Direct Synthesis of [α-[(*tert*-Butoxycarbonyl)amino]alkyl]-boronates from (α-Haloalkyl)boronates

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Introduction

α-Carboxamido boronic acids or boropeptides have been extensively studied as inhibitors of serine proteases.[1b] Thrombin, factor Xa (fXa), and factor VIIa (fVIIa) are serine proteases of the blood coagulation cascade that play important roles in the formation of blood clots. Inhibitors of thrombin, fXA, and fVIIa have potential as antithrombotic agents for the treatment of thromboembolic disorders. D-Phe-Pro-BoroArg (DuP 714), one of the most potent thrombin inhibitors, has been extensively investigated as an antithrombotic agent. Protein crystallography studies of thrombin-DuP 714 complex have revealed that the active-site serine hydroxyl forms a covalent bond with the boron atom of the inhibitor.[1] The ability of highly electron-deficient sp^2 boron species to accept a nucleophilic hydroxyl from the Ser-His-Asp catalytic triad with great ease makes boropeptides very attractive transition state analogs of serine proteases.[2] In general, α-carboxamido boronates are obtained in three steps from α-chloro boronates.[3−5] The reported procedure involves the use of [α-(hexamethylsilylamino)-alkyl]boronate, which is difficult to handle on large scale because of its instability at ambient temperatures. We became interested in investigating alternative approaches for the synthesis of α-carboxamido boronates since large quantities of boropeptides were needed for preclinical studies. We thought that it may be possible to form boropeptides in one step by nucleophilic displacement of highly electrophilic α-chloro boronates with *N*-metalated carbamates or amides. Synthesis of α-carboxamido boronates from α-chloro boronates has been unsuccessfully attempted.[6] Treatment of *N*-lithioacetamide with α-chloroboronate resulted in the formation of *O*-linked α-imido boronate as the major product.[7]

It is well documented that the outcome of alkylation products of enolates can be controlled by the choice of reaction solvent, the cation used for generating the enolates, and the nature of a leaving group in the substrate. Use of polar aprotic solvents, such as dimethyl sulfoxide (DMSO) or hexamethylphosphoric triamide (HMPA), and potassium as a counterion results in the formation of O-alkylated product. C-Alkylated products can be exclusively obtained by alkylation of lithium enolates in tetrahydrofuran (THF).[8] A practical synthesis of α-carboxamido boronates has been developed by systematic investigation of solvent, cation, and leaving group conditions. In this paper, the details of our study on the synthesis of α-[(alkoxycarbonyl)amino] boronates and α-[(alkylcarbonyl)amino] boronates from (α-haloalkyl)boronates are reported.

Results and Discussion

Treatment of *N*-sodiocarbamates **2**[9] with pinacol (1-bromopentyl)boronate (**3**) provided α-[(alkoxycarbonyl)-amino] boronates **4** in varying yields under different conditions (Table 1). *N*-Sodiocarbamates **2** were generated by the treatment of *tert*-butyl carbamate **1a** or methyl carbamate **1b** with sodium hexamethyldisilazane (NaHMDS) in the presence (condition A) or absence (condition B) of (1-bromopentyl)boronate **3** (Figure 1). The method of generation of *N*-sodiocarbamates **2** had a dramatic effect on the yield of the desired product. Treatment of preformed *tert*-butyl *N*-sodiocarbamate (**2a**) with (1-bromopentyl)boronate **3** (condition B) in either DMSO/THF (5:1) or THF resulted in the formation of only trace amounts of the desired product **4a**. However, *in-situ* generated *tert*-butyl *N*-sodiocarbamate (**2a**) (condition A) in THF provided **4a**[10,11] in 40% yield. There was a dramatic increase in yield (89%) and purity (>95%) when the *in-situ* generated *tert*-butyl *N*-sodiocarbamate (**2a**) was used in a mixture of DMSO and THF (5:1) (Table 1, entry 1). Interestingly, methyl *N*-sodiocarbamate (**2b**) provided **4b** in moderate yields under both reaction conditions (Table 1, entries 5 and 6).

