

Water: A Suitable Medium for the Petasis Borono-Mannich Reaction

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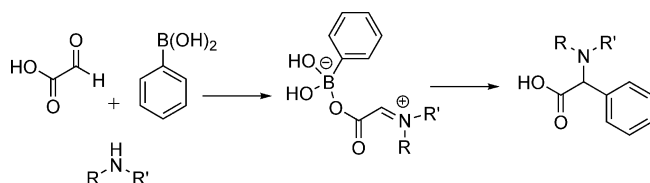
Water was used as the solvent in the Petasis borono-Mannich reaction. With the use of salicylaldehyde, secondary amines and boronic acids, several alkylaminophenols were obtained in considerably high yields in water. By using the same methodology, 2*H*-chromenes were prepared with the use of vinyl

boronic acids. The reaction mechanism was studied by DFT calculations, and the results obtained corroborate the solvent effect experimentally observed.

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Introduction

Multicomponent transformations have recently gathered considerable attention in synthetic organic chemistry.^[1] The one-pot combination of several organic molecules is an open door to molecular diversity, which can be achieved, in some cases, with high atom efficiency.^[1] Among the reported multicomponent transformations, the Mannich-type condensation involving boronic acids developed by Petasis and coworkers is quite remarkable, because the boronic acid component is inert towards the aldehyde functionality, though it quite efficiently traps the imine or iminium double bond.^[2] As a result of this exquisite reactivity, the Petasis reaction (Scheme 1) has become an attractive method for the preparation of an assortment of compounds, among which amino acids, heterocycles and alkylaminophenols are the most easily accessible.^[3]



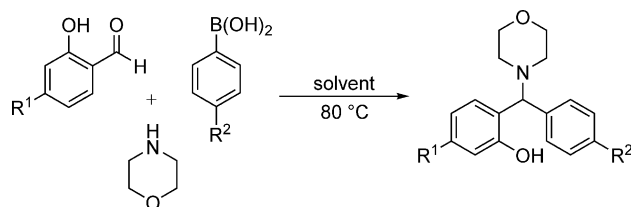
Scheme 1. Example of a Petasis borono-Mannich reaction.

Water is certainly one of the most desirable solvents available, because it is abundant, inexpensive and safe.^[4] Nevertheless, water notoriety does not end with this greener

relevance, as it quite often exerts a remarkable influence over the chemical transformations performed in this media.^[4] Therefore, it is with no surprise that we witness the efforts of numerous research groups to introduce water as solvent in many organic transformations, namely, multicomponent transformations.^[5] Hence, it is rather surprising that the Petasis borono-Mannich reaction has never been reported in water. This is the aim of this communication.^[6]

Results and Discussion

To test the possibility of using water as the reaction medium for the Petasis borono-Mannich reaction (Scheme 2) we combined salicylaldehyde, morpholine and phenyl boronic acid. To our delight, the reaction afforded the desired product in 75% yield after 24 h at 80 °C (Table 1, Entry 1). Extending the protocol to other aldehydes the reaction proceeded equally efficiently. Electron-donating substituents on the boronic acid moiety appeared to promote the reaction (Table 1, Entries 6 and 7), whereas the aryl substituents of the aldehydes had almost no observable influence on the reaction outcome (Table 1, Entries 1–3). Ethanol proved to be a less efficient solvent for this transformation and afforded the product in only 63% yield (Table 1, Entry 8).



Scheme 2. Petasis borono-Mannich reaction with salicylaldehyde.

Encouraged by these results, we extended the scope of this protocol to a variety of secondary amines and boronic acids (Scheme 3). The reaction proceeded mostly in high yields whether cyclic or acyclic secondary amines were used.

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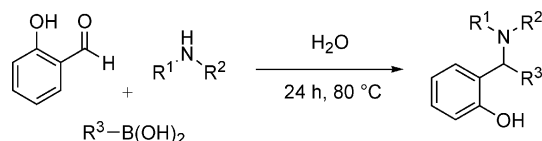
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Table 1. Substituent effects in the Petasis borono-Mannich reaction with salicylaldehyde.

Entry	R ¹	R ²	Conditions	Product	Yield [%] ^[a]
1	H	H	24 h, H ₂ O	1	75
2	Me	H	24 h, H ₂ O	2	70
3	OMe	H	24 h, H ₂ O	3	72
4	H	H	4.5 h, H ₂ O	1	54
5	H	F	4.5 h, H ₂ O	4	75
6	H	Me	4.5 h, H ₂ O	5	85
7	H	OMe	4.5 h, H ₂ O	6	81
8	H	H	24 h, EtOH	1	63

[a] Isolated yield by preparative thin-layer chromatography (hexane/AcOEt).

