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An improved protocol for Petasis reaction of 2-pyridinecarbaldehydes

Hiroki Mandai *, Kyouta Murota, Takashi Sakai

Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan

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ABSTRACT

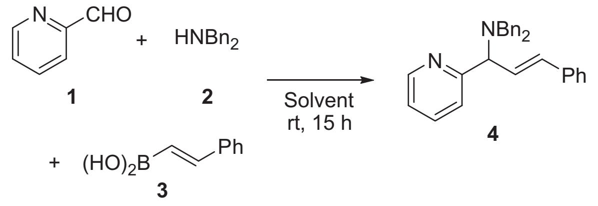
A highly efficient and improved method has been developed for Petasis reactions of various 2-pyridinecarbaldehydes with secondary amines and boronic acids under catalyst-free conditions. The desired products are obtained in up to 96% yield in refluxed acetonitrile.

Multicomponent reactions are highly efficient and atom economical transformations in synthetic organic chemistry.[1] They can be used for constructing an array of compound libraries in the medicinal chemistry field. In the course of our research program, we have been showing interest in the boron Mannich reaction disclosed by Petasis.[2] Three substrates (aldehyde, amine, and boronic acid) react sequentially to afford a Mannich adduct without any catalyst. However, only a few aldehydes (e.g., glyoxylic acid[3] and α-hydroxyl aldehyde[4]) have been employed in this reaction, and successful examples of aromatic aldehydes have been limited to salicyl aldehydes.[5] In 2000, Bryce and Hansen reported Petasis Mannich reactions of 2-pyridinecarbaldehyde with morpholine and vinyl boronic acid under catalyst-free conditions, affording the desired products in 10% yield.[6] They finally found that using the more reactive alkenyl trifluoroborate salt and chlorotrimethylsilane as activators improved the yield of the desired product up to 54% yield. Thus, there are no efficient methods for Petasis Mannich reactions of 2-pyridinecarbaldehydes with amine and boronic acid under catalyst-free conditions. In this Letter, we would like to report on an improved method for Petasis reaction of 2-pyridinecarbaldehydes with various amines and boronic acids under catalyst-free conditions.

Initially, we examined various solvents for the Petasis reaction of 2-pyridinecarbaldehyde **1** with dibenzylamine **2** and vinyl boronic acid **3** at room temperature. As illustrated in Table 1, CH_2Cl_2, dichloroethane, MeCN, and hexafluoroisopropanol (HFIP)[7] underwent Petasis reactions in 55–78% conversion; however, other solvents, such as MeOH, H_2O,[5d] and 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim]BF_4),[8] which were often utilized in Petasis reactions, resulted in <10% conversion. Although the effect of the solvent is unclear, MeCN clearly enhanced the reaction rate and was found to be the optimal solvent.

Next, to improve the conversion of the desired product, we screened the substrate concentration and reaction temperature (Table 2). Reaction in 0.1 or 0.2 M of the solvent gave a slightly better conversion than that in 0.5 M which caused solubility issue of vinyl boronic acid (entries 1–3). In addition, reaction at refluxed temperature in 0.2 M of MeCN gave the product in >98% conversion after 15 h (entry 5), and later TLC analysis of the reaction mixture revealed that full consumption of aldehyde was observed after 3 h under the same conditions (entry 6). Accordingly, the Petasis reaction of 2-pyridinecarbaldehyde **1** with dibenzylamine **2** and vinyl boronic acid **3** proceeded smoothly in MeCN at refluxed temperature within 3 h, affording the Mannich adduct **4** in >98% conversion (96% isolated yield after silica gel column chromatography).[9]

Table 1
Solvent effect on Petasis reaction[a]



Entry	Solvent	Conv.[b] (%)
1	CH_2Cl_2	55
2	Dichloroethane	46
3	MeCN	73
4	HFIP	58
5	MeOH	<10
6	Toluene	<10
7	THF	<2
8	Et_2O	<2
9	DMF	<10
10	H_2O	<10
11	[bdmim]BF_4	<2

[a] Reactions performed under an atmosphere of N_2 with 1.0 equiv of aldehyde **1** and amine **2** in the presence of 1.0 equiv of vinyl boronic acid at room temperature for 15 h.

[b] Conversions were determined by analysis of ^{1}H NMR spectra of the unpurified reaction mixtures.

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* Corresponding author. Tel.: +81 86 251 8604; fax: +81 86 251 8082.
E-mail address: mandai@cc.okayama-u.ac.jp (H. Mandai).

