Mild Oxidative Cleavage of Borane−Amine Adducts from Amide Reductions: Efficient Solution- and Solid-Phase Synthesis of *N*-Alkylamino Acids and Chiral Oligoamines

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Received November 19, 1998

Unsymmetrical secondary amines such as oligoamines and *N*-alkylamino acids possess a wide range of biological properties and potential applications in drug discovery.[1] For instance, *N*-alkylamino acids are useful intermediates in the solid-phase organic synthesis (SPOS) of small-molecule libraries.[2] They are generally synthesized by reductive alkylation of primary amines,[3] a rather capricious reaction particularly inefficient with small unbranched aliphatic aldehydes, such as formaldehyde, which tend to give over-alkylation and cross-linking.[4] Alternatively, the reduction of amides[6] and peptides[7] with diborane is a very general method for the synthesis of secondary amines in the solution phase. However, traditional workup procedures effect cleavage of the resulting borane−amine adducts under strongly acidic conditions (e.g., refluxing aqueous 1 N HCl). Such treatment is clearly not desirable in SPOS as most resin linkers would be incompatible.[8] Similarly, the use of a basic workup to dissociate borane−amine adducts by ligand exchange[9] usually requires extended reaction times and temperatures higher than ambient.[10,11]

Scheme 1

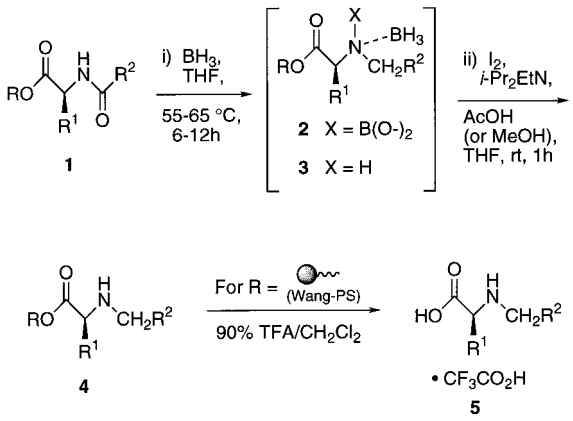

Table 1. Solid-Phase Synthesis of *N*-Alkylamino Acids 5[a]

	R (in **1**)	R^1	R^2	Yield[b] (%)	Purity[c] (%)
a	(Wang-PS)	CH_3	H	72	75
b	"	$CH(CH_3)_2$	H	84	90
c	"	CH_2O-*t*-Bu	H	86[d]	90
d	"	CH_2Ph	H	73	> 90
e	"	CH_2Ph	CH_3	66	> 90
f	"	$CH(CH_3)_2$	CH_3	69	95
g	"	$CH(CH_3)_2$	CH_2CH_3	74	95

[a] Typical scale 0.1−0.5 g. Obtained and characterized as trifluoroacetate salts. [b] Crude yield of product according to the loading level of starting commercial resin (pre-amino acid loaded). [c] Determined by ^{1}H NMR and RP-HPLC.[19] [d] Obtained as a free alcohol (cleavage cocktail containing 2% EDT).

Herein, we report on a mild and highly practical workup procedure for the synthesis of secondary amines from the diborane reduction of secondary amides. It employs iodine to promote the fast oxidative cleavage of borane−amine adducts. This preliminary account discloses the solution- and solid-phase synthesis of *N*-alkylamino acids that are difficult to obtain by reductive amination, and chiral oligoamines derived from peptides. When performed on solid-support, this mild method prevents premature release of products from acid-sensitive resins and provides free secondary amines that can be further derivatized.