For those cases in which phenyl boronic acid was used (Table 2, Entries 1 and 8), slightly lower yields were obtained, as previously observed (Table 1). Amines such as dibenzylamine and diallylamine^[7] performed extremely well in water (Table 2, Entries 5, 8 and 9).



Scheme 3. Petasis borono-Mannich reaction in water – scope of the reaction.

Expanding the usefulness of this multicomponent reaction, Finn and coworkers reported the preparation of 2*H*-chromenes by using salicylaldehydes, a resin-bounded amine and vinylic boronic acids.^[8] In this reaction (Scheme 4), after condensation of the three components, an intramolecular cyclisation promoted by the phenol hydroxy group with consequent ejection of the amine moiety occurs. On the basis of this precedent, we tested this transformation in water with the use of different amines as cyclisation promoters.

Different from the method reported by Finn and coworkers, in water a stoichiometric amount of amine is necessary to achieve an efficient transformation (Table 3, Entries 3 and 4). Among the amines tested, diethylamine was the most competent, affording the cyclised product in 92% yield. Under the optimized reaction conditions, satisfying yields of 2*H*-chromenes **17** and **18** were obtained (Scheme 5).

Careful observation of the reaction mixture revealed that the salicylaldehyde formed an oil phase when added to water even at 80 °C, whereas the phenyl boronic acid was completely solubilised. When the secondary amine is added to the heterogeneous mixture, the iminium species is readily formed, which partitions to the aqueous phase. The iminium species can then react with the solubilised boronic acid to yield the Petasis borono-Mannich reaction product, which then cyclises to give the hydrophobic chromene product that precipitates. This was the case for product **11**, which completely precipitated from the aqueous phase once formed.

Table 2. Petasis borono-Mannich reaction in water – scope of the reaction.

Entry	Amine	Boronic acid	Product	Yield [%] ^[a]
1				78
2				94
3				96
4				91
5				99
6				98
7				79
8				82
9				96

[a] Isolated yields by preparative thin-layer chromatography (hexane/AcOEt).

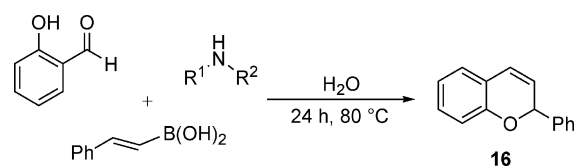
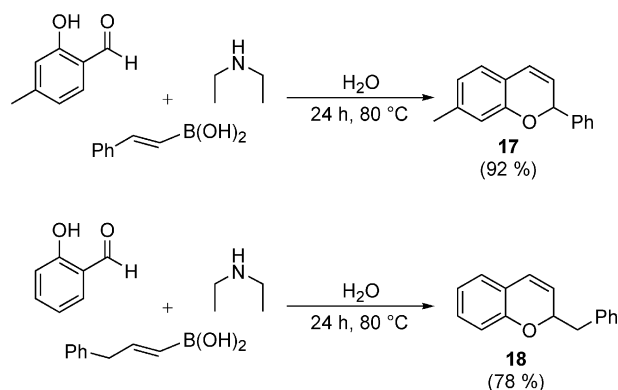
Scheme 4. Preparation of 2*H*-chromene in water by using the Petasis borono-Mannich reaction.

Table 3. 2H-Chromene synthesis in water by using the Petasis borono-Mannich reaction.

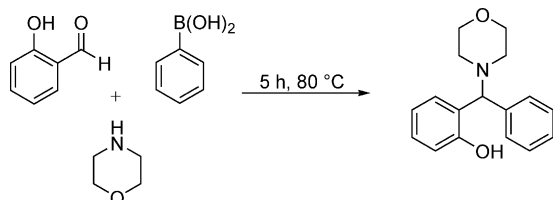
Entry	Conditions	Yield [%] ^[a]
1	Dimethylamine-HCl (1.2 equiv.) and NaOH (2 equiv.)	79
2	Dibenzylamine (1.2 equiv.)	58 ^[b]
3	Diethylamine (1.2 equiv.)	92
4	Diethylamine (20 mol-%)	49

[a] Isolated yield by preparative thin-layer chromatography (hexane/AcOEt). [b] Along with the 2H-chromene, 15% of a product that did not undergo cyclisation was isolated.



