Pergamon

Tetrahedron Letters 41 (2000) 9607–9611

TETRAHEDRON LETTERS

Synthesis of piperazinones and benzopiperazinones from 1,2-diamines and organoboronic acids†

Nicos A. Petasis* and Zubin D. Patel

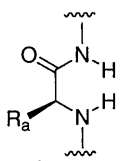
Department of Chemistry and Loker Hydrocarbon Research Institute, University of Southern California, Los Angeles, CA 90089-1661, USA

Received 31 August 2000; revised 2 October 2000; accepted 3 October 2000

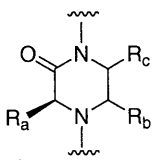
Abstract

Alkenyl, aryl and heteroaryl boronic acids react with 1,2-diamines and glyoxylic acid to give directly in one step the corresponding piperazinones (2-oxopiperazines). Similarly, the use of monoprotected 1,2-phenylenediamine leads to benzopiperazinones (1,2,3,4-tetrahydroquinoxalin-2-ones).

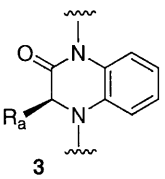
The design and synthesis of peptidomimetics continues to be an area of intense interest in medicinal and combinatorial chemistry.[1] Among the most common approaches is the development of conformationally restricted molecules which mimic a given peptide conformation. Two interesting examples that mimic conformation (**1**) in peptides are the piperazinones[2] (2-oxopiperazines) (**2**) and the benzopiperazinones[3] (1,2,3,4-tetrahydro-quinoxalin-2-ones) (**3**). Herein we report a new synthesis of these types of molecules.



1



2



3

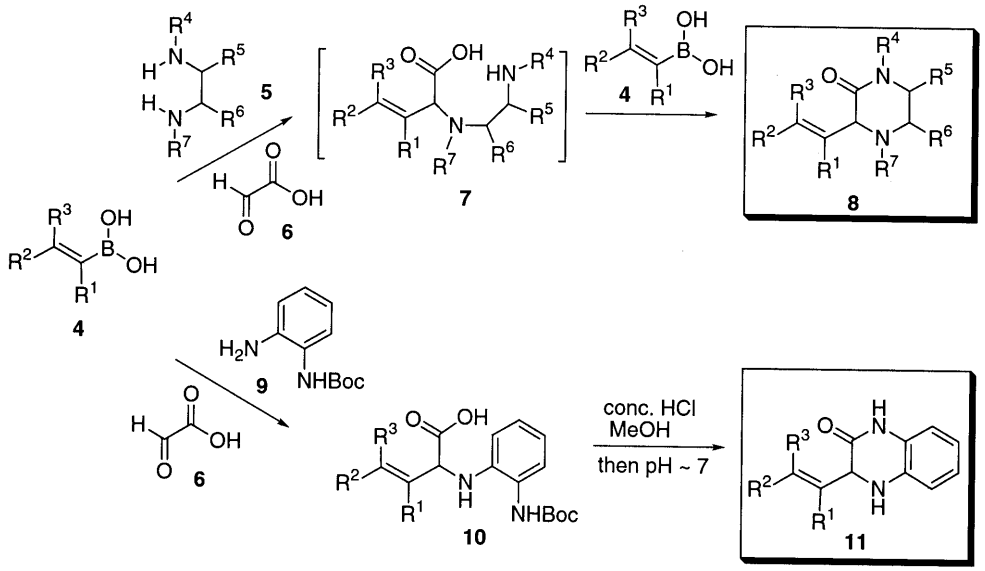
Following our earlier report on the use of organoboronic acids in a Mannich type reaction,[4a] we have recently introduced a new multi-component process[4b–d] involving the one-step condensation of alkenyl, aryl or heteroaryl boronic acids with amines and certain carbonyl compounds to form new functionalized amine derivatives. We have used this concept to devise a new, general and practical one-step approach to the synthesis of α-amino acids[4b,c] as well as β-amino

* Corresponding author. Fax: 213 740-6684; e-mail: petasis@usc.edu

† Dedicated to Professor Harry H. Wasserman, on the occasion of his 80th birthday.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01717-2

alcohols.[4d] Herein, we report the use of this chemistry for the direct synthesis of piperazinones (**8**) and benzopiperazinones (**11**) (Scheme 1).



Scheme 1.

