Utilization of Aminophosphonates in the Petasis Boronic Acid Mannich Reaction

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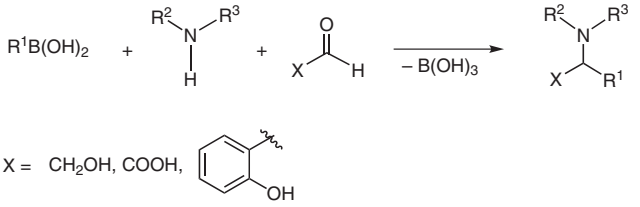
Abstract: Aminophosphonates were used as amine components in the Petasis boronic acid Mannich reaction. With the use of α-aminophosphonates, several *N*-phosphonomethylglycine derivatives were prepared in modest to good yields and high diastereoselectivities. The method affords the possibility of variation for the substituents in the position α to the phosphorus and nitrogen atoms. By using the same methodology, highly functionalized amino acids were prepared starting from (*R*)-β-amino-α,α-difluoromethylphosphonate.

Key words: boronic acids, aminophosphonates, multicomponent reaction, amino acids, stereoselective synthesis

Multicomponent reactions (MCR), in which at least three chemical entities are brought together to produce a polyfunctional compound, play an increasingly significant role in the development of modern synthetic organic and bioorganic chemistry.[1] Among these, the Petasis three-component boronic acid Mannich reaction has been the focus of attention in the last decade because of some features of the organoboron compounds such as (i) compatibility with many functional groups allowing the facile synthesis of multifunctional molecules without the excessive use of protective groups, (ii) availability of reagents in a large variety of structural configurations, (iii) possibility of using water and alcohols as the reaction medium, and (iv) low toxicity and environmental friendliness.[2] In most of the described cases, the Petasis reaction includes the interaction of an organoboronic acid, an amine, and certain carbonyl compounds, such as α-hydroxy aldehydes, α-keto acids, and salicylaldehydes, leading to α-amino acids, β-amino alcohols, and aminophenol derivatives, correspondingly (Scheme 1).[3] It is believed that the reaction proceeds through condensation of an amine and an aldehyde to give a transient iminium species followed by intramolecular transfer of the organyl ligand from the activated 'ate' complex of organoboronic acid.[4] Several biologically important imino biscarboxylic acid derivatives have been obtained via the one-step reaction among organoboronic acids, glyoxylic acid, and amino acids.[3,5] A specific example is an efficient and highly stereocontrolled synthesis of the angiotensin converting enzyme (ACE) inhibitor enalapril.[6]



Scheme 1 Typical examples of the Petasis one-pot, three-component coupling

Aminophosphonic acids are a class of amino acid isosteres in which the carboxylic acid group has been replaced by a phosphonic group.[7] Phosphonate derivatives are able to mimic the tetrahedral transition states of enzyme-mediated peptide-bond hydrolysis. Such structural feature causes a unique enzyme response which led to the discovery of herbicides, antifungal, antibacterial, and antihypertensive agents, inhibitors of proteases, including HIV-protease, and haptens of catalytic antibodies.[7,8] Different synthetic routes to aminophosphonic acid derivatives have been reported in the literature.[9] The most frequently used are nucleophilic addition of a dialkyl phosphite to an imine (Pudovik reaction) or condensation of an aldehyde, an amine, and a dialkyl phosphite (Kabachnik–Fields reaction), but for the preparation of functionalized *N*-phosphonomethylglycines the use of catalysts, protective groups, and multistep processes are necessary. To the best of our knowledge, aminophosphonic acid derivatives have not been studied as substrates for the Petasis boronic acid reaction. Herein, we report an easy and efficient method for the synthesis of compounds of the general formula **2**, **4**, and **7** based on the reaction of aminophosphonates with glyoxylic acid in the presence of organoboronic acids.