Scheme 5. Preparation of 2H-chromenes under the optimized conditions.

In line with recent reports regarding the water acceleration effect over reactions where at least one of the reactants forms an oil phase with water, we decided to compare the water system with other organic solvents (Scheme 6).^[9] The results shown in Table 4 suggest that water does not appear to have a favourable acceleration effect over the reaction, and solvents such as 1,2-dichloroethane (DCE) and toluene promoted the reaction slightly more efficiently.



Scheme 6. Petasis borono-Mannich reaction with salicylaldehyde in different solvent systems – solvent comparison.

Table 4. Petasis borono-Mannich reaction with salicylaldehyde – solvent comparison.

Entry	Solvent	Yield [%] ^[a]
1	H ₂ O	53
2	DME	69
3	DMF	41
4	Toluene	75
5	DCE	77

[a] Isolated yield of product **1** by preparative thin-layer chromatography (hexane/AcOEt).

The mechanism generally assumed for the Petasis borono-Mannich involves the activation of the boronic acid by the hydroxy group to generate what has been referred to as the “ate complex”, which is able to transfer the aryl moiety to the imine or iminium bond. The evidence that strongly supports this proposal is the fact that no reaction takes place in the absence of such an activating hydroxy group. Despite the general agreement around this proposal, as far as our knowledge goes, no theoretical analysis was ever performed for this system.

The mechanism of the Petasis reaction was studied by density functional theory (DFT)^[10] by using dimethylamine, phenylboronic acid and salicylaldehyde as model reactants (see Supporting Information for computational details). The effect of solvent (water in the following discussion) was accounted for by the polarisable continuum model (PCM).^[11] The reaction was studied starting from the iminium formed after condensation of dimethylamine with salicylaldehyde. Two different sets of reactants were tested: a positive iminium reactant (keeping the hydroxy group) and a zwitterionic species with the phenol group deprotonated. Equivalent mechanisms were obtained in both cases, corresponding to a one-step path from the “ate complex” to the tertiary amine. However, the mechanism obtained for the positive iminium reactant (keeping the OH group) is less favourable than the one calculated for the zwitterionic reagent, as demonstrated by the energy calculated for the corresponding transition states: 36 and 23 kcal/mol, respectively. Thus, the following discussion will refer to the reaction of the zwitterionic iminium. The energy profile calculated for the positive iminium reactant is presented in the Supporting Information. It is interesting to note that despite a positive value obtained for the free energy of the “ate complex” in water (4.0 kcal/mol), in comparison to the isolated reagents, the corresponding electronic energy is negative (−2.8 kcal/mol), which reflects the stabilization that results from the formation of the B–O bond.

The transition state obtained (TS) has an intermediate geometry between the “ate complex” (ATE) and the tertiary amine (TA). In TS, the phenyl group is clearly migrating from the boron atom to the carbon atom of the iminium group. The B–C(Ph) bond is weakened ($d = 1.81 \text{ \AA}$, WI = 0.51) relative to the one present in the “ate complex” ($d = 1.62 \text{ \AA}$, WI = 0.77), and the new C–C bond is starting to form. However, the long distance and small Wiberg index associated with this interaction ($d = 2.00 \text{ \AA}$, WI = 0.47) indicate an early transition state with only incipient C–C bond formation.

The influence of the *para* substituent in the boronic acid phenyl group (R^2 in Scheme 2) was also investigated computationally. In the energy profile obtained for $R^2 = \text{MeO}$ (dashed lined in Figure 1) the corresponding transition state is more stable than the one calculated for $R^2 = \text{H}$ (solid line) by 5.1 kcal/mol, indicating a significantly more facile reaction in the former case, in excellent agreement with the experimental results (Table 1, Entries 1 and 6).

Finally, the influence of the solvent was also investigated through comparison of energy calculations with the PCM