As shown in Scheme 1, the complete reduction of a secondary amide such as the *N*-acylamino acids **1** requires six hydride equivalents and leads to an aminoborane borane−amine intermediate (**2**) that must be cleaved cleanly to afford the desired secondary amine **4**.[6] Whereas aminoborane moieties are easily protolyzed,[12] borane−amine adducts (e.g., **3**) are extremely robust.[13] However, it has been suggested that they can be titrated with iodine in a process that ultimately liberates the amine.[14] We have adapted this method to resin-bound or sensitive substrates by using a buffered solvent system to trap the released hydriodic acid. As shown in Table 1, diverse *N*-acylamino acids attached to Wang 1% DVB polystyrene resin were monoalkylated successfully. Typically, resin-bound *N*-formyl amino acids **1a**−**d** were treated with diborane (3.0−3.5 equiv) at 55 °C for 6 h, while other *N*-acyl derivatives (**1e**−**g**) required slightly more rigorous conditions (3.5−4.0 equiv BH_3, 65 °C, 6−12 h). As expected, the 4-alkoxybenzyl ester linker (Wang) is highly

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(1) For instance, *N*-methylamino acids are important constituents of the therapeutically promising class of *N*-methylated peptides. Recent example: Schmidt, R.; Kalman, A.; Chung, N. N.; Lemieux, C.; Horvath, C.; Schiller, P. W. *Int. J. Pept. Protein Res.* **1995**, *46*, 47.

(2) For reviews, see: (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (b) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288.

(3) For selected examples, see: (a) Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47. (b) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 6090. (c) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800. (d) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1998**, *63*, 4808.

(4) Alternatively, two groups recently reported a three-step sequence for amino acid N-methylation centered either on base-promoted alkylation[5a] or on the Mitsunobu reaction[5b] of sulfonamide derivatives. The scope of these methods, however, was not demonstrated beyond N-methylation.

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(6) (a) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912. (b) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 441. (c) Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315. (d) Bonnat, M.; Hercouet, A.; Le Corre, M. *Synth. Commun.* **1991**, *21*, 1579.

(7) (a) Roeske, R. W.; Weitl, F. L.; Prasad, K. U.; Thompson, R. M. *J. Org. Chem.* **1976**, *41*, 1260. (b) Northrop, R. C., Jr.; Russ, P. L. *J. Org. Chem.* **1977**, *42*, 4148. (c) Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem.* **1991**, *56*, 5196. (d) Cuervo, J. H.; Weitl, F.; Ostresh, J. M.; Hamashin, V. T.; Hannah, A. L.; Houghten, R. A. In *Peptides 1994, Proceedings of the 23rd European Peptide Symposium*; Maia, H. L. S., Ed.; ESCOM: Leiden, 1995; p 465.

(8) For an example of a solid-phase synthesis of triamines from peptides on Merrifield resin, see: Nefzi, A.; Ostresh, J. M.; Meyer, J.-P.; Houghten, R. A. *Tetrahedron Lett.* **1997**, *38*, 931. Therein, acidic cleavage of borane−amine adducts is carried out with 1 M HCl/MeOH (65 °C, >12 h). Also, with this support, product cleavage with HF requires special equipment.

(9) (a) Reetz, T. *J. Am. Chem. Soc.* **1960**, *82*, 5039. (b) Baldwin, R. A.; Washburn, R. M. *J. Org. Chem.* **1961**, *26*, 3549. (c) Young, D. E.; McAchran, G. E.; Shore, S. G. *J. Am. Chem. Soc.* **1966**, *88*, 4390.

(10) For examples of amide reductions, see: (a) Paikoff, S. J.; Wilson, T. E.; Cho, C. Y.; Schultz, P. G. *Tetrahedron Lett.* **1996**, *37*, 5653. (b) Brown, P. J.; Hurley, K. P.; Stuart, L. W.; Willson, T. M. *Synthesis* **1997**, 778.

(11) For a recent example of peptide reduction/piperidine treatment on methylbenzhydrylamine polystyrene resin followed by HF cleavage, see: Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622.

