Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8865–8868

TETRAHEDRON LETTERS

Hydroxylamines and sulfinamide as amine components in the Petasis boronic acid–Mannich reaction: synthesis of *N*-hydroxy or alkoxy-α-aminocarboxylicacids and *N*-(*tert*-butyl sulfinyl)-α-amino carboxylicacids

Dinabandhu Naskar,[a,*] Amrita Roy,[a] William L. Seibel[b] and David E. Portlock[b,†]

[a]*Chembiotek Research International, Block BN, Sector-V, Plot 7, Salt Lake Electronic Complex, Kolkata 700 091, India*
[b]*Combinatorial Chemistry Section, Procter & Gamble Pharmaceuticals Health Care Research Center, 8700 Mason Montgomery Road, Mason, OH 45040, USA*

Accepted 19 September 2003

Abstract—An efficient synthesis of *N*-hydroxy or alkoxy-α-aminocarboxylic acids and *N*-(*tert*-butyl sulfinyl)-α-amino carboxylic acids has been developed from *N*,*O*-alkyl or hydroxylamines and *tert*-butyl sulfinamide utilizing a Petasis boronic acid–Mannich reaction. The scope and limitations of this method have been examined.

The development of an efficient synthesis of *N*-hydroxy-α-amino acids and derivatives[1] thereof represents a challenging goal in organic synthesis since these compounds are key intermediates in metabolic pathways and can be found in human and animal tumors.[1,2] In our earlier report, it was shown that hydrazines can participate in the Petasis boronic acid–Mannich reaction, providing a powerful and convenient method for the preparation of α-amino acids[3–5] which is quite useful for the synthesis of combinatorial libraries.[6] We have investigated the scope and limitations of using substituted hydroxylamines and *tert*-butyl sulfinamide as amine components in the Petasis boronic acid–Mannich reaction. To the best of our knowledge hydroxylamines and *tert*-butyl sulfinamide have not previously been studied as substrates for this reaction.[3–5]

General methods for the synthesis of enantiomerically pure or enriched *N*-hydroxy-α-amino acids have had scant mention in the literature until recently.[7] Various methods have already been reported for obtaining *N*-hydroxy or alkoxy amino acid esters which can be converted into the corresponding acid derivatives by S_N2 displacement[8] but such methods are not advantageous. There are relatively few methods for the synthesis of *N*-hydroxy amino acids. These involve asymmetric oxyamination,[9] oxidation by dioxiranes,[10] Mitsunobu condition,[11] and oxidation of amines.[12]

We describe herein an efficient synthesis of *N*-hydroxy or alkoxy-α-aminocarboxylic acids and *tert*-butyl sulfinamide by the Petasis boronic acid–Mannich reaction. Commercially available substrates (**1** and **3**) were subjected to standard Petasis boronic acid–Mannich reaction conditions, i.e. 1 equiv. each of **1** and **3**, glyoxylic acid monohydrate, and an organoboronic acid stirred at ambient temperature in DCM (Tables 1 and 2).

When R^1 = methyl, R^2 = methyl, R^3 = aryl (**2a**–**b**), the reactions proceeded in excellent yields, ranging from 95–96% of the corresponding *N*-alkoxy-α-amino acid after purification by column chromatography (Table 1).[13] When R^1 = methyl, R^2 = H, R^3 = aryl or heterocyclic (**2c**–**d**), the reactions afforded good yield of the desired product in 79–87% after purification. When R^3 = aryl containing electron withdrawing group (**2e**), the corresponding *N*-alkoxy-α-amino acid was obtained in 89% yield after purification. Remarkably, when R^1 = benzyl, cyclohexyl and *tert*-butyl, R^2 = H, R^3 = aryl (**2f**–**h**), this reaction gave 41–80% yield after purification by column chromatography. It was also observed that

* Corresponding author. E-mail: naskar.d@pg.com, dinabandhu@chembiotek.com
† Present address: Wright State University, Department of Chemistry, Dayton, OH 45435, USA.