The products are obtained in lower yields when the anion is generated in the absence of boronate. It appears that *tert*-butyl *N*-sodiocarbamate (**2a**) decomposes at room temperature to yield isocyanic acid and *tert*-butoxide. However, *in-situ* generation of the anion in the presence of boronate results in immediate capture of the

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(10) The structure of **4** was determined by a 2D NMR experiment in which the cross peak between NH and BCH in the Cosy45 spectrum was identified.

(11) Boronate **4** was readily purified by "flash chromatography" on silica gel. However, the longer residence time (>45 min) on silica gel resulted in hydrolysis of boronate **4** to boronic acid. Fortunately, the boronic acid can be completely recovered by elution of the silica gel column with pinanediol to obtain pinanediol boronic ester.

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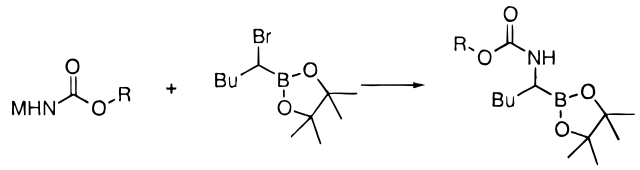
Table 1. Reaction of *N*-Sodiocarbamate with Pinacol (1-Bromopentyl)boronate (3)

entry	**1**	condns[a]	base	solvent[b]	**4** yield (%)
1	**1a**	A	NaHMDS	DMSO/THF	89
2	**1a**	A	NaHMDS	THF	40
3	**1a**	B	NaH	DMSO	trace
4	**1a**	B	NaHMDS	DMSO/THF	trace
5	**1b**	A	NaHMDS	DMSO/THF	46
6	**1b**	B	NaH	DMSO	50

[a] Condition A: base was added to the mixture of **1** and **3** at room temperature; Condition B: **1** was stirred with base for 30 min, followed by addition of **3**. [b] The ratio of DMSO to THF was 5:1.



1a R = t-Bu M = H
1b R = Me M = H
2a R = t-Bu M = Na^+
2b R= Me M = Na^+

3

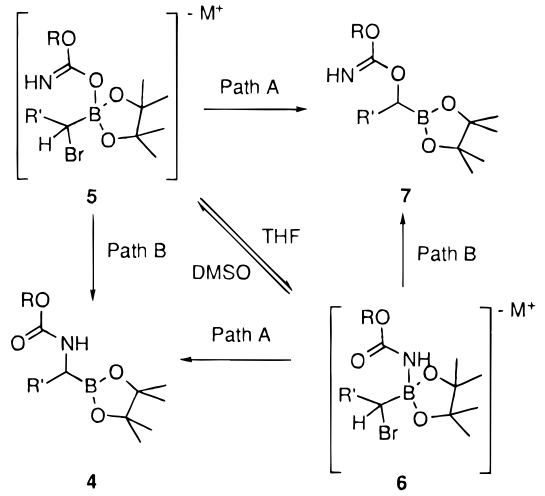
4a R= *t*-Bu
4b R= Me

Figure 1.

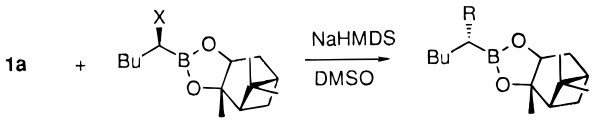
anion by boronate to form a borate complex. It is known that NaHMDS reacts with boronates to form borate complexes even at low temperatures. Apparently, the proton abstraction by the hindered base from the carbamate **1** is faster than the formation of borate complex.[12] The nucleophilic displacement of the leaving group in the subsequent step occurs faster in DMSO than in THF.

