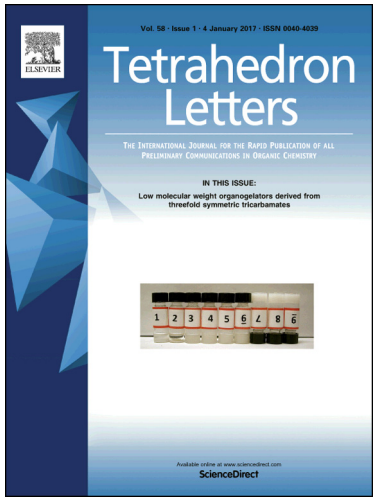

The modified-Mannich reaction: conversion of arylboronic acids and subsequent coupling with paraformaldehyde and amines toward the one-pot synthesis of Mannich bases and benzoxazines

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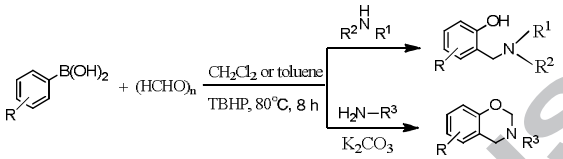

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The modified-Mannich reaction: conversion of arylboronic acids and subsequent coupling with paraformaldehyde and amines toward the one-pot synthesis of Mannich bases and benzoxazines

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ABSTRACT

A modified Mannich reaction has been developed for the synthesis of Mannich bases and benzoxazines via the oxidative hydroxylation of arylboronic acids and subsequent coupling with paraformaldehyde and amines in one pot. This modified Mannich reaction is easily carried out to afford the target products in good to excellent yields and tolerates a variety of functional groups.

Introduction

Mannich bases and benzoxazines have attracted much attention during the past decades since they have many applications in various fields. For example, some investigations have indicated that the compounds with Mannich base pharmacophore motif show a good antimalarial performance[1] and anticonvulsant activity.[2] Mannich bases can also serve as phase transfer catalysts and chiral auxiliary ligands in asymmetric synthesis,[3] and be extensively utilized as potential precursors to obtain new BINOLAMS [2,2'-bis(aminomethyl)-1,1'-dihydroxy-4,4'-binaphthalenes] and o-quinone methides.[4] As a sort of heterocyclic compounds, benzoxazines have excellent mechanical properties, thermal stability, and low dielectric constant. Thus, they are widely used for ring-opening polymerization.[5]

The Mannich reaction is one of the most important C–C bond constructions in organic synthesis. Many efforts were devoted to synthesis of Mannich bases via the Mannich reactions.[6] Recently, Chang *et al.* developed Brønsted acid-surfactant-combined catalysts for the three-component Mannich reaction with aldehyde, acetone and amine in water at room temperature.[7] Seidel and co-workers synthesized a series of ring-substituted *β*-amino ketones via the redox-Mannich Reaction.[8] Han *et al.* made use of diaryliodonium salts as Lewis acid catalysts for three component Mannich reactions.[9] These investigations have greatly extended the application scope of the Mannich reaction.

Over the past decades, arylboronic acids have gained an extensive application and been recognized as valuable and efficient precursors owing to their stability toward water and air, low toxicity as well as tolerance to several functional groups, which make them play an important role in organic synthesis, material and medicinal chemistry.[10]

Some researchers have investigated the conversion of phenylboronic acids to phenols,[11] and the reaction of phenols with formaldehyde and amines.[12] However, to the best of our knowledge, it has not been explored to date that the multi-component reaction contains both the conversion of phenylboronic acid and subsequent coupling with paraformaldehyde and amines for Mannich bases and benzoxazines in one pot. We herein report such a novel one-pot synthesis of Mannich bases and benzoxazines via the reaction of arylboronic acid with paraformaldehyde and secondary/primary amines. This modified Mannich reaction could be smoothly carried out to afford the target products in high to excellent yields.

Result and Discussion

Our study first focused on the model reaction between phenylboronic acid (**1a**), paraformaldehyde and morpholine in MeCN solvent at 80 □ for 8 h (Table 1). Compared with H_2O_2, Oxidant TBHP gave a relatively higher yield (Table 1, entries 1 and 2). However, if an oxidant was absent, the desired product was not obtained at all (Table 1, entry 9), which revealed that an oxidant was necessary for this transformation. The effect of

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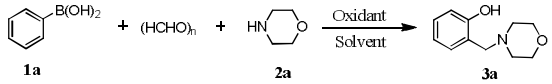
solvents on the reaction was further examined. It was found that CH_2Cl_2 and toluene could give better results than MeCN (Table 1, entries 1, 6 and 8), whereas high polar solvents (such as DMSO, DMF, especially C_2H_5OH and H_2O) afforded relatively low yields of the target product (Table 1, entries 3–5 and 7). In addition, as the temperature was dropped, the yield decreased obviously (Table 1, entries 8–10). The screening of the amount of the oxidant indicated that 1.5 equiv of TBHP was the most suitable for the reaction (Table 1, entries 6 and 13–15).