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10.1021/jo982290w CCC: $18.00
Published on Web 01/12/1999

Table 2. Synthesis of *N*-Alkylamino Acid Esters 4[a]

	R	R^1	R^2	yield[b] (%)	purity[c] (%)
h	$C(CH_3)_3$	CH_2Ph	H	84	>90
i	CH_3	CH_2Ph	CH_3	86	90
j	CH_3CH_2	$CH(CH_3)CH_2CH_3$[d]	CH_2CH_3	71	>90

[a] Obtained and characterized as free amines. [b] Crude yield of product. [c] Determined by ^{1}H NMR. [d] Isoleucine (Ile).

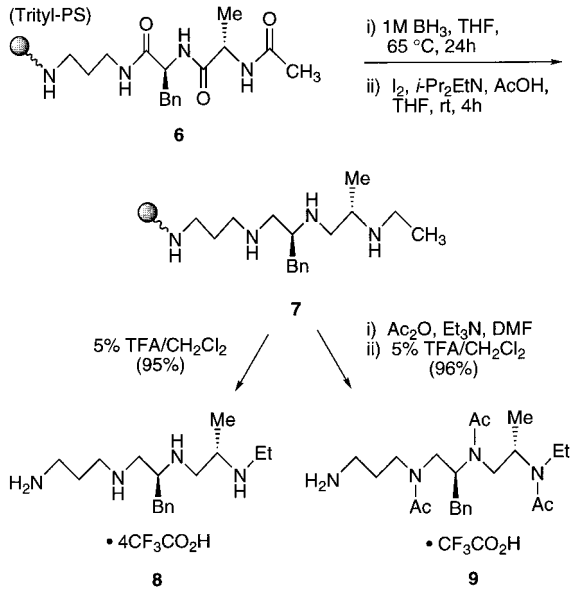
resistant to the diborane reduction step, especially with hindered amino acids (Phe, Val).[15] After the reduction step and extensive washing, the resin was swelled in a THF−AcOH−*i*-Pr_2EtN buffer solvent mixture (approximately 7:2:1, pH ∼5).[17] Methanol can be used as a proton source in place of acetic acid if a higher pH is required. Then, iodine (2 equiv in THF) was added, and the mixture was shaken for 1 h during which time the purple solution became discolored as the iodine was consumed. All steps can be monitored qualitatively with the bromophenol blue (BPB) assay.[18] The resulting *N*-methyl- and other *N*-alkylamino acid acids were then released from the Wang resin to give the corresponding trifluoracetate salts **5a**−**g**, generally in good yields and with a high degree of purity as determined by ^{1}H NMR and RP-HPLC[19] analysis.

In addition, a sample of newly formed resin-bound **4d** was protected as a Fmoc carbamate and then cleaved from the support and purified. Its optical rotation was found to be identical, within reasonable error, to an authentic commercial sample of Fmoc-MePhe-OH, showing that this N-alkylation process occurs with no apparent epimerization.

We have also applied this iodine-based workup procedure to solution-phase synthesis (Table 2). As shown with **4h**, its mildness allowed the isolation of sensitive *N*-alkylamino acid *tert*-butyl esters that could not be obtained with a traditional acidic workup. Compounds **4h**−**j** were obtained and characterized as free bases, constituting definitive evidence that borane−amine cleavage in the solid-phase examples (Table 1) is truly occurring through the action of iodine and is therefore not resulting from the acidolytic release of final products from the resin.

Since a mild and general method for the solid-phase synthesis of oligoamines has yet to be achieved on practical acid-sensitive resins, we wished to extend the new oxidative workup to the construction of chiral oligoamines derived from peptides. To this end, we have found that a mild acid-labile aminotrityl linker was highly appropriate. It is