The coupling of diethyl 1-amino-(4-methoxyphenyl)-methylphosphonate (**1a**) with glyoxylic acid monohydrate and styrylboronic acid was selected as a model reaction. In this process, the interaction of reagents at room temperature or higher in a variety of solvents (toluene, dichlorometane, dioxane, acetonitrile, ethyl acetate, ethanol, methanol) proceeded to furnish the corresponding

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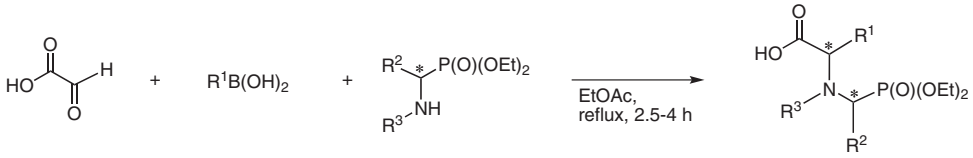
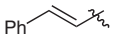
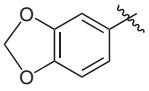
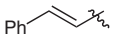
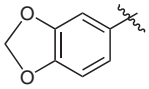
Table 1 Reaction of Aminophosphonates and Glyoxylic Acid with Various Boronic Acids



1a: R^2 = 4-$MeOC_6H_4$, R^3 = H
1b: R^2 = Ph, R^3 = Bn

1a,b **2a–h**

Entry	Product[a]	R^1	R^2	R^3	Reaction conditions[b]	dr[c]	Isolated yield (%)[d]
1	**2a**		4-$MeOC_6H_4$	H	A	9:1	75
2	**2b**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	A	9:1	76
3	**2c**		4-$MeOC_6H_4$	H	B	9:1	53[e]
4	**2d**		4-$MeOC_6H_4$	H	B	9:1	43[e]
5	**2e**		Ph	Bn	A	>95:5	80
6	**2f**	4-$MeOC_6H_4$	Ph	Bn	A	>95:5	95
7	**2g**		Ph	Bn	A	>95:5	88
8	**2h**		Ph	Bn	B	>95:5	69

[a] All compounds have been characterized by microanalytical, LC-MS, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR data.
[b] Glyoxylic acid monohydrate (1.05 equiv), $R^1B(OH)_2$ (1.05 equiv), $R^2CH(NHR^3)PO_3Et_2$ (1.0 equiv). A: EtOAc, reflux for 2.5 h, product was purified by recrystallization from EtOAc–hexane (4:1, v/v). B: EtOAc, reflux for 4 h, product was purified by flash chromatography on silica gel ($CHCl_3$–EtOAc–MeOH, 35:55:10, v/v).
[c] Determined by ^{1}H NMR and ^{31}P NMR of the unpurified reaction mixture.
[d] Isolated yield of the major diastereomer, unless otherwise stated.
[e] Diastereomeric mixture isolated.

N-(phosphonomethyl)-substituted amino acid **2a** without detection of any intermediate products.

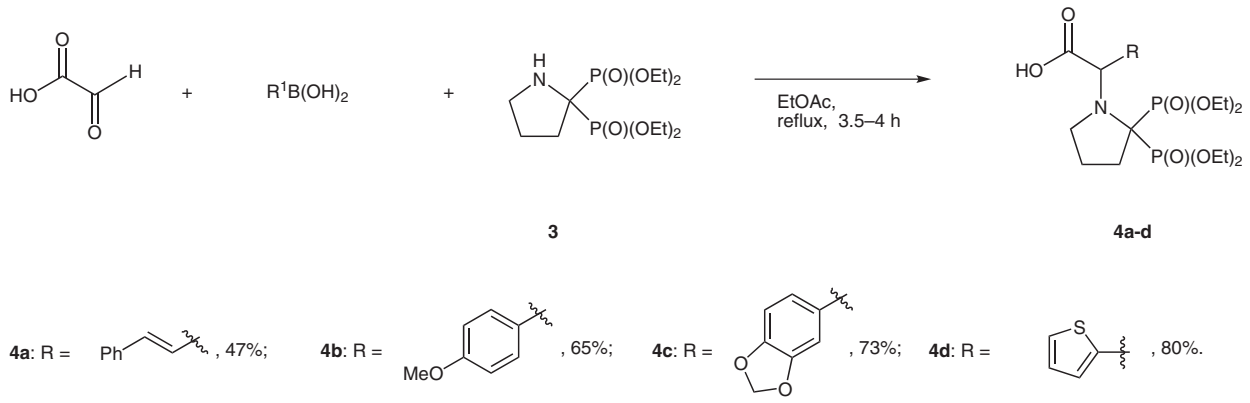
The best yield and diastereoselectivity (75% yield, ca. 9:1 dr; Table 1, entry 1) was achieved in ethyl acetate at reflux. Solvents having a high dielectric constant such as ethanol, acetonitrile, and THF gave a lower yield of **2a**. Water proved to be also a suitable solvent for this reaction and afforded the product in 66% yield. In a next step, different organoboronic acids were evaluated. The use of phenylboronic acid only gave trace amounts of the corresponding *N*-phosphonomethylglycine. However, electron-rich 4-methoxyphenyl-, 3,4-methylenedioxyphenyl-, and 2-thiopheneboronic acids were successful as the boron reactants (entries 2–4, Table 1).