The nucleophilic substitution of (α-haloalkyl)boronates with carbon nucleophiles proceeds with the formation of the "borate" complex followed by 1,2-migration of the alkyl group from boron to carbon.[13] A similar 1,2-migration process from boron to carbon may be in operation for the current reaction (Scheme 1, path A). However, an alternative mechanism involving intramolecular nucleophilic displacement *via* a 5-membered transition state[14] cannot be ruled out (Scheme 1, path B). Interestingly, formation of both the possible products, *viz.* α-imido boronate **7** or α-carboxamido boronate **4** can be envisioned by invoking either of the mechanistic pathways. α-Imido boronate **7** can be obtained from **5** by path A or from **6** by path B. Similarly, the desired α-carboxamido boronate **4** can be obtained from **5** by path B or from **6** by path A. It appears that a 5-membered transition state may be more favored over the 1,2-migration process. In the presence of a weakly polar solvent (THF) and cation of reduced electropositivity (Li^+) ion pairing occurs between oxygen and lithium. The unsolvated nitrogen reacts with boron to form the "N−B borate" complex **6**, which rearranges to α-imido boronate

Scheme 1[a]



[a] Path A: 1,2-migration from boron to carbon. Path B: intramolecular nucleophilic displacement *via* a 5-membered cyclic intermediate.



8 X = Cl
9 X = Br

10 R = *t*-BuOOCNH
11 R = *t*-BuO

Figure 2.

7 via path B. On the contrary, use of polar aprotic solvents (DMSO) and cations of higher electropositivity (Na^+), a condition more favorable for separation of ion pairs, may allow the capture of boronate by bare oxygen ion to form the "O−B borate" complex **5**. The lone-pair of nitrogen then can attack the carbon-bearing bromine via a 5-membered transition state to provide **4**.

The conditions optimized for pinacol boronates were used to develop asymmetric synthesis of α-carboxamido boronates using chiral boronic esters **8** and **9** (Figure 2). Thus, treatment of enantiomerically pure (*S*)-pinanediol (1(*S*)-chloropentyl)boronate **8** with either *tert*-butyl sodio- or potassiocarbamate in DMSO provided a mixture of α-[(alkoxycarbonyl)amino] boronates **10** and [(*tert*-butyloxy)pentyl]boronate **11** in a 1:1 ratio (84% combined yield). α-[(Alkoxycarbonyl)amino] boronates **10** were found to be enantiomerically pure as examined by 300 MHz ^{1}H NMR. However, under the same reaction conditions, *tert*-butyl lithiocarbamate yielded α-[(alkoxycarbonyl)amino] boronates **10** in <10% yield. The reaction product was a mixture of **11** and unidentified materials. Treatment of enantiomerically pure bromide **9** with **2a** in DMSO afforded **10** without any trace of **11**; unfortunately, the product **10** was completely racemized. Use of THF instead of DMSO as the solvent minimized the racemization (50% ee), but the reaction was very sluggish.

In general, the rate of 1,2-migration of the alkyl group from boron to carbon is slow in the case of boronates derived from hindered diols.[15] Therefore, it is not surprising that the rearrangement of the borate complex derived from pinanediol boronate was much slower than

(12) Other examples of *in-situ* generation and capture of reactive anions by boronic esters: (a) Sadhu, K. M.; Matteson, D. S. *Organometalics* **1985**, *4*, 1687. (b) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795. (c) Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, *51*, 3150. (d) Brown, H. C.; Phadke, A. S.; Rangaishenvi, M. V. *J. Am. Chem. Soc.* **1988**, *110*, 6263. (e) Michnik, T. J.; Matteson, D. S. *Synlett* **1991**, 631. (f) Wallace, R., II; Zong, K. K. *Tetrahedron Lett.* **1992**, *33*, 6941.