Scheme 2



resistant to stringent reduction conditions and the ensuing workup, and the final oligoamines can be liberated upon treatment with dilute TFA. As a significant example, diborane reduction of model tripeptide **6** followed by iodine treatment and cleavage of resin **7** gave a high yield of essentially pure tetraamine **8** isolated and characterized (NMR, ES-MS) as its tetrakis(trifluoroacetate) salt (Scheme 2). According to ^{1}H NMR analysis, the absence of diastereomeric methyl signals in **8** is favorable evidence that in addition to the benzyl side chain (vide supra) no epimerization occurs at the N-terminal alanine center either. Indeed, the ^{13}C NMR spectrum of tetraamine salt **8** shows a single diastereomer. It was also further characterized as its triacetylated derivative **9**, which was isolated with >95% purity as determined by RP-HPLC analysis.[21] To our knowledge, the only reported example of such a chiral oligo(*N*-acylaziridines) synthesis employed the cationic ring-opening polymerization of 2-oxazolines.[22] By allowing control on oligomer sequence and length, the current solid-phase synthetic route to these oligoamides (i.e., **6** → **7** → **9**) is highly advantageous.

In conclusion, we have developed a new oxidative workup using iodine to cleave borane−amine adducts from the reduction of amides and peptides with diborane. This mild and practical method, compatible with acid-sensitive resin linkers and protective groups, serves as a general solution- and solid-phase procedure for the synthesis of unsymmetrical secondary amines. Herein, we have demonstrated its use for the efficient synthesis of *N*-methyl- and other *N*-alkylamino acids that are difficult to obtain by reductive amination. In addition, this method is the first one to provide chiral oligoamines and oligo(*N*-acylaziridines) from peptides attached to the popular trityl resin. We are currently exploring promising combinatorial library applications of this effective solid-phase synthesis of chiral oligoamines.

Acknowledgment. This work was funded by the National Science and Engineering Research Council (NSERC) of Canada and the University of Alberta.

Supporting Information Available: Experimental details for the synthesis and selected NMR, MS, and HPLC data for all compounds.

JO982290W

(15) It was found that the reduction of unhindered *N*-acylamino acids such as **1a** is accompanied by significant loss of material from the resin, presumably through reductive cleavage of the ester-based linker (ref 16) if more then 3 equiv of diborane is employed.

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(17) **General Procedure.** Solid phase (Table 1): A portion of resin **1** (200 mg, made from the acylation of preloaded resin from Novabiochem) was weighed out into a 10 mL silanized round-bottom flask and swelled in dry THF (1−2 mL) under nitrogen. The diborane solution (1 M in THF, 3−4 equiv, see text) was added dropwise at room temperature, after which the flask was equipped with a condenser and the suspension stirred gently at 55−65 °C for 6−12 h (see the text for exact conditions). Upon cooling to room temperature, the resin suspension was transferred with a silanized pipet to a small polypropylene filter vessel by using dry THF to rinse out the flask and wash the resin. Then, THF (2.0 mL), diisopropylethylamine (0.4 mL), and glacial acetic acid or methanol (0.8 mL) were added. To the homogenized suspension was added iodine (2 equiv as a concentrated THF solution), and the vessel was shaken for 1 h. Then, the resin was washed (3× each) with THF, DMF/Et_3N 3:1, MeOH, and CH_2Cl_2 and dried under high vacuum for >12 h.

(18) Beads bearing the resulting borane−amine complex give a negative on the BPB test (yellow-green beads). A strong positive result (dark blue beads) is obtained following oxidative workup and neutralizing washes of the resin-bound secondary amine.

(19) Performed with precolumn derivatization as a Fmoc carbamate.[20] Column: Zorbax SB-C18 (4.6 × 150 mm, 5 mm). Eluent: linear gradient of 60−20% 0.1% aqueous TFA/acetonitrile over 20 min. Flow rate: 1 mL/min. Analysis: UV diode-array detection, 190−400 nm.

(20) Einarsson, S.; Josefsson, B.; Lagerkvist, S. *J. Chromatogr.* **1983**, *282*, 609.

(21) Conditions similar to those of ref 19 except for the eluent: 60−10% over 50 min.

(22) Saegusa, T.; Kobayashi, S.; Ishiguro, M. *Macromolecules* **1974**, *7*, 958.