It was also found that diethyl 1-(*N*-benzylamino)-1-phenylmethylphosphonate (**1b**) containing a secondary amino group successfully underwent similar transformations (entries 5–8, Table 1). For these reactions, higher diastereoselectivity (>95:5 dr) and slightly higher yields of products were obtained in good agreement with previous experimental findings and DFT calculations.[4,9]

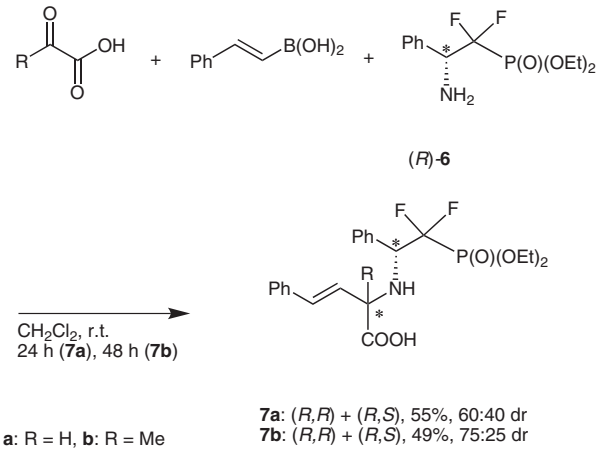
An analogous series of reactions was then performed with the sterically hindered tetraethyl (pyrrolidine-2,2-diyl)bisphosphonate **3**. As shown in Scheme 2, the reactions provided modest to good yields of the corresponding bisphosphonate derivatives **4**.[10]

Finally we expanded our substrates to include β-aminophosphonates. The one-step, three-component reaction of styrylboronic acid, glyoxylic acid monohydrate and previously synthesized (*R*)-β-amino-α,α-difluoromethylphosphonate (**6**),[11] in a variety of solvents, including methanol, ethyl acetate, and dichloromethane, resulted in the formation of desired compound **7a** in modest isolated yield. Dichloromethane provided shorter reaction times and slightly higher conversion than methanol and other aprotic solvents. However, in all cases, poor level of diastereoselectivity (ca. 60:40 dr) was observed. When pyruvic acid was used as a carbonyl component, the corresponding product **7b** was obtained in 49% yield with a diastereomeric ratio of 75:25 (Scheme 3).[12]

In summary, we have reported a facile multicomponent synthesis of highly functionalized *N*-phosphonomethyl-