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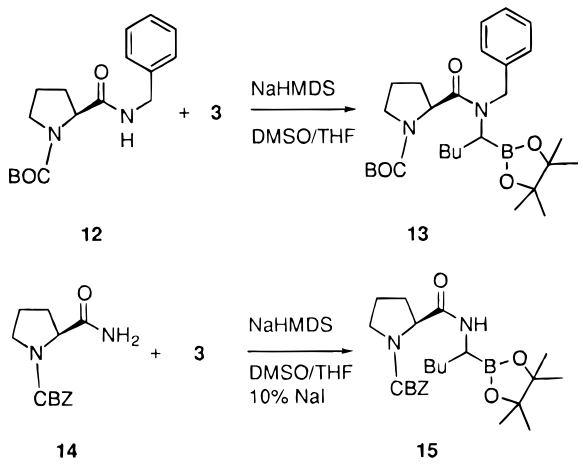

Figure 3.

that derived from pinacol boronate. The slow rate of migration results in dissociation of the borate complex causing decomposition of the anion to form isocyanic acid and *tert*-butoxide, which in turn reacts with chloride **8** to give **11**. The decomposition of carbamate anion was avoided by increasing the rate of migration by changing the leaving group from chlorine to bromine. Unfortunately, bromide **9** readily racemized under the reaction conditions to yield a 1:1 diastereomeric mixture of **10**.[16]

In order to further improve the efficiency of the synthesis, we explored the possibility of treating anions derived from peptide derivatives with **3** to obtain boropeptides in one step. Thus, treatment of anions derived from proline amides **12** with pinacol (1-bromopentyl)boronate (**3**) afforded boropeptides **13** in 45% yield (Figure 3). The reaction proceeded better in the case of secondary amide **12** than **14**. Treatment of the anion derived from amide **14** gave no desired product under the same conditions. However, addition of a catalytic amount (10 mol %) of sodium iodide provided **15** in 27% yield.

There are several advantages of the method described herein. The [α-[(*tert*-butoxycarbonyl)amino]alkyl]boronates are obtained in moderate and excellent yields and purities. The reaction can be carried out at room temperature, and the product can be subjected to aqueous workup and purified (if necessary) by silica gel chromatography.[11] The product is stable when stored at room temperature for several months without any deterioration. It can be readily deprotected by treatment with trifluoroacetic acid in chloroform to provide the trifluoroacetate salt of (1-aminopentyl)boronate. We have demonstrated that by proper choice of solvent, cation, and the leaving group, it is possible to optimize synthesis of boropeptides suitable for large-scale synthesis. The current method provides a direct approach to the synthesis of boropeptides from α-halo boronates.

Experimental Section

General Procedures. All commercially available compounds were used without further purification. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded in either $CDCl_3$ or CD_3OD with a 300 MHz spectrometer.

Pinacol [1-[[(1,1-Dimethylethoxy)carbonyl]amino]pentyl]-boronate (4a). To a mixture of *tert*-butylcarbamate **1a** (0.35 g, 3 mmol) and pinacol (1-bromopentyl)boronate (**3**) (0.83 g, 3 mmol) in DMSO (15 mL), was slowly added (1 drop/s) NaHMDS (3 mL, 1 M, 3 mmol) in THF at room temperature. After 3 h, ether (100 mL) was added to the reaction mixture, and the solution was poured into an ice and brine mixture (30 mL with 10 g of ice). The phases were separated, and the aqueous layer was extracted with ether (50 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried over $MgSO_4$. Removal of solvent under vacuum followed by purification by flash chromatography (silica gel, 0%, 1.5% and 2.5% MeOH/$CHCl_3$, R_f = 0.65, 2.5% MeOH/$CHCl_3$) gave **4a** as an oil 0.84 g (89%): ^{1}H NMR ($CDCl_3$) δ 0.80−0.95 (m, 3H), 1.26 (s, 12H), 1.05−1.4 (m, 4H), 1.436 (s, 9H), 1.45−1.7 (m, 2H), 3.01 (dd, J = 6, 8.2 Hz, 1H), 4.73−4.9 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.89, 22.57, 24.65, 24.71, 28.28, 29.03, 30.78, 79.22, 83.49,156.67; ^{11}B NMR ($CDCl_3$) δ 29.50; HRMS(NH_3-CI) calcd for $C_{16}H_{33}NO_4B$ (M + H)$^+$ 314.2503, found 314.2513.