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Table 2
Effect of concentration and reaction temperature[a]

Entry	Concn (M)	Temp (°C)	Conv.[b] (%)
1	0.1	rt	73
2	0.2	rt	73
3	0.5	rt	59
4	0.2	50	84
5	0.2	Reflux	>98 (96)[d]
6[c]	0.2	Reflux	>98 (96)[d]

[a] Reactions performed under an atmosphere of N_2 with 1.0 equiv of aldehyde **1** and amine **2** in the presence of 1.0 equiv of vinyl boronic acid **3** for 15 h except entry 6.

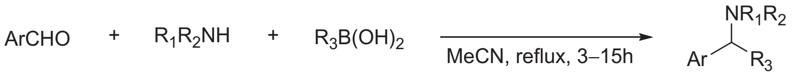
[b] Conversions were determined by analysis of ^1H NMR spectra of the unpurified reaction mixtures.

[c] The reaction time was 3 h.

[d] Isolated yield of the product.

Various amines, aldehydes, and boronic acids were examined under optimized conditions (Table 3). As alternative nitrogen sources, both acyclic- and cyclic amines could be used in the Petasis reaction, affording the desired products in 72–96% yields (entries 1–5).[10] In contrast, the structure of an aldehyde component had a great influence on the yield of the product (entries 6–12). For example, reactions of 6-methoxy- and 6-bromo-2-pyridinecarbaldehydes with dibenzylamine and vinyl boronic acid dramatically decreased the reaction efficiency under the optimized conditions (16% for **9** and 11% for **10**, respectively; entries 6 and 8), and use of excess vinyl boronic acid (1.5 equiv) slightly increased the yield of the products (31% and 23%, respectively, entries 7 and 9). Whereas 5-bromo-2-pyridinecarbaldehyde with 1.0 equiv of dibenzylamine and vinyl boronic acid reacted smoothly to deliver the Petasis adduct **11** in 91% yield (entry 10). These results clearly indicate that steric hinderance adjacent to pyridine nitrogen dominates the reactivity of the aldehyde component. For this reason, 6-bromo-2-pyridinecarbaldehyde suffered reactivity and resulted in a low yield (entry 8 vs 10). It might be considered that an α-heteroatom moiety played an important role in taking boronic acid close to the reaction site and/or in intramolecular activation of boronic acid (e.g., ate complex formation by nitrogen atom).[1] Reaction of 4-chloro- and 4-dimethylamino-2-

Table 3
Scope of the substrate for Petasis reaction[a]