Scheme 2



Scheme 3

glycines and their analogues. The method is shorter and more convenient than traditional routes.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) To a stirred suspension of glyoxylic acid monohydrate (92 mg, 1.00 mmol) in EtOAc (5 mL) tetraethyl pyrrolidine-2,2-diyldiphosphonate (**3**, 343 mg, 1.00 mmol) was added dropwise, after 5 min 2-thiopheneboronic acid (128 mg, 1.00 mmol) was added in one portion, and the reaction mixture was refluxed over 4 h while monitored by TLC (5% MeOH in $CHCl_3$). After the completion of the reaction the solvent was evaporated yielding the crude product as yellow oil. Flash chromatography using 5% of MeOH in CH_2Cl_2 afforded 390 mg (80%) of compound **4d** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, 3 H, OCH_2CH_3),1.15 (t, 3 H, OCH_2CH_3), 1.30 (t, 3 H, OCH_2CH_3), 1.31 (t, 3 H, OCH_2CH_3), 1.77–1.84 (m, 2 H, CH_2), 2.19 (m, 2 H, CH_2), 3.01–3.07 (m, 1 H, CH_2), 3.17–3.23 (m, 1 H, CH_2), 3.78–3.88 (m, 1 H, OCH_2CH_3), 3.90–4.10 (m, 3 H, OCH_2CH_3), 4.14–4.26 (m, 4 H, OCH_2CH_3), 5.83 (s, 1 H, CHCOOH), 6.87 (dd, J_{HH} = 3.7 Hz, J_{HH} = 5.1 Hz, 1 H, $H_{thiophene}$), 7.08 (dd, J_{HH} = 1.0 Hz, J_{HH} = 3.7 Hz, 1 H, $H_{thiophene}$), 7.20 (dd, J_{HH} = 1.0 Hz, J_{HH} = 5.1 Hz, 1 H, $H_{thiophene}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2 (d, J_{CP} = 6.0 Hz, OCH_2CH_3), 16.5 (d, J_{CP} = 6.0 Hz, OCH_2CH_3), 16.5 (d, J_{CP} = 6.0 Hz, OCH_2CH_3), 16.6 (d, J_{CP} = 6.0 Hz, OCH_2CH_3), 24.0 (t, J_{CP} = 3.0 Hz, CH_2), 32.3 (t, J_{CP} = 4.0 Hz, CH_2), 48.1 (d, J_{CP} = 4.0 Hz, CH_2), 59.8 (s, CHCOOH), 62.3 (d, J_{CP} = 7.0 Hz, OCH_2CH_3), 63.2 (d, J_{CP} = 7.0 Hz, OCH_2CH_3), 63.5 (d, J_{CP} = 7.0 Hz, OCH_2CH_3), 63.5 (dd, J_{CP} = 150.0 Hz, J_{CP} = 155.0 Hz, PCP), 64.6 (d, J_{CP} = 7.0 Hz, OCH_2CH_3), 125.9, 125.9, 128.7, 138.3, 172.5 (s, COOH). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.8 (d, J_{PP} = 92.3 Hz, 1 P), 23.3 (d, J_{PP} = 92.3 Hz, 1 P). CI MS (CI, pos.): *m/z* (%) = 346 (100), 206 (15); MS (CI, neg.): *m/z* (%) = 482 (100) [M – H]$^-$, 438 (10), 328 (10), 233 (40), 138 (10), 103 (30), 85

(45). Anal. Calcd for $C_{18}H_{31}NO_8P_2S$: C, 44.72; H, 6.46, N, 2.90, S, 6.63. Found: C, 44.61; H, 6.41; N, 2.87; S, 6.68.

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(12) To a stirred solution of pyruvic acid (44 mg, 0.50 mmol) in CH_2Cl_2 (3 mL) aminophosphonate **6** (147 mg, 0.50 mmol) was added dropwise, after 5 min (*E*)-2-phenylethenyl boronic acid (74 mg, 0.50 mmol) was added in one portion, and the reaction mixture was stirred for 24 h while monitored by TLC (5% MeOH in $CHCl_3$). The solvent was evaporated, and the residual oil was chromatographed using a gradient of *i*-PrOH (7 → 13%) in CH_2Cl_2 to yield 75 mg (34%) as a mixture of diastereomers **7b**, and 35 mg (15%) as pure major diastereomer. Summary yield 110 mg (49%). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, 3 H, OCH_2CH_3),1.33 (t, 3 H, OCH_2CH_3), 1.50 (s, 3 H, CH_3), 4.09–4.33 (m, 4 H, OCH_2CH_3), 4.38 (dd, J_{HF} = 23.0 Hz, J_{HF} = 8.0 Hz, 1 H, CF_2CH), 5.94 (d, J_{HH} = 16.0 Hz, 1 H, PhCH=C*H*), 6.48 (d, J_{HH} = 16.0 Hz, 1 H, PhC*H*=CH), 6.40 (br s, NH), 7.07 (d, J_{HH} = 7.0 Hz, 2 H, H_{Ph}), 7.18–7.39 (m, 8 H, H_{Ph}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (m, OCH_2CH_3), 22.2 (s, CH_3), 63.5 (s, *C*HCOOH), 64.7 (d, J_{CP} = 7.0 Hz, OCH_2CH_3), 65.2 (d, J_{CP} = 7.0 Hz, OCH_2CH_3), 126.7, 128.07, 128.5, 128.6, 128.6, 129.1, 130.9, 131.5, 136.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –121.6 (ddd, J_{FF} = 304.0 Hz, J_{FP} = 108.0 Hz, J_{FH} = 23.0 Hz, 1 F), –110.6 (ddd, J_{FF} = 304.0 Hz, J_{FP} = 104.0 Hz, J_{FH} = 8.0 Hz, 1 F). ^{19}P NMR (162 MHz, $CDCl_3$): δ = 6.7 (dd, J_{PF} = 108.0 Hz, J_{PF} = 104.0 Hz). Anal. Calcd for $C_{23}H_{28}F_2NO_5P$: C, 59.10; H, 6.04. Found: C, 59.06; H, 6.14.