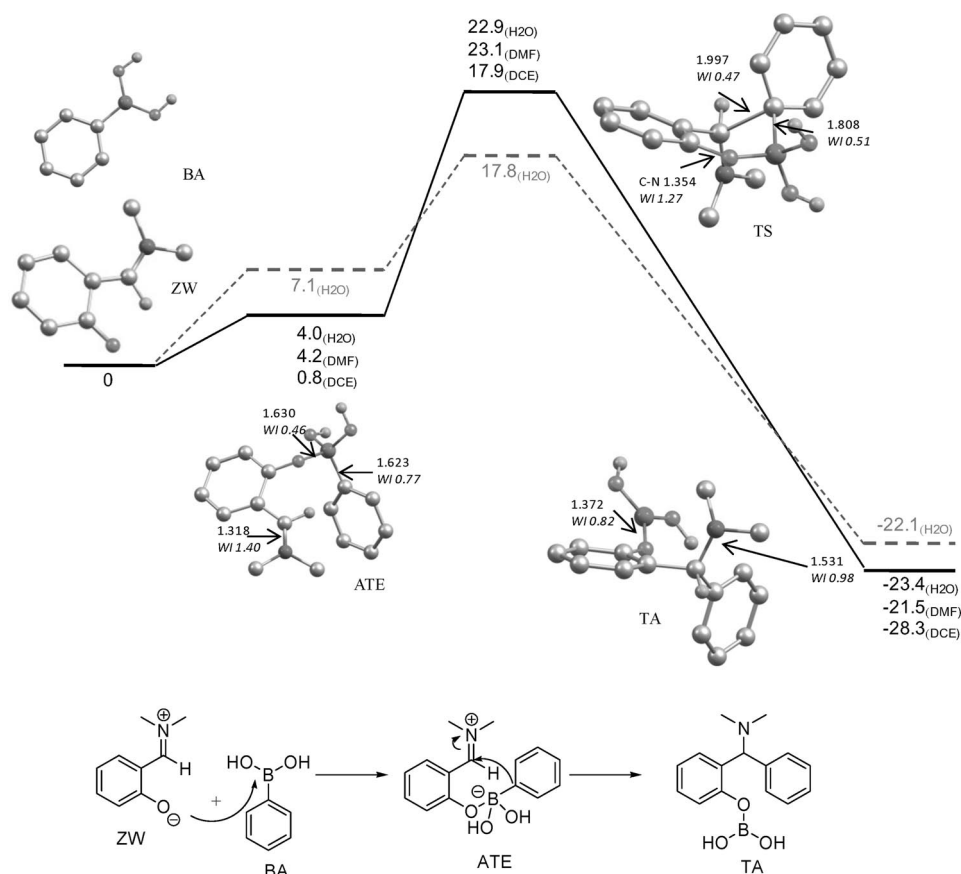


Figure 1. Energy profiles calculated for the Petasis reaction between dimethylamine, salicylaldehyde and phenyl boronic acid (solid lines) or 4-methoxyphenyl boronic acid (dashed lines). The geometries optimized for the reaction with phenyl boronic acid (solid lines) are presented. The relevant bond lengths (Å) are indicated, as well as the respective Wiberg indices (WI, italics). The minima and the transition states were optimized and the energy values [kcal/mol] are referred to the isolated reagents, zwitterionic 2-[(dimethyliminio)-methyl]phenolate (ZW) and boronic acid (BA). H atoms on the phenyl and methyl substituents are omitted for clarity.

model for dimethyl formamide and 1,2-dichloroethane with those calculated for water, discussed above. The results obtained (see Figure 1) indicate that the reaction should be slightly less favourable in DMF than in water and, more importantly, that DCE should be the better solvent for the reaction, in good accordance with the experimental findings (see Table 4). In fact, the energy of the transition state, calculated for DCE, is 5 kcal/mol lower than the equivalent one obtained for water.

Conclusions

Water was successfully used as the solvent in the Petasis borono-Mannich reaction. An assortment of alkylamino-phenols was obtained in yields up to 99% by using different secondary amines, salicylaldehydes and boronic acids. By combining vinyl boronic acids with salicylaldehydes and diethylamine, 2*H*-chromenes were obtained in up to 92%. DFT mechanistic calculations were performed, and the results obtained corroborate the generally accepted mechanism for this multicomponent transformation and the solvent effect experimentally observed.

Experimental Section

General Procedure: A round-bottomed flask equipped with a condenser and magnetic stirrer and under an argon atmosphere was charged with boronic acid (1.2 equiv.) and distilled water (1.0 mL). This suspension was stirred at 80 °C for 3 min, after which the salicylaldehyde (0.41 mmol) and the amine (1.2 equiv.) were subsequently added. The mixture was stirred at 80 °C for 24 h (or 4.5 h for 4–6), after which the product was filtered or the water was evaporated under reduced pressure. The product was further purified by preparative thin-layer chromatography.

Supporting Information (see footnote on the first page of this article): Full characterisation of all new compounds; tables with atomic coordinates for all optimized species.

Acknowledgments

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