Diastereomer (*S*)-Pinanediol [1-[[(1,1-Dimethylethoxy)-carbonyl]amino]pentyl]boronate (10). The solution of boronate **4a** (200 mg, 0.6 mmol) and (*S*)-pinanediol (120 mg, 0.6 mmol) in ether (10 mL) was stirred at room temperature for 1 h. Removal of solvent under vacuum followed by purification by flash chromatography (silica gel, 0%, 1.5%, and 2.5% MeOH/$CHCl_3$, R_f = 0.60, 2.5% MeOH/$CHCl_3$) gave **10** as an oil 0.21 g, (95% yield): ^{1}H NMR ($CDCl_3$) [(1*R*)-**10**] δ 0.83 (s, 3H), 0.84−0.89 (m, 3H), 1.12−1.32 (m, containing 1.27, s, 9H), 1.37 (s, 3H), 1.41(s, 9H), 1.48−1.70 (m, 4H), 1.81−1.92 (m, 2H), 2.02 (t, J = 5.1 Hz, 1H), 2.1−2.22 (m, 1H), 2.26−2.33 (m, 1H), 3.03 (q, J = 6.6 Hz, 1H), [3.08 (q, J = 6.4 Hz, 1H)], 4.28−4.32 (m, 1H), [4.80 (br d, J = 5.4 Hz, 1H)], 4.90 (br d, J = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.80, 22.46, 23.79, 26.11, 26.86, 28.20, 28.33, 28.93, 30.85 and 31.07, 35.27, 37.8 (br), 37.92, 39.29, 51.08, 77.77, 78.69 and 78.79, 85.74, 156.33 and 156.44; ^{11}B NMR ($CDCl_3$) δ 29.71; HRMS (NH_3-CI) calcd for $C_{20}H_{37}NO_4B$ (M + H)$^+$ 366.2816, found 366.2819.

(*S*)-Pinanediol [(1*R*)-1-[[(1,1-dimethylethoxy)carbonyl]-amino]pentyl]boronate (10): ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H), 0.85−0.91 (m, 3H), 1.23 (d, J = 1.05 Hz, 1H), 1.28 (s, 3H), 1.26−1.36 (m, 3H), 1.39 (s, 3H), 1.43(s, 9H), 1.48-1.70 (m, 4H), 1.81−1.94 (m, 2H), 2.05 (t, J = 4.8 Hz, 1H), 2.14−2.25 (m, 1H), 2.29−2.40 (m, 1H), 3.08 (q, J = 6.6 Hz, 1H), 4.28−4.32 (m, 1H), 4.75 (br d, J = 5.4 Hz, 1H).

Pinacol [1-[(Methoxycarbonyl)amino]pentyl]boronate (4b). To a mixture of **1b** (0.34 g, 4.53 mmol) and NaH (0.18 g, 60% in oil, 4.5 mmol) was added DMSO (5 mL) at room temperature. After 1.5 h, **3** (1 g, 4.53 mmol) was added. After 3 h, the solution was poured into ice−brine (50 mL with 10 g of ice) and then extracted with ethyl acetate (50 mL). The organic layer was washed with brine (2 × 30 mL) and dried over $MgSO_4$. Removal of solvent and chromatography (silica gel, 2% MeOH/$CHCl_3$, R_f 0.54) gave **4b** as an oil: 0.34 g, 58% yield; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3), 1.2−1.4 (m, 2), 1.26 (s, 12), 1.45−1.70 (m, 4), 3.17 (q, J = 6.5 Hz, 1), 3.64 (s, 3), 4.92 (br d, J = 4.8 Hz, 1); ^{13}C NMR ($CDCl_3$) δ 13.84, 22.54, 24.58, 24.67, 28.79, 30.98, 37.99 (br), 51.82, 83.84, 157.30; ^{11}B NMR ($CDCl_3$) δ 30.38; HRMS (NH_3-CI) calcd for $C_9H_{19}O_4NB$ (M + H)$^+$ 216.1407, found 216.1404.