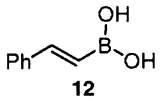
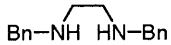
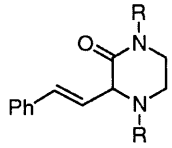
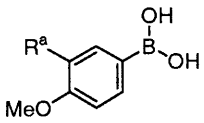
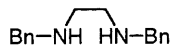
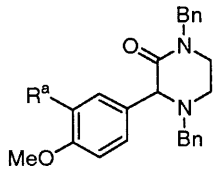
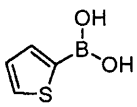
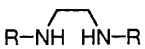
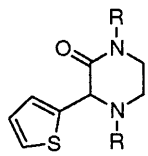
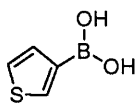
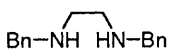
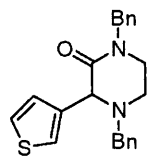
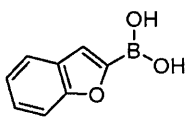
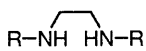
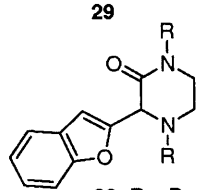
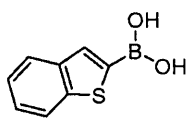
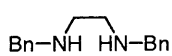
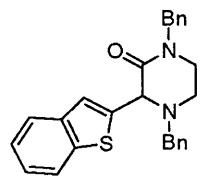
For the synthesis of piperazinones (**8**), we explored the one-step reaction among 1,2-diamines (**5**), organoboronic acids (**4**), and glyoxylic acid (**6**). Based on a recent report by Yamamoto,[5] we expected that the resulting amino acid adduct (**7**) might undergo in situ cyclization catalyzed by the boronic acid **4**. Indeed, we have found that the desired heterocyclic products **8** could be formed *in one step* by reacting **4**, **5**, and **6**. Noteworthy in this process is the dual role of organoboronic acids (**4**) serving both as reactants and as catalysts for the subsequent cyclization step.

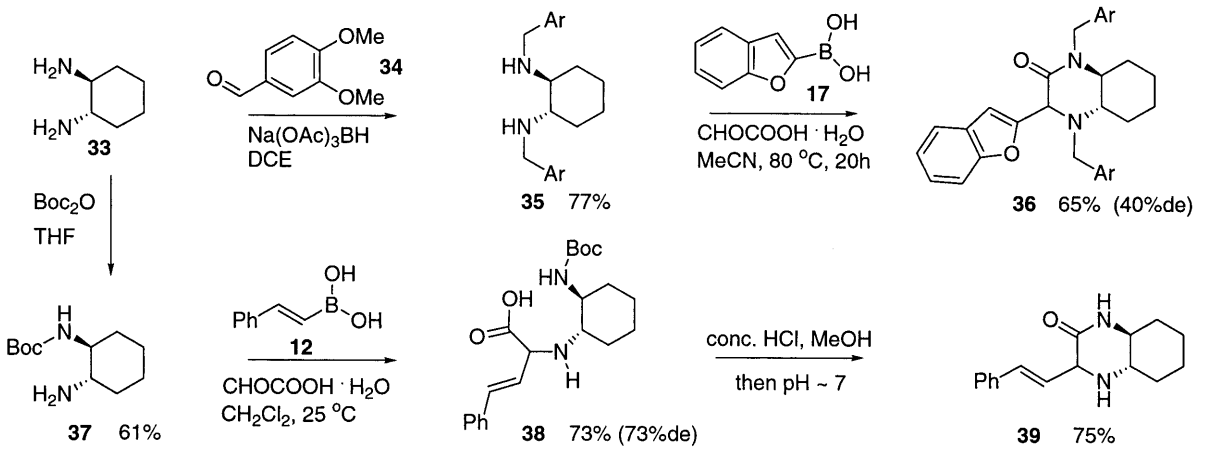
Table 1 shows several examples of this chemistry. By examining a variety of reaction conditions, we have found that this process is usually most efficient in refluxing acetonitrile. Several types of alkenyl (**12**), aryl (**13** and **14**) and heteroaryl (**15–18**) boronic acids afforded the expected piperazinones in variable yields (not optimized).[6]

Typical experimental procedure (entry 4): To a mixture of diamine **19** (240 mg, 1 mmol) and glyoxylic acid monohydrate (92 mg, 1.0 mmol) in acetonitrile (20 mL), was added (*E*)-2-phenylethenyl boronic acid (**12**, 144 mg, 1.0 mmol) and the solution was heated at reflux while monitored by TLC (2:3 EtOAc–hexanes). After 2 hours, the solvent was evaporated and the product was isolated by flash chromatography using 3:7 EtOAc–hexanes affording piperazinone **22** (291 mg, 76%).[7]