Table 1 Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	Oxidant	Solvent	Yield (%)[b]
1	TBHP	MeCN	92
2	H_2O_2	MeCN	78
3	TBHP	DMSO	84
4	TBHP	DMF	76
5	TBHP	C_2H_5OH	64
6	**TBHP**	**CH_2Cl_2**	**98**
7	TBHP	H_2O	55
8	**TBHP**	**toluene**	**96**
9	—	CH_2Cl_2	0
10[c]	TBHP	CH_2Cl_2	81
11[d]	TBHP	CH_2Cl_2	77
12[e]	TBHP	CH_2Cl_2	5
13	TBHP (0.5 equiv)	CH_2Cl_2	59
14	TBHP (1 equiv)	CH_2Cl_2	90
15	TBHP (2 equiv)	CH_2Cl_2	88

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), $(HCHO)_n$ (0.5 mmol), solvent (2 mL), oxidant (1.5 equiv, aqueous solution, TBHP (70%), H_2O_2 (30%)) and 80 □ for 8 h in a sealed tube.

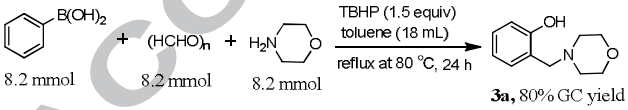
[b] Determined by GC-MS.

[c] Reaction temperature 60 □.

[d] Reaction temperature 40 □.

[e] Room temperature.

When the reaction was carried out on a gram-scale, **3a** could be obtained with 80% GC yield (Scheme 1), demonstrating its scalability and practicality.

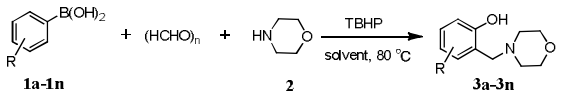


3a, 80% GC yield

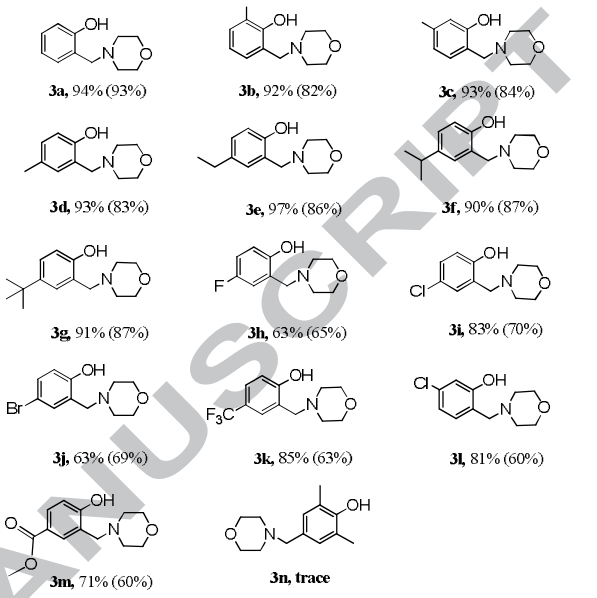
Scheme 1. The reaction on a gram-scale.

On the basis of the optimized conditions (Table 1, entry 6 or 8), we further examined the generality of the protocol. As shown in Table 2, various substituted phenylboronic acids proceeded smoothly to afford the corresponding products in moderate to excellent yields. It is worth mentioning that the reaction was quite regioselective without producing any other isomers besides amino methylated products at the ortho-position. The similar phenomenon was observed in the previous studies with phenol, formaldehyde and amines as the starting materials.[12n-12q] Moreover, the process could well tolerate various functional groups such as halogen (F, Cl and Br) (Table 2, **3h**–**3j** and **3l**), –CH_3, –CF_3, –CH_2CH_3, and –$COOCH_3$ (Table 2, **3b**–**3e** and **3k**),

Table 2 Scope of arylboronic acids.[a,b]