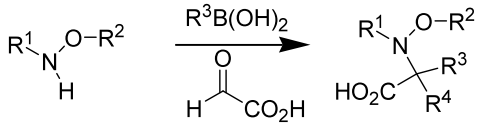
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.179

these compounds slowly decomposed on long standing at ambient temperature.

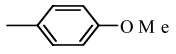
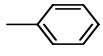
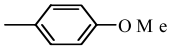
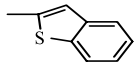
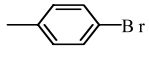
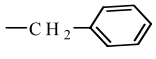
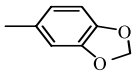
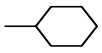
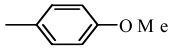
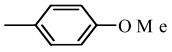
When R^2 = aryl, R^3 = H (**4a–e**), these reactions proceeded in very good yields to afford the desired product in 50–73% yield after purification by column chromatography (Table 2).[14] When R^2 = heterocyclic (**4f–h**), the reactions also proceeded in good yields to afford the desired product in 66–68% yield. When the α-keto acid was varied from R^3 = H to R^3 = Me (**4i–j**), these reactions afforded only 37–39% yields of the product. Together, these results suggest the steric environment at the reaction center plays a significant role in the yield of the reaction. As expected, the product consisted of a 50:50 mixture of racemic diastereomers (LC–MS). In the example **4a**, the racemic diastereomers (1:1) were separated by preparative HPLC and characterized by LCMS, ^{1}H and ^{13}C NMR, and HRMS.[14]

In summary, we have demonstrated that hydroxylamines and sulfinamides can serve as amine substrates for the Petasis boronic acid–Mannich reaction, providing a practical synthetic route for the preparation of *N*-hydroxy or alkoxy-α-aminocarboxylic acids and *N*-(*tert*-butyl sulfinyl)-α-aminocarboxylic acids. These *N*-protected amino acids can be activated either as the acid chloride or with HATU to provide excellent coupling partners for amide bond formation, and should be versatile intermediates for the synthesis of hindered peptides and drugs.

Table 1. Petasis boronic acid–Mannich reactions of substituted hydroxylamines

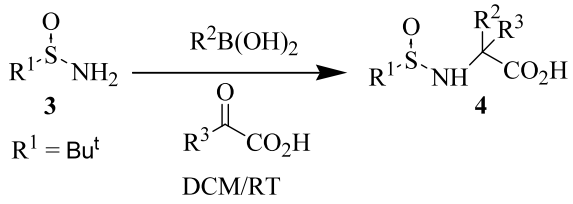


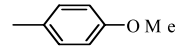
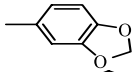
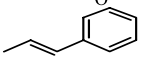
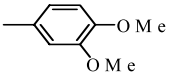
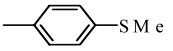
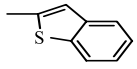
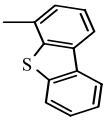
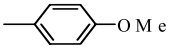
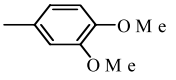
1 DCM/RT **2**

Compound	R^1	R^2	R^3	Yield[a]
2a	—Me	—Me		95%
2b	—Me	—Me		96%
2c	—Me	—H		87%
2d	—Me	—H		79%
2e	—Me	—Me		89%
2f		—H		80%
2g		—H		41[b]%
2h		—H		75[b]%

[a]All yields refer to pure, isolated products. All compounds have been characterized by LC-MS, ^{1}HNMR, and ^{13}CNMR. [b]Decomposition was observed.

Table 2. Petasis boronic acid–Mannich reactions of sulfinamide



Compound	R^2	R^3	Yield[a]
4a		—H	72%
4b		—H	70%
4c		—H	57%
4d		—H	73%
4e		—H	50%
4f		—H	67%
4g		—H	66%
4h		—H	68%
4i		—Me	37%
4j		—Me	39%

[a]All yields refer to pure, isolated products. All compounds have been characterized by LC-MS, ^{1}HNMR, and ^{13}CNMR.