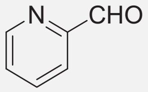
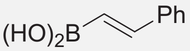
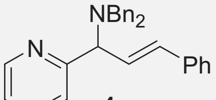
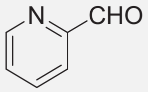
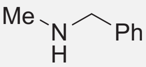
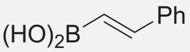
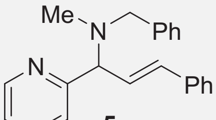
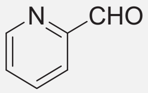
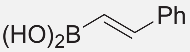
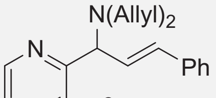
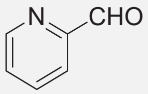
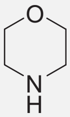
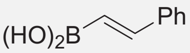
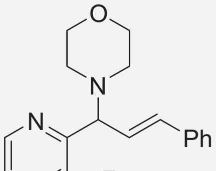
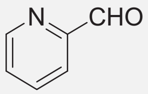
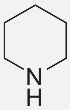
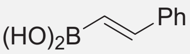
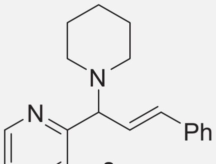
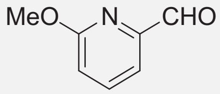
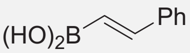
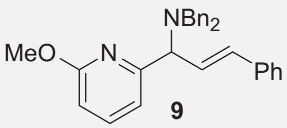
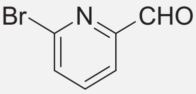
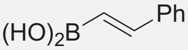
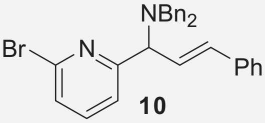
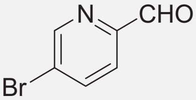
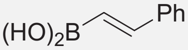
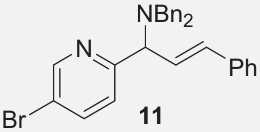
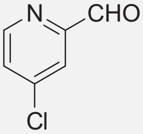
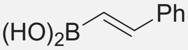
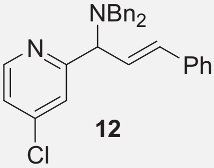
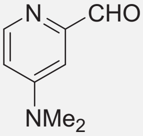
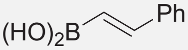
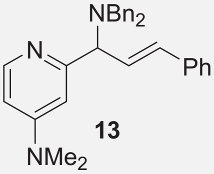
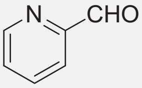
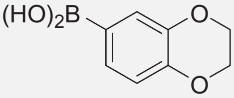
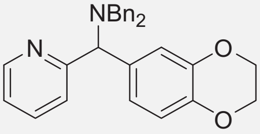
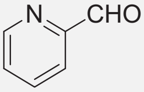
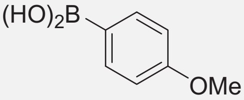
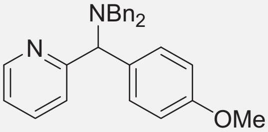
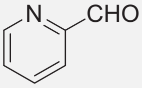
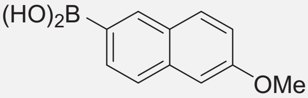
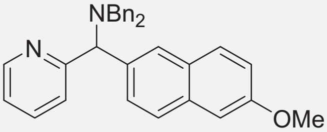
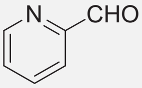
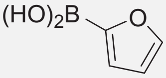
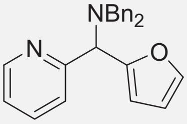
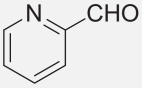
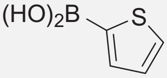
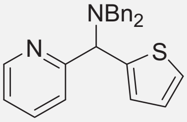
Entry	ArCHO	Amine	Boronic acid	Product	Yield[b] (%)
1[c]		HNBn₂		 **4**	96
2				 **5**	77
3[d]		HN(Allyl)₂		 **6**	72
4				 **7**	95
5				 **8**	75
6 7[e]		HNBn₂		 **9**	16 31

Table 3 (*continued*)

Entry	ArCHO	Amine	Boronic acid	Product	Yield[b] (%)
8 9[e]		$HNBn_2$		 **10**	11 23
10		$HNBn_2$		 **11**	91
11		$HNBn_2$		 **12**	74
12		$HNBn_2$		 **13**	35
13		$HNBn_2$		 **14**	90
14		$HNBn_2$		 **15**	70
15 16[e]		$HNBn_2$		 **16**	27 46
17		$HNBn_2$		 **17**	80
18 19[e]		$HNBn_2$		 **18**	32 78

[a] Reactions performed under an atmosphere of N_2 with 1.0 equiv of aldehyde and amine in the presence of 1.0 equiv of boronic acid in refluxed MeCN for 15 h.
[b] Isolated yield of the product after silica gel column chromatography.
[c] The reaction time was 3 h.
[d] The reaction time was 12 h.
[e] 1.5 equiv of boronic acid was used.

pyridinecarbaldehyde proceeded to afford the products **12** and **13** in 74% and 35%[11] yields, respectively. Other heteroaromatic aldehydes involving 3-pyridinecarbaldehyde, pyrrole-2-carboxaldehyde, imidazole-2-carboxaldehyde, and 2-quinolinecarboxaldehyde resulted in no conversion or a complex mixture (data not shown), and the reasons for these results remained obscure. As a result, Petasis reactions of various 2-pyridinecarbaldehyde analogs took place, and these phenomena were consistent with previous observations.[6]

With regard to the boronic acid component, a variety of aromatic boronic acids could be used in this reaction, delivering the desired products **14**–**18** in 46–90% yields (entries 13–17). In some cases, 1.5 equiv of boronic acid was required to obtain a reasonable yield (entry 15 vs 16 and 18 vs 19). However, no desirable products were obtained when the reactions were performed with electron-deficient phenylboronic acid and 3,5-bis(trifluoromethyl)phenylboronic acid (data not shown). It seems that the boronic acid component should have enough nucleophilicity to react with the iminium intermediate.

In conclusion, we have developed Petasis reactions of various 2-pyridinecarbaldehydes with various amines and boronic acids without any catalyst. Our method allows us to access a wide range of amines adjacent to heteroaromatic rings, which may be useful compounds for medicinal and material chemistry. Further investigations regarding Petasis reactions of heteroaromatic aldehydes with or without an α-heteroatom are now in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.039.

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