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Efficient synthesis of pyrazine boronic esters via palladium-catalyzed Miyaura borylation

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ABSTRACT

A facile and efficient protocol for palladium-catalyzed Miyaura borylation reaction of chloropyrazines with B_2pin_2 has been developed. A certain range of difficult-to-access pyrazine boronic esters can be easily prepared from the corresponding chloropyrazines in moderate to good yields.

Introduction

Heterocyclic boronic esters have been widely utilized in many useful chemical transformations as a kind of versatile synthetic intermediates.[1] For example, the Suzuki-Miyaura cross-coupling reactions,[2] Cu-catalyzed Chan-Lam-Evans reactions,[3] oxidation reactions,[4] and carboxylation reactions,[5] etc. Pyrazine boronic esters are essential chemical building blocks in medicinal chemistry.[6] Pyrazine derivatives are an important class of compounds found in bioactive natural products and medicinally valuable molecules, which show cytostatic, antifungal, and antitumor properties (Fig. 1).[7] In addition, pyrazine derivatives are widely used in fragrances and functional materials.[8] Consequently, the development of efficient methods for functionalization of pyrazines has gained much attention from medicinal and synthetic organic chemists.

Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of halogenated pyrazines with arylboron reagents is a classical tool in the synthesis of these functionalized pyrazines.[9] However, pyrazinyl boronic esters are less commonly employed in these Suzuki-Miyaura cross couplings, which are likely due to their instability as 2-pyridyl boronates.[10] In 2010, Burke and co-workers developed the only air-stable pyrazinyl borane building block example of 2-pyrazinyl MIDA boronate, which was synthesized by direct translation of 2-pyrazine trialkoxyborate salts with *N*-methyliminodiaceticacid (MIDA).[11] Additionally, the pyrazine boronic esters can be prepared via transition-metal-catalyzed borylation. One is Ir-catalyzed direct C-H borylation of pyrazines,[12] this method showed poor regioselectivity and offered only three examples of alkyl substituted pyrazinyl boronic esters. The other is Pd-catalyzed Miyaura borylation of halogenated pyrazines.[13] The existing literature about Pd-catalyzed Miyaura borylation of bromopyrazines usually need microwave-assistance and long reaction time. Moreover, all above-mentioned methods did not obtain chemically pure products, and the commercially available pyrazine boronic esters are very expensive.[14] Therefore, it is still highly required to develop economical and efficient methods to prepare pyrazinyl boronic esters and get pure form. We have an ongoing interest in the synthesis and application of heteroaryl boronates,[15] and herein we report a facile and efficient method for the synthesis of the pyrazine boronic esters.

Results and discussion

Chloropyrazines are the most desirable substrates because of their low cost and broad availability, which are easily modified by some nucleophilic substitution reactions.[16] Accordingly, 2-tert-butoxy-6-chloro-pyrazine **1a** was selected as the model substrate for our studies on the optimal condition (Table 1). Initially,

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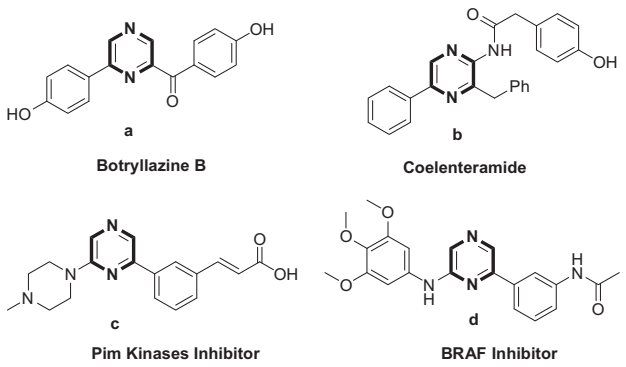
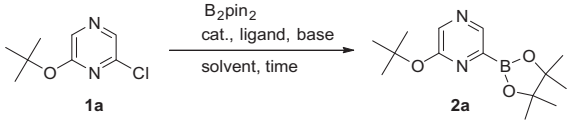


Fig. 1. Bioactive compounds containing pyrazine moiety.

