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9-BBN: An Amino Acid Protecting Group for Functionalization of Amino Acid Side Chains in Organic Solvents

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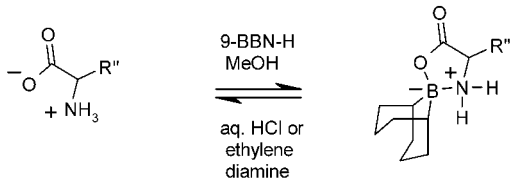
ABSTRACT



9-Borabicyclononane (9-BBN) has been utilized to protect functionalized amino acids for potential chemoselective side chain manipulation. The 9-BBN group imparts organic solubility to otherwise hydrophilic molecules and is tolerant of a wide range of reaction conditions. The high degree of solubility of these molecules in THF is particularly noteworthy. It is cleaved with either aqueous HCl or by exchange with ethylenediamine in methanol.

Electrophilic atoms have long been used to complex amino acids into five-membered rings.[1,2] Complexes with boron, in particular, have gained popularity owing to their ease of manipulation and mild conditions required for conversion back to the parent amino acid. Heterocycle **1** first appeared in the German patent literature.[3] Subsequent reports included the preparation of complexes **2** with alkyl groups, hydrogens, and halogens on boron[4] and preparation of complexes **3** with nonfunctionalized, lipophilic amino acid side chains.[5,6] Despite the extension of this technology to a wide variety of amino acids, applications using these complexes have been limited. Nefkens and Zwanenburg were among the first researchers to recognize the potential utility of these complexes, stating that the boroxazolidinone complexes **1** and **2a** "can serve as protected amino acids... while the side chain remains free for further reactions".[6] In this and related work,[7] aspartic and glutamic acids were converted to β- and γ-benzyl, *p*-nitrophenol, and Fmoc protected analogues. The carboxylate side chain of the aspartic acid complex has also been chemoselectively reduced with borane.[8] Complex **2a**, derived from glycine, was reacted with aromatic aldehydes to form imines and subsequently cyclized to form isoquinoline and isoindolinone derivatives.[9] In another enolate application, asymmetric alkylation reactions have been employed to functionalize only the amino acid α-carbon and not the side chain.[10] Finally, oxazaborolidinone complexes have found further utility as complexing agents to purify

(1) Copper: (a) Ojima, I.; Inaba, S. *Tetrahedron Lett.* **1980**, *21*, 2077. (b) Schwyzer, R.; Rittel, W. *Helv. Chim. Acta* **1961**, *44*, 159. (c) Neuberger, A.; Sanger, F. *Biochem. J.* **1943**, *37*, 515. (d) Sato, M.; Okawa, K.; Akabori, S. *Bull. Chem. Soc. Jpn.* **1957**, *30*, 937.

(2) Nickel: Belekon, Y. N.; Dolgoya, M. M.; Kuznetsova, N. I.; Vitt, S. V.; Belikov, V. M. *Izv. Akad. Nauk. SSSR. Ser. Khim.* **1973**, 156.

(3) Lang, K.; Nuetzel, K.; Schubert, F. German Patent 1130445, 1962; *Chem. Abstr.* **1963**, *58*, 1488a.

(4) (a) R = Ph: Skoog, I. H. *J. Org. Chem.* **1964**, *29*, 492. Baum, G. *J. Organomet. Chem.* **1970**, *22*, 269. (b) R = Et: Koster, R.; Rothgery, E. *Liebigs Ann. Chem.* **1974**, 112. (c) R = H: Miller, N. E. *Inorg. Chem.* **1974**, *13*, 1459. (d) R = F: Halstrom, J.; Nebelin, E.; Pedersen, E. J. *J. Chem. Res.* **1978**, 80. (e) R = Ipc: Brown, H. C.; Gupta, A. K. *J. Organomet. Chem.* **1988**, *34*, 73.

(5) Reference 4e: R″ = H, methyl, *i*-propyl, phenyl, benzyl.

(6) Nefkens, G. H. L.; Zwanenburg, B. *Tetrahedron* **1983**, *39*, 2995.

(7) Albericio, F.; Nicolas, E.; Rizo, J.; Ruiz-Gayo, M.; Pedroso, E.; Giralt, E. *Synthesis* **1990**, 119.

(8) Gong, B.; Lynn, D. G. *J. Org. Chem.* **1990**, *55*, 4763.

(9) Nefkens, G. H. L.; Zwanenburg, B. *Tetrahedron* **1985**, *41*, 6063.

(10) Vedejs, E.; Fields, S. C.; Lin, L. S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3028.

