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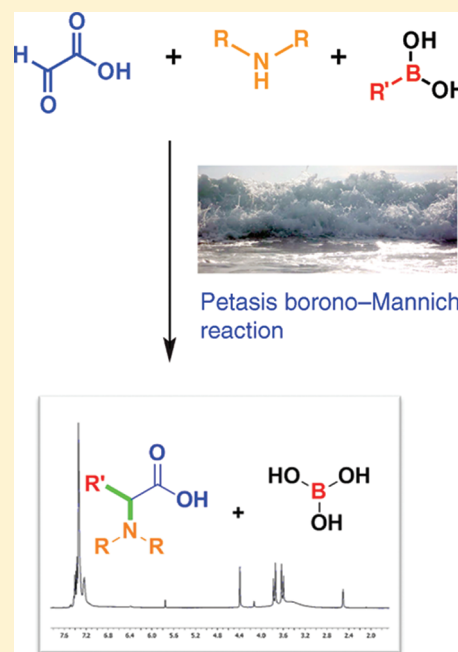
A Sustainable Protocol for the Aqueous Multicomponent Petasis Borono–Mannich Reaction

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Supporting Information

ABSTRACT: A protocol for the preparation of Petasis borono–Mannich products suitable for advanced organic chemistry experiments, using water as a reaction medium, was developed. The experiment is carried out in less than 4 h (with a 30 min pre-session on the day before) using commercially available starting materials in the preparation of phenylglycine and 2-hydroxymorpholine derivatives. These experiments are useful in the organic chemistry curriculum for the introduction of multicomponent reactions and for the use of boronic acids and water as environmentally friendly reagents and solvent, respectively.



KEYWORDS: Upper-Division Undergraduate, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Amines/Ammonium Compounds, Diastereomers, NMR Spectroscopy, Synthesis, Water/Water Chemistry

The low cost and the lack of flammability, explosive, mutagenic, and carcinogenic properties are some of the economic and environmental benefits that have been associated with the use of water as a solvent. Moreover, the hydrogen bonding network, the large surface tension, the high specific heat capacity, the high cohesive energy, and the high polarity can dramatically change the rates of reaction kinetics when performed in this media.^{1,2} Other characteristics arising from the use of water as solvent are the possibility to add additives such as salts (inducing salting-in or salting-out effects), surfactants, and cyclodextrins and enabling of pH variation, creating an additional way to tune the reactivity of chemical transformations. Furthermore, in many cases the products can be obtained in excellent purity by a simple filtration of the reaction medium.^{3,4}