the reaction was carried out in the presence of 2.0 mol% $Pd(OAc)_2$, 4.0 mol% PCy_3 and 1.1 equiv. B_2pin_2 in dry dioxane at 90 °C under nitrogen for 8 h (entry 1). The desired product was detected in 94% yield by GC–MS. Through the screening of ligand, PCy_3 was found to be the best one. Almost no reaction occurred when PPh_3 and DPPF was used (Table 1, entry 1 *vs* entries 2, 3). Then, $PdCl_2$, Pd $(PPh_3)_4$, and $Pd_2(dba)_3$ were studied as Pd sources. $Pd(OAc)_2$ was used due to the low cost which has similar effects in the reaction compared to $Pd_2(dba)_3$ (Table 1, entries 4–6). Furthermore, the effect of solvent was researched, both DMF and dioxane can obtain good results. Dioxane was selected because it is easier to be removed by distillation in comparison to DMF (Table 1, entries 7–9). After screening of the reaction time and temperature, to our delight, the reaction time was shortened to 10 min at 110 °C without decreasing its efficiency (Table 1, entry 12). Further studies showed the effect of atmosphere had little influence on this reaction (Table 1, entry 13). Finally, the optimal reaction condition was achieved as the combination of 2.0 mol% $Pd(OAc)_2$, 4.0 mol% PCy_3, 1.1 equiv. B_2pin_2 and 2.5 equiv. AcOK in dioxane at 110 °C under N_2 atmosphere for 10 min. However, we encountered difficulties in purification step. After doing work-up with water according to the literature method, 2-tert-butoxy pyrazine was observed in GC-MS as a major byproduct indicating that protodeborylation of the pyrazinyl boronic ester **2a** was occurred. In addition, purification was failed by column chromatography. At last, recrystallization was found to be essential for purification of these products. The reaction mixture was filtered and concentrated, resulting residue was precipitated from n-hexane/Et_2O to afford **2a** as white solid.

With the optimized conditions in hand, we applied this borylation reaction to a variety of functionalized chloropyrazines (Table 2). Alkoxy substituted chloropyrazines (**1a**–**1f**) were suitable for this borylation and the desired boron compounds were obtained in moderate to good yields. Interestingly, the 6-methoxypyrazin-2-ylboronic acid (**2c**) instead of its boronic ester was easily to get by work-up with water. Other substrates were not suitable for work-up by water. Alkyl substituents did not obviously affect the efficacy, and the desired products were prepared in credible yields (**2g** and **2h**). Unfortunately, the pure compound **2g** was difficult to get, because it is easy to decompose before purification as literature reported.[12a] Chloropyrazine boronic ester (**2i**) can be produced from 2,6-dichloropyrazine, the pure form was difficult to get because of its unstability. Primary amino substituted chloropyrazines (**1j**) could not transform to the desired boronic ester except 2-amino-5-bromopyrazin (**1k**). Secondary amine were greatly influenced by the solvent effect. The reaction worked smoothly when DMF was used as a solvent in place of dioxane (**2l** and **2m**). Tertiary amine substituted chloropyrazines can be easily transform to corresponding boronic esters (**2n**-**2p**). Specifically, 6-amino-2-pyrazinyl subunits were widely found in a variety of pharmaceuticals. Additionally, aryl-containing substrates such as 2-chloro-6-phenylpyrazine (**1q**), 2-chloro-6-(4-methoxyphenyl)-pyrazine (**1r**) and 2-chloro-6-(3-fluorophenyl)pyrazine (**1s**) were also suitable, and the corresponding boronates were obtained in good yields. However, 2-chloro-3-substituted pyrazines (**1t** and **1u**) could not convert to the corresponding boronic esters possibly due to their steric effect. This reaction conditions were also applied to other related

Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst	Ligand	Base	Solvent	Time (h)	Yield[b] (%)
1	$Pd(OAc)_2$	PCy_3	AcOK	Dioxane	8	94
2	$Pd(OAc)_2$	PPh_3	AcOK	Dioxane	8	Trace
3	$Pd(OAc)_2$	DPPF	AcOK	Dioxane	8	Trace
4	$Pd_2(dba)_3$	PCy_3	AcOK	Dioxane	8	93
5	$Pd(PPh_3)_4$	PCy_3	AcOK	Dioxane	8	86
6	$PdCl_2$	PCy_3	AcOK	Dioxane	8	55
7	$Pd(OAc)_2$	PCy_3	AcOK	DMF	8	90
8	$Pd(OAc)_2$	PCy_3	AcOK	Toluene	8	66
9	$Pd(OAc)_2$	PCy_3	AcOK	THF	8	83
10[c]	$Pd(OAc)_2$	PCy_3	AcOK	Dioxane	0.5	90
11[d]	$Pd(OAc)_2$	PCy_3	AcOK	Dioxane	0.5	92
12[e]	$Pd(OAc)_2$	PCy_3	AcOK	Dioxane	1/6	98/85[f]
13[e,g]	$Pd(OAc)_2$	PCy_3	AcOK	Dioxane	1/6	95

[a] Reaction conditions: **1a** (1.0 mmol), B_2pin_2 (1.1 equiv), catalyst (2.0 mol%), ligand (4.0 mol%), AcOK (2.5 equiv), solvent (3.0 mL), 90 °C, N_2 atmosphere.
[b] GC–MS yield.
[c] 80 °C.
[d] 100 °C.
[e] 110 °C, 10 min.
[f] Isolated yield.
[g] Air atmosphere.