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amino acid/peptide mixtures[11] and to upgrade the optical purity of borane precursors.[4e]

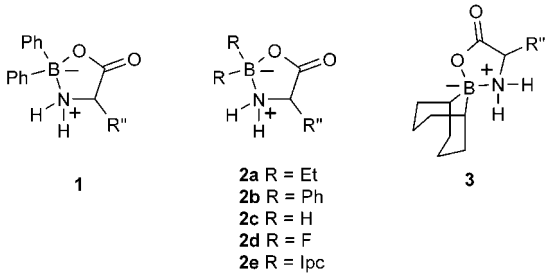
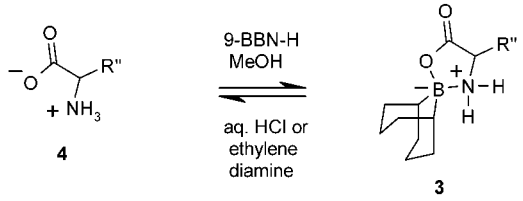


Figure 1. Boron complexes of amino acids.

In the course of synthesizing several ornithine-based natural products,[12] we were presented with two challenges. First, we desired to differentiate between the side chain functional groups and the amino acid functionality. Second, we desired to perform nonaqueous reactions despite the fact that amino acids are only soluble in water. One of the most difficult cases of functional group differentiation, one might imagine, would be selecting between the two primary amino groups of the amino acids lysine and ornithine. Selective complexation of the α-amine of lysine has been reported in the literature via copper and diethylboryl complexes.[6] However, these complexes were generally soluble in few organic solvents.[13] In particular, the diethylboryl complex **2a** of lysine ($R = CH_2CH_2NH_2$) can only be made in polar solvents such as DMF or DMSO (60% yield) and crystallizes with a mole of adherent solvent.[6] We reasoned that in order to infer greater organic solubility to these complexes, one could increase the lipophilicity of the substituents attached to the complexing agent. We settled on 9-borabicyclononane (9-BBN) owing to its high degree of lipophilicity and its commercial availability.[14] While such complexes have previously been prepared, the advantages of this particular substituent for boron have not been utilized to its full extent.[5,6,15]

In a typical preparative procedure, a slight excess of commercially available crystalline 9-BBN dimer was dissolved in hot methanol and heated to reflux with free amino acid **4**. The suspension became nearly homogeneous over 1 h. Filtration of unreacted amino acid and evaporation of the methanol, followed by trituration of the gummy residue with hexanes, afforded ^{1}H NMR pure **3**, which was best used without further purification.[16]

Scheme 1



This protecting group could be removed without epimerization of the amino acid under extremely mild conditions, either by exchange with ethylenediamine (heat to reflux for 30 s in methanol, followed by trituration with diethyl ether to remove excess ethylenediamine and the 9-BBN complex) or dilute methanolic HCl.[6] Examination of several other functionalized amino acids revealed that the favorable soluble properties and good yields for preparation and cleavage of the complexes was general (Tables 1 and 2).

Table 1. Formation and Cleavage of 9-BBN Complexes

entry	R	formation % yield[a]	cleavage A[b]	cleavage B[c]
3a	$(CH_2)_4NH_2$ lysine	90	78	91
3b	$(CH_2)_3NH_3Cl$ ornithine HCl	96	75	94
3c	C_6H_5OH tyrosine	92	89	94
3d	CH_2OH serine	86	62	*d*
3e	CH_2SH cysteine	50	75	83
3f	CH_2CO_2H aspartic acid	98	80	76
3g	$(CH_2)_3NHC(=NH)NH_2$ arginine	70	78	62

[a] See Supporting Information for specific details. [b] Aqueous HCl cleavage. [c] Ethylenediamine cleavage. [d] Oiled out as a complex mixture of borylated products that were difficult to purify.

In contrast to the aforementioned copper and diethylboryl complexes with lysine, we found the analogous 9-BBN derivative to be remarkably soluble in THF, acetone, dioxane, DMF, methanol, and water, while it was insoluble in diethyl ether, hexane, and the halocarbons. This prompted us to

(11) Strang, C. J.; Henson, E.; Okamoto, Y.; Paz, M. A.; Gallop, P. M. *Anal. Biochem.* **1989**, *178*, 276.

(12) (a) *9-BBN-Protected Amino Acids and Their Use in Natural Product Synthesis.* Fields, S. C.; Graupner, P. L.; Tromiczak, E. G. Oral presentation at the Gulf Coast Chemistry Conference, September 19, 1996, Pensacola, FL. (b) *Pyridazocidin: A Novel Quaternary Amine Phytotoxin.* Chapin, E. L.; Cleveland, J. A.; Fields, S. C.; Gerwick, B. C.; Graupner, P. R. Poster Presentation at the American Chemical Society for Pharacognosy, May 10, 1996. (c) *9-BBN-Protected Amino Acids and Their Use in Natural Product Synthesis. Part I. Electrophilic Reactions. Total Synthesis of Octicidin.* Dent, W. H.; Fields, S. C.; Graupner, P. R.; Tromiczak, E. G. Poster presentation at the CU-Roche/Syntex Symposium, May 22, 1996, Boulder, CO. (d) *9-BBN-Protected Amino Acids and Their Use in Natural Product Synthesis. Part II. Nucleophilic Reactions. Total Synthesis of Pyridazocidin.* Fields, S. C.; Gerwick, B. C.; Graupner, P. R.; Tromiczak, E. G. Poster presentation at the CU-Roche/Syntex Symposium, May 22, 1996, Boulder, CO.