Pinacol 1-[1-[Benzyl[[1-[(1,1-dimethylethoxy)carbonyl]-2-pyrrolidinyl]carbonyl]amino]pentyl]boronate (13). To a mixture of proline amide **12** (0.2 g, 0.66 mmol) and boronate **3** (0.18 g, 0.65 mmol) in DMSO (5 mL), was slowly added (1 drop/s) NaHMDS (0.7 mL, 1M, 0.7 mmol) in THF at room temperature. After 3 h, ethyl acetate (50 mL) was added to the reaction mixture. The solid was filtered, and the solution was poured into an ice and brine mixture (30 mL with 10 g of ice). The phases were separated, and the aqueous layer was extracted with ether (50 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried over $MgSO_4$. Removal of solvent under vacuum followed by purification by flash chromatography (silica gel, 1:1 hexane/ethyl acetate, R_f 0.33 and 0.42) gave **13** as an oil: 0.15 g (two diastereomers), 45% yield; ^{1}H NMR (CD_3OD) δ 0.85−0.95 (m, 3H), 1.16 (s, 12H), 1.2−1.6 (m, 6H), 1.48 and 1.52 (2 s, 9H), 1.84−2.22 (m, 4H), 2.43 (dd, J = 3.6, 8.7 Hz, 1H), 2.48 (dd, J = 3, 7.8 Hz, 1H), 3.41−3.49 (m, 2H), 4.6 (d, J = 16 Hz, 1H), 4.81 (dd, J = 3.6, 7.5 Hz, 1H), 4.96 (dd, J = 3.3, 8.1 Hz, 1H), 5.02 (d, J = 15.6 Hz, 1H), 5.17 (d, J = 16.2 Hz, 1H), 7.25−7.45 (m, 5H); ^{11}B NMR (CD_3OD) δ 10.1; HRMS (NH_3-CI) calcd for $C_{28}H_{46}N_2O_5B$ (M + H)$^+$ 501.3500, found 501.3482.

Pinacol [1-[[[1-(Benzyloxycarbonyl)-2-pyrrolidinyl]carbonyl]amino]pentyl]boronate (15). To a mixture of CBZ-

(16) Matteson, D. S.; Erdik, E. *Organometallics* **1983**, *2*, 1083.

proline amide **14** (0.248 g, 1 mmol) and boronate **3** (0.277 g, 1 mmol) in DMSO (5 mL) was added NaHMDS (1 mL, 1 M, 1 mmol) in THF slowly (1 drop/s) at room temperature and followed by addition of NaI (15 mg, 0.1 mmol). After 24 h, ethyl acetate (100 mL) was added to the reaction mixture, and the solution was poured into an ice and brine mixture (30 mL with 10 g of ice). The phases were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried over $MgSO_4$. Removal of solvent under vacuum followed by purification by flash chromatography (silica gel, 3:1 ethyl acetate/hexane, R_f 0.1) gave **15** as an oil: 0.12 g (two diastereomers), 27% yield; ^{1}H NMR (CD_3OD) δ 0.8−1.0 (m, 3H), 1.18 and 1.20 (2s, 12H), 1.2−2.7 (m, 11H), 3.4−3.65 (m, 2H), 4.1−4.2 (m, 1H), 4.4−4.6 (m, 1H), 5.0−5.2 (m, 2H), 7.3−7.4 (m, 5H); ^{11}B NMR δ 12.658 (CD_3OD) 23.253 ($CDCl_3$); HRMS (NH_3-CI) calcd for $C_{24}H_{38}N_2O_5B$ $(M + H)^+$ 445.2874, found 445.2887.

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