References

1. (a) Merino, P.; Castillo, E.; Santiago, F.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 2371; (b) Merino, P.; Santiago, F.; Merchan, F.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 5627.
2. Ottenheijm, H. C. J.; Herscheid, J. D. M. *Chem. Rev.* **1986**, *86*, 697.
3. (a) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445; (b) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463; (c) Hansen, T. K.; Schlienger, N.; Hansen, B. S.; Andersen, P. H.; Bryce, M. R. *Tetrahedron* **1999**, *40*, 3651; (d) Jiang, B.; Yang, C.-G.; Gu, X.-H. *Tetrahedron Lett.* **2001**, *42*, 2545.
4. The Petasis boronic acid–Mannich reaction has also been applied to the synthesis of heterocyclic systems. See: (a) Batey, R. A.; MacKay, D. B.; Santhakumar, V. J. *J. Am. Chem. Soc.* **1999**, *121*, 5075; (b) Petasis, N. A.; Patel, Z. D. *Tetrahedron Lett.* **2000**, *41*, 9607; (c) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063; (d) Berree, F.; Debache, A.; Marsac, Y.; Carboni, B. *Tetrahedron Lett.* **2001**, *42*, 3591, and references cited therein.
5. (a) Portlock, D. E.; Naskar, D.; West, L.; Li, M. *Tetrahedron Lett.* **2002**, *43*, 6845; (b) Portlock, D. E.; Ostaszewski, R.; Naskar, D.; West, L. *Tetrahedron Lett.* **2003**, *44*, 603; (c) Portlock, D. E.; Naskar, D.; West, L.; Ostaszewski, R.; Chen, J. J. *Tetrahedron Lett.* **2003**, *44*, 5121.
6. (a) Klopfenstein, S. R.; Chen, J. J.; Golebiowski, A.; Li, M.; Peng, S. X.; Shao, X. *Tetrahedron Lett.* **2000**, *41*, 4835; (b) Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron* **2000**, *56*, 10023; (c) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (d) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.

