 (m, 3H), 4.52 (br s, 1H), 4.0–3.9 (br m, 1H), 3.15 (ABX, $J_{AB} = 12.5$ Hz, $J_{AX} = 5$ Hz, $J_{BX} = 7.5$ Hz, $\Delta\nu_{AB} = 24.5$ Hz, 2H), 1.46 (s, 9H), 1.23 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 156.0, 147.9, 129.3 × 2, 117.8, 113.0 × 2, 79.6, 50.8, 46.4, 28.4 × 3, 19.1. Compound **11b**: ^{1}H NMR ($CDCl_3$): δ 7.4–7.2 (m, 5H), 3.80 (ABq, $J_{AB} = 13.5$ Hz, $\Delta\nu_{AB} = 13$ Hz, 2H), 3.8–3.7 (br m, 1H), 2.64 (ABX, $J_{AB} = 12$ Hz, $J_{AX} = 5$ Hz, $J_{BX} = 6.5$ Hz, $\Delta\nu_{AB} = 12.5$ Hz, 2H), 1.46 (s, 9H), 1.15 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 155.7, 140.4, 128.4 × 2, 128.1 × 2, 127.0, 79.1, 59.2, 54.5, 53.8, 28.5 × 3, 19.3. Compound **11c**: ^{1}H NMR ($CDCl_3$): δ 4.74 (br s, 1H), 3.8–3.6 (br m, 1H), 2.7–2.5 (m, 4H), 1.42 (s, 9H), 1.10 (d, $J = 6.5$ Hz, 3H), 1.06 (t, $J = 7$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 155.7, 79.1, 54.9, 46.2, 44.0, 28.4 × 3, 19.3, 15.3. Compound **11d**: ^{1}H NMR ($CDCl_3$): δ 7.3–7.1 (m, 5H), 4.90 (d, $J = 7$ Hz, 1H), 4.0–3.8 (br m, 1H), 2.9–2.5 (m, 6H), 1.39 (s, 9H), 1.04 (t, $J = 7$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 155.8, 138.2, 129.4 × 2, 128.4 × 2, 126.3, 79.1, 51.9, 51.5, 44.0, 39.3, 28.4 × 3, 15.3. Compound **11e**: ^{1}H NMR ($CDCl_3$): δ 7.4–7.1 (m, 5H), 4.90 (br s, 1H), 3.9–3.7 (br m, 1H), 2.89 (dd, $J = 13.5$, 6 Hz, 1H), 2.74 (dd, $J = 13.5$, 7.5 Hz, 1H), 2.7–2.5 (m, 2H), 1.42 (s, 9H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 155.7, 138.5, 129.4 × 2, 128.4 × 2, 126.3, 79.1, 52.2, 50.2, 44.5, 39.0, 29.1 × 3, 28.4 × 3. Compound **11f**: ^{1}H NMR ($CDCl_3$): δ 7.4–7.1 (m, 10 H), 4.84 (d, $J = 7$ Hz, 1H), 3.90 (br s, 1H), 3.75 (q, $J = 6.5$ Hz, 2H), 2.84 (br d, $J = 6.5$ Hz, 2H), 2.55 (ABX, $J_{AB} = 12.5$ Hz, $J_{AX} = 6$ Hz, $J_{BX} = 5.5$ Hz, $\Delta\nu_{AB} = 13.5$ Hz, 2H), 1.46 (s, 9H), 1.36 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 155.7, 145.7, 138.3, 129.5 × 2, 128.5 × 2, 128.4 × 2, 127.0, 126.8 × 2, 126.4, 79.1, 58.3, 51.6, 50.1, 39.0, 28.5 × 3, 24.3. Compound **11g**: ^{1}H NMR ($CDCl_3$): δ 7.3–7.0 (m, 2H), 6.8–6.5 (m, 3H), 4.54 (br d, $J = 8$ Hz, 1H), 4.04 (br s, 1H), 3.8–3.6 (br m, 1H), 3.27 (dd, $J = 12$, 4 Hz, 1H), 3.04 (br t, $J = 12$ Hz, 1H), 1.88 (oct, $J = 7$ Hz, 1H), 1.47 (s, 9H), 1.01 (d, $J = 7$ Hz, 3H), 0.98 (d, $J = 7$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 156.7, 148.5, 129.3 × 2, 117.3, 112.7 × 2, 79.5, 55.6, 47.1, 30.6, 28.4 × 3, 19.5, 18.1. Compound **13**: ^{1}H NMR ($CDCl_3$): δ 7.4–7.1 (m, 5H), 4.60 (br s, 1H), 3.80 (br m, 1H), 3.59 (dd, $J = 10.5$, 4 Hz, 1H), 3.22 (dd, $J = 10.5$, 6.5 Hz, 1H), 2.82 (ABX, $J_{AB} = 13.5$ Hz, $J_{AX} = 6.5$ Hz, $J_{BX} = 7$ Hz, $\Delta\nu_{AB} = 24.5$ Hz, 2H), 2.65 (d, $J = 6$ Hz, 2H), 2.7–2.5 (m, 1H), 1.59 (non, $J = 7$ Hz, 1H), 1.42 (s, 9H), 1.4–1.1 (m, 2H), 0.88 (d, $J = 7$ Hz, 3H), 0.88 (d, $J = 7$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 155.9, 137.9, 129.3 × 2, 128.5 × 2, 126.5, 79.5, 63.7, 57.0, 51.9, 49.8, 41.4, 39.4, 28.4 × 3, 25.0, 23.1, 22.7. Compound **15**: ^{1}H NMR ($CDCl_3$): δ 7.4–7.0 (m, 5H), 5.10 (br s, 1H), 3.7–3.5 (br m, 1H), 3.60 (dd, $J = 10.5$, 3.5 Hz, 1H), 3.35 (dd, $J = 10.5$, 5.5 Hz, 1H), 2.9–2.2 (m, 10H), 2.07 (s, 3H), 1.7–1.3 (m, 3H), 1.42 (s, 9H), 1.3–1.0 (m, 3H), 1.16 (s, 3H), 0.84 (d, $J = 6.5$ Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 155.9, 139.0, 129.2 × 2, 128.5 × 2, 126.3, 79.2, 63.3, 55.9, 50.6, 50.4, 50.1, 42.7, 38.4, 32.8, 31.0, 28.5 × 3, 27.0, 25.0, 23.1, 22.8, 15.7.

17. The stereochemical integrity of each reduction was assumed based on the analysis of compound **18** (Scheme 4).

18. Fmoc-Phe-Ala-OMe has been previously reduced in 60% yield using $LiBH_4$/TMSCl: Giannis, A.; Sandhoff, K. *Angew. Chem.* **1989**, *101*, 220.

19. Chiral SFC method: Chiralpak AD-H column; 4% MeOH/CO_2, ramp to 40% MeOH/CO_2 at 2% per min with a 3 min hold at 40% MeOH; 1.5 mL/min; 200 bar; 35 °C; 215 nm; retention times: (*R*)-**18** = 16.8 min, (*S*)-**18** = 15.5 min.