The present process was most efficient with secondary 1,2-diamines, while primary 1,2-diamines (e.g. **33**) did not work in this manner. However, conversion of **33** to a secondary 1,2-diamine (**35**) via reductive amination with an aldehyde (**34**), followed by the three-component process, gave the piperazinone (**36**) with modest diastereoselectivity (40% de) (Scheme 2). Removal of the benzyl groups from **36** can give the piperazinone that would have been produced from **33**. Alternatively, use of the monoprotected derivative **37** gave the amino acid product **38** with somewhat improved diastereoselectivity (73% de) (configuration unknown). Treatment of **38** with acid gave the corresponding N-unsubstituted piperazinone (**39**). It should be noted that

Table 1
One step synthesis of piperazinones from organoboronic acids, diamines and glyoxylic acid monohydrate

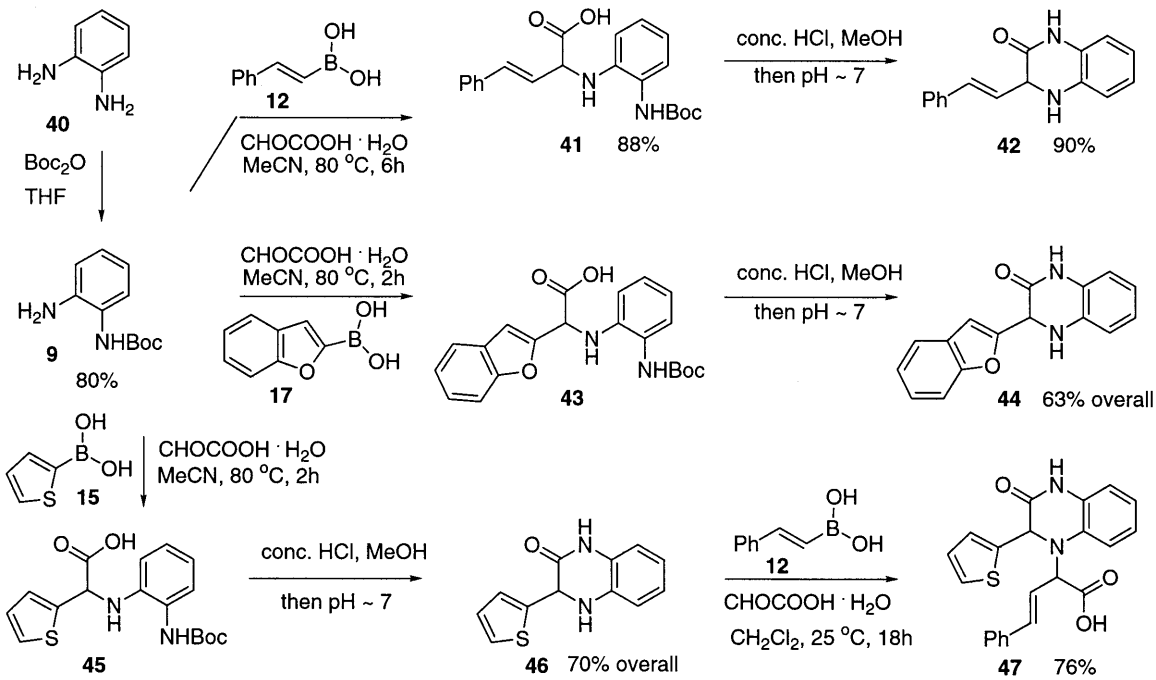
Entry	Boronic acid	Diamine	Conditions	Product	Yield
1	 **12**	 **19**	CH_2Cl_2, 25 °C, 24h		73%
2			MeOH, 65 °C, 24h		13%
3			PhMe, 110 °C, 2h		75%
4			MeCN, 80 °C, 2h	**22**, R = Bn	76%
5	**12**	 **20**	MeCN, 80 °C, 20h	**23**, R = Me	50%
6			CH_2Cl_2, 25 °C, 24h		46%
7			MeCN, 80 °C, 4h		50%
8	**13**, R^a =H	**19**	PhMe, 110 °C, 2h	**24**, R^a =H	50%
9	**14**, R^a =OMe		MeCN, 80 °C, 2h	**25**, R^a =OMe	50%
10			CH_2Cl_2, 25 °C, 24h		45%
11			EtOAc, 25 °C, 24h		28%
12			MeCN, 80 °C, 4h		65%
13	**15**	**19**, R = Bn	PhMe, 110 °C, 2h	**26**, R = Bn	42%
14	**15**	**20**, R = Me	MeCN, 80 °C, 24h	**27**, R = Me	48%
15	**15**	**21**, R = i-Pr	MeCN, 80 °C, 12h	**28**, R = i-Pr	71%
16	 **16**	 **19**	MeCN, 80 °C, 24h	 **29**	35%
17	 **17**	 **19**, R =Bn	MeCN, 80 °C, 3h	 **30**, R = Bn	85%
18	**17**	**20**, R = Me	MeCN, 80 °C, 3h	**31**, R = Me	80%
19	 **18**	 **19**	THF, 65 °C, 24h	 **32**	30%