7. For an excellent recent review, see: (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; See also: (b) Williams, R. M. *Synthesis of Optically Acitve α-Amino Acids*; Baldwin, J. E.; Magnus, P. D., Eds.; Oxford: Pergamon Press, 1989.
8. (a) Yasuhiro, C.; Mitsuo, M.; Masaki, O. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 224; (b) Kolasa, T. *Can. J. Chem.* **1985**, *63*, 2139; (c) Kolasa, T.; Chimiak, A. *Tetrahedron* **1977**, *33*, 3285; (d) Kolasa, T.; Chimiak, A.; Kitowaka, A. *J. Prakt. Chem.* **1975**, *317*, 252; (e) Kolasa, T.; Chimiak, A. *Tetrahedron* **1974**, *30*, 3591; (f) Cook, A. H.; Slater, C. A. *J. Chem. Soc.* **1956**, 4130; (g) Chimiak, A. *Roczniki Chem.* **1968**, *42*, 225.
9. (a) Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991; (b) Oppolzer, W.; Tamura, O.; Deerberg, J. *Helv. Chim. Acta* **1992**, *75*, 1965.
10. Detomaso, A.; Curci, R. *Tetrahedron Lett.* **2001**, *42*, 755.
11. Hanessian, S.; Yang, R.-Y. *Synlett* **1995**, 633.
12. Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1981.
13. General procedure for the Petasis boronic acid–Mannich reaction of substituted hydroxyl amine **1** to prepare *N*-hydroxy or alkoxy-α-aminocarboxylic acids 2 (Table 1): To a stirred mixture of glyoxylic acid monohydrate (368 mg, 4.0 mmol) in DCM (12 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (390 mg, 4.0 mmol) followed by phenyl boronic acid (488 mg, 4.0 mmol). The resulting mixture was stirred at ambient temperature for 24 h, and after this time, the solid was filtered and washed with DCM several times, dried under reduced pressure and purified by column chromatography to afford 750 mg (96%) of **2b** as a white solid, mp (Met-TempII): 152–153°C (uncorrected): $R_f = 0.16$ (5% MeOH:DCM); analytical HPLC: Polaris C18 column (4.6×250 mm, 3 micron particle size), mobile phase 0.1% aqueous phosphoric acid/CH_3CN linear gradient over 30 min, 1 mL/min, one peak detected by ELS and UV at 214 nm, $t_R = 9.32$ min; ^{1}H NMR (MeOH-d_4, 300 MHz): δ 2.84 (s, 3H), 3.94 (s, 3H), 5.12(s, 1H), 7.49–7.58 (m, 5H); ^{13}C NMR (MeOH-d_4, 75 MHz): δ 41.49, 62.27, 77.30, 130.75, 131.38, 132.33, 133.11, 170.45; LCMS (ELSD): 196 ($M+H^+$); HRMS: 196.096608 [calcd for $C_{10}H_{13}NO_3$ 196.097368 $(M+H)^+$].
14. General procedure for the Petasis boronic acid–Mannich reaction of sulfinamide **3** to prepare **4** (Table 2): To a stirred mixture of glyoxylic acid monohydrate (460 mg, 5.0 mmol) in DCM (15 mL) was added (*S*)-(−)-2-methyl-2-propanesulfinamide (606 mg, 5.0 mmol) followed by 4-methoxyphenylboronic acid (760 mg, 5.0 mmol). The resulting mixture was stirred at ambient temperature for 48 h and after this time, the DCM was removed under reduced pressure. The residue was purified by chromatography (silica gel, 40% EtOAc:hexanes) to give 1.04 g (72%) of **4a** as a 50:50 mixture of racemic diastereomers. The diastereomers (**A** and **B**) have been separated by preparative HPLC; [Polaris C18 column (250×500 mm, 10 micron particle size), mobile phase 0.1% aqueous TFA/CH_3CN linear gradient over 55 min, 60 mL/min]; analytical HPLC: Polaris C18 column (4.6×250 mm, 3 micron particle size), mobile phase 0.1% aqueous phosphoric acid/CH_3CN linear gradient over 30 min, 1 mL/min, one peak detected by ELS and UV at 220 nm, $t_R = 9.078$ (**A**), another peak detected by ELS and UV at 220 nm, $t_R = 9.840$ (**B**).

4a(A): $R_f = 0.13$, 10% MeOH:DCM; white solid, mp (Met-TempII): 140–141°C (uncorrected); ^{1}H NMR (CD_3OD, 300 MHz): δ 1.24 (s, 9H), 3.82 (s, 3H), 5.02 (s, 1H), 6.96 (d, $J = 8.7$ Hz, 2H), 7.39 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (CD_3OD, 75 MHz): δ 21.83, 54.59, 56.73, 59.63, 113.90, 128.93, 129.98, 160.11, 173.31; LCMS (ELSD): 286 ($M+H^+$); HRMS: 286.110069 [calcd for $C_{13}H_{19}NO_4S$ 286.111305 $(M+H)^+$].

4a(B): $R_f = 0.14$, 10% MeOH:DCM; white solid, mp (Met-TempII): 109–110°C (uncorrected); ^{1}H NMR (CD_3OD, 300 MHz): δ 1.24 (s, 9H), 3.80 (s, 3H), 4.96 (s, 1H), 6.93 (d, $J = 9$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (CD_3OD, 75 MHz): δ 23.33, 56.16, 57.52 61.85, 115.46, 131.03, 131.53, 161.68, 174.84; LCMS (ELSD): 286 ($M+H^+$); HRMS: 286.110228 [calcd for $C_{13}H_{19}NO_4S$ 286.111305 $(M+H)^+$].