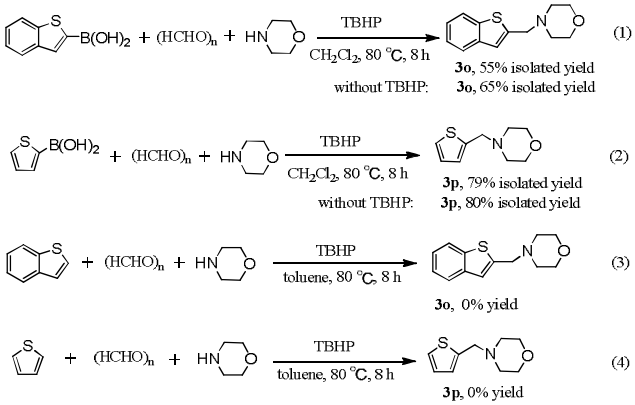


1a-1n **2** **3a-3n**



[a] Reaction conditions: arylboronic acids (0.5 mmol), morpoline (0.5 mmol), $(HCHO)_n$ (0.5 mmol), CH_2Cl_2 or toluene (2 mL), TBHP (1.5 equiv,70% in water) and 80 □ for 8 h in a sealed tube .

[b] Isolated yield, the number in parentheses was obtained with toluene as the solvent.



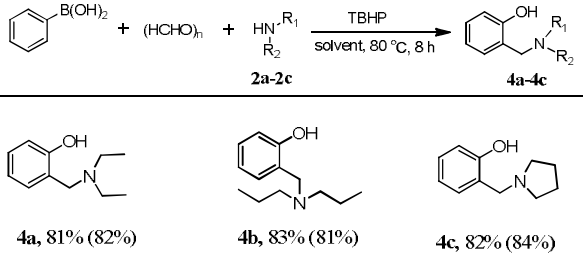
Scheme 2. Contrast experiments.

which provided the possibility for further functionalization. The electron-donating groups attached to phenylboronic ring afforded higher yields compared with the electron-withdrawing groups. For instance, 2-(morpholinomethyl)phenol with –CH_3 at the para-position gave a higher yield (93%, Table 2, **3d**), while 2-(morpholinomethyl)phenol bearing a chlorine group provided a relatively low yield (83%, Table 2, **3i**). With (2,6-dimethylphenyl)boronic acid as the substrate, a trace amount of the product **3n** corresponding to para position could be only observed (Table 2, 3n), further indicating that this reaction proceeds with a remarkable ortho-selectivity. Notably, using benzo[*b*]thiophen-2-ylboronic acid and thiophen-2-ylboronic acid

as the starting material failed to generate the corresponding phenols but gave unexpected products 4-(benzo[*b*]thiophen-2-ylmethyl)morpholine **3o** and 4-(thiophen-2-ylmethyl)morpholine **3p** in the presence or absence of TBHP (Scheme 2, Eqs 1 and 2), respectively. With benzothiophene or thiophene as the substrate, **3o** or **3p** was not obtained at all (Scheme 2, Eqs 3 and 4), and the substrate was almost quantitatively recovered. So, it could be concluded that the formation of **3o** or **3p** does not undergo the generation process of intermediate benzothiophene or thiophene.

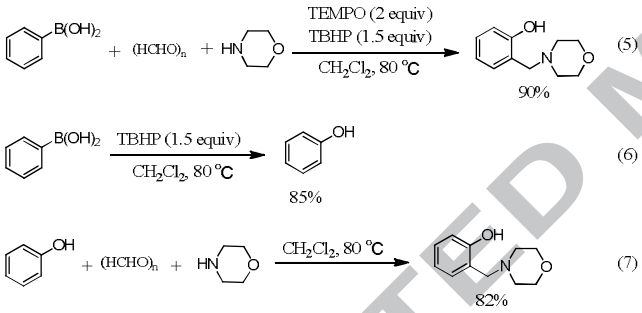
Being similar to morpholine, other secondary amines such as diethylamine, dipropylamine and pyrrolidine could give satisfactory results as well (Table 3, **4a**–**4c**).

Table 3 Scope of secondary amines. [a,b]



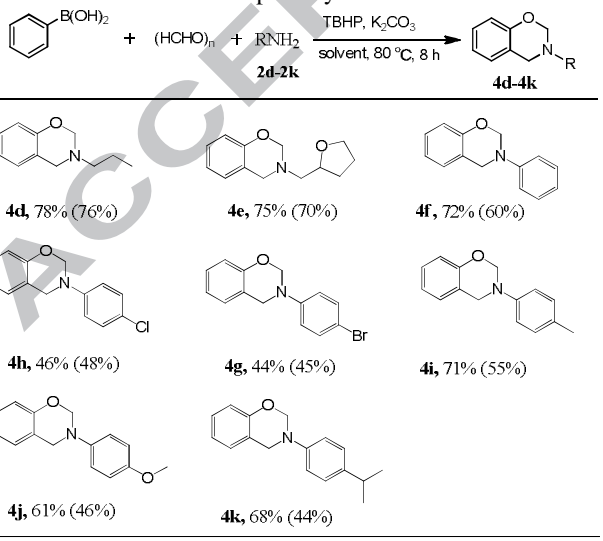
[a] Reaction conditions as shown in Table 2.