Scheme 2.

the diastereoselectivity in this case was comparable to other chiral amines, but it was not as high as that observed previously with phenylglycinol.[4b]

A similar stepwise approach was found to be quite useful for the synthesis of benzopiperazinones (Scheme 3). Thus, while the parent 1,2-phenylenediamine (**40**) was not effective in our process, the reaction of the monoprotected derivative (**9**) with boronic acids and glyoxylic acid, followed by acidic treatment, gave the expected products (e.g. **42**, **44** and **46**) in good overall yields. Interestingly, since the resulting heterocycles have the N-atoms differentiated, they can be used again in our three-component process to react selectively at the available amine site to give even more functionalized peptidomimetic heterocycles (e.g. **47**).



Scheme 3.

In summary, we have shown that organoboronic acids and 1,2-diamines can serve as versatile precursors for the synthesis of peptidomimetics, such as **8** and **11**. This direct approach to such complex heterocycles from readily available components is very useful for the synthesis of combinatorial libraries of these potentially bioactive molecules. Further use of this chemistry for the synthesis of other heterocyclic systems is currently under way.

Acknowledgements

We gratefully acknowledge the National Institutes of Health (grant GM 45970) for support of this research. We also thank the Loker Hydrocarbon Research Institute for a Harold Moulton Graduate Fellowship to Z.D.P.

References

1. (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. (b) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449. (c) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359. (d) *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; Jai Press: Greenwich, CT, 1999; Vol. 2, pp. 1–301. (e) Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195.
2. (a) Pohlmann, A.; Schanen, V.; Guillaume, D.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1997**, *62*, 1016. (b) Shreder, K.; Zhang, L.; Goodman, M. *Tetrahedron Lett.* **1998**, *39*, 221. (c) Goff, D. A. *Tetrahedron Lett.* **1998**, *39*, 1473. (d) Weissman, S. A.; Lewis, S.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 7459. (e) Hulme, C.; Peng, J.; Louridas, B.; Menard, P.; Krolikowski, P.; Kumar, N. V. *Tetrahedron Lett.* **1998**, *39*, 8047. (f) Mohamed, N.; Bhatt, U.; Just, G. *Tetrahedron Lett.* **1998**, *39*, 8213. (g) Hansen, T. K.; Schlienger, N.; Hansen, B. S.; Andersen, P. H.; Bryce, M. R. *Tetrahedron Lett.* **1999**, *40*, 3651. (h) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484. (i) Dinsmore, C. J.; Zartman, C. B. *Tetrahedron Lett.* **2000**, *41*, 6309 and references cited therein.
3. (a) Lee, J.; Murray, W. V.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 3874. (b) Morales, G. A.; Corbett, J. W.; DeGrado, W. F. *J. Org. Chem.* **1998**, *63*, 1172. (c) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **1999**, *64*, 2555. (d) Mazurov, A. *Tetrahedron Lett.* **2000**, *41*, 7.
4. (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (c) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463. (d) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
5. (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196. (b) Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem.* **1999**, 527.
6. The indicated yields are of purified products, after flash column chromatography. All products gave satisfactory spectroscopic and analytical data.
7. Data for **22**: ^{1}H NMR (250 MHz, CD_3OD) δ 7.48–7.20 (m, 15H), 6.76 (d, $J=15.9$ Hz, 1H), 6.33 (dd, $J=15.9$ Hz, 7.9 Hz, 1H), 4.64 (dd, $J=17.5$ Hz, 4.7 Hz, 1H), 3.92 (d, $J=13.3$ Hz, 1H), 3.86 (d, $J=7.9$ Hz, 1H), 3.43 (d, $J=13.3$ Hz, 1H), 3.23 (t, $J=5.2$ Hz, 2H), 3.02 (m, 1H), 2.54 (m, 1H). ^{13}C NMR (62.5 MHz, CD_3OD) δ 170.52, 139.02, 137.91, 137.87, 137.06, 130.10, 129.78, 129.67, 129.47, 129.10, 128.97, 128.71, 128.42, 127.63, 126.32, 69.15, 59.43, 51.15, 46.82, 46.50. HRMS calcd for $C_{26}H_{27}N_2O^+$: 383.2045, found 383.2127.