(13) In fact, we were unable to react lysine with triethylborane in a variety of solvents. We ultimately obtained this complex by reacting diethylborinic acid with lysine in aqueous methanol.

(14) Aldrich: $4.11/g, available as the crystalline dimer.

(15) Gonzalez, A.; Granell, J.; Piniella, J. F.; Alvarez-Larena, A. *Tetrahedron* **1998**, *54*, 13313.

(16) If the complexes are further purified to powders rather than using the initially formed amorphous solids "as is", they generally require greater effort (e.g., sonication) to redissolve in organic solvents, but they will redissolve. This is most likely a result of the micelle-like ordering of the complexes, which interferes with solvation in solvents of low to medium polarity.

Table 2. Solubility Properties of 9-BBN Complexes of α-Amino Acids[a]

solvent	lysine[17] **3a**	ornithine HCl[17] **3b**	tyrosine **3c**	serine **3d**	cysteine **3e**	aspartic acid **3f**	arginine **3g**
ether	I	I	I	I	I	SS	I
THF[16]	VS	I	VS	VS	VS	VS	S
EtOAc[16]	SS	I	VS	SS	VS	VS	VS
CH_3CN[16]	S	I	VS	I	VS	VS	I
acetone[16]	VS	I	VS	VS	VS	VS	VS
DMF	VS	VS	VS	VS	VS	VS	VS
DMSO	VS	VS	VS	VS	VS	VS	VS
CH_3OH	VS	VS	VS	VS	VS	VS	VS
EtOH	VS	VS	VS	VS	VS	VS	VS
$CHCl_3$	I	I	I	I	I	I	I
CH_2Cl_2	I	I	I	I	I	I	I
H_2O	VS	VS	I	I	I	I	I

[a] I = insoluble, SS = slightly soluble (0.05 M), S = soluble (0.1 M), VS = very soluble (0.5 M).

examine whether these favorable solubility properties held true with other amino acids. As apparent from Table 2, 9-BBN can be used to impart organic solubility to all of the other side chain functionalized amino acids we tested with the exception of the hydrochloride salts of the basic amino acids lysine and ornithine.[17] In addition, histidine was the only amino acid that we tried that did not form a stable complex. An additional advantage of these complexes is that there is a significant chromophore at 220 nm, which makes monitoring reactions via HPLC with UV detection more practical. The exclusive formation of the five-membered oxazaborolidinones **3** is in agreement with the findings of Nefkens and Zwanenburg in the case of their ethyl and phenyl substituted series.[6]

In our own studies, the 9-BBN protecting group has been found to be amazingly tolerant of a wide variety of reaction conditions. While not exhaustively researched, we have had occasion to treat complexes **3** with alkyl halides, acid halides, sulfur trioxide, ammonia, $POCl_3$, $PSCl_3$, *m*-chloroperoxybenzoic acid (*m*CPBA), monoperoxyphthalic acid magnesium salt (MMPP), Arbusov conditions (110 °C, neat triethyl phosphite), and Finkelstein conditions (refluxing sodium iodide, acetone). Each of these reagents has been used without incidental cleavage of the oxazaborolidinone, although it is necessary to include an HCl scavenger such as triethylamine when HCl may be produced. The fact that none of the aforementioned reaction conditions caused reaction at the complexed amine or cleaved the oxazaborolidinone is significant for another reason. As has been previously observed, this complex demonstrates the strength of the boron−nitrogen bond and the unavailability of the vacant π-orbital of boron and the nitrogen lone pair of electrons that normally dominate the reactivity of these atoms. The use of oxidants is particularly noteworthy because this is generally how products from olefin hydroboration are cleaved to alcohols.[18]

In summary, 9-borabicyclononane (9-BBN) can be used to protect functionalized amino acids for chemoselective side chain manipulation. The 9-BBN group imparts organic solubility to otherwise hydrophilic molecules and is tolerant of a wide range of reaction conditions. The protecting group is removed under mild conditions by treatment with either aqueous HCl or by exchange with ethylenediamine in methanol. A paper describing the use of this protecting group for the synthesis of several ornithine-based natural products is forthcoming.

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Supporting Information Available: Experimental details of the formation, cleavage and solubility studies of all complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) While the 9-BBN complexes of lysine and ornithine are soluble in THF, EtOAc, CH_3CN, and acetone, the HCl salts of these complexes are not *once they have been purified to homogeneity* (see Table 2).

(18) Zweifel, G.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 2066.