[b] Isolated yield, the number in parentheses was obtained with toluene as the solvent.



Scheme 3. Control experiments.

Table 4 Reaction results of primary amines. [a,b]

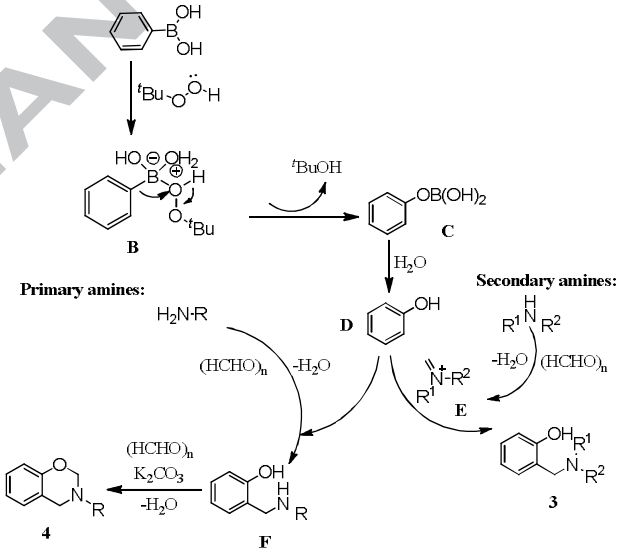


[a] Reaction conditions: **1a** (0.5 mmol), primary amine (0.5 mmol), $(HCHO)_n$ (1 mmol), CH_2Cl_2 or toluene (2 mL), TBHP (1.5 equiv, 70% in water), K_2CO_3 (2 mmol) and 80 ℃ for 8 h in a sealed tube.

[b] Isolated yield, the number in parentheses was obtained with toluene as the solvent.

Differing from secondary amines, primary amines resulted in new product benzoxazines (Table 4). As shown in Table 4, both primary aliphatic amines, aniline and substituted anilines could afford the corresponding benzoxazines in moderate to high yields (Table 4, **4d**–**4k**). Generally, the anilines with electron-deficient substituent groups furnished lower yields than those with electron-rich groups (Table 4, **4f**–**4k**).

Several control experiments were carried out to give an insight into the reaction mechanism (Scheme 3). The reaction could proceed well in the presence of radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), which indicated that the reaction may not involve a radical pathway (Eq. 5). When the phenylboronic acid alone was treated under the standard conditions, the corresponding phenol was obtained (Eq. 6). In addition, phenol could smoothly react with paraformaldehyde and morpholine to form the target product with 82% yield under the similar conditions (Eq. 7). Therefore, we deduce that the reaction mechanism may undergo the conversion of phenylboronic acid to phenol, which is a key process.



Scheme 4. Proposed reaction mechanism.

Based on the control experimental results and the literatures reported, a possible reaction route is proposed in Scheme 4. Phenolboronic acid firstly undergoes an oxidative process to give the intermediate product **C**, followed by the hydrolysis to generate a key intermediate product phenol **D**.[11a,11c,11d] Meanwhile, paraformaldehyde reacts with secondary amines to give an intermediate **E**,[13] and then subsequent combination with the formed *in-situ* phenol **D** to produce the target product Mannich base **3**.[12a,12b] In addition, primary amines could react with paraformaldehyde and the phenol **D** to afford an *o*-alkylaminomethyl-*p*-substituted phenol intermediate **F**.[12a] In the presence of base K_2CO_3, the intermediate **F** could be readily converted to the target product benzoxazine **4**.[12a] When primary amines used as the substrates, the intermediate **F** has been detected by GC-MS analysis, which further supports this reaction mechanism.

Conclusions

In summary, we have successfully carried out the conversion of arylboronic acids to phenols and subsequent coupling with

paraformaldehyde and amines for the synthesis of Mannich bases and benzoxazines in one pot. The present work making use of the stable and wide commercial available arylboronic acids as the starting materials provides a new route for the synthesis of Mannich bases and benzoxazines.

Acknowledgments

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

- A novel one-pot route is developed to synthesize Mannich bases and benzoxazines.
- The reaction proceeds with high yields and a remarkable ortho-selectivity.
- Secondary amines with arylboronic acids and paraformaldehyde yield Mannich bases.
- Primary amines with arylboronic acids and paraformaldehyde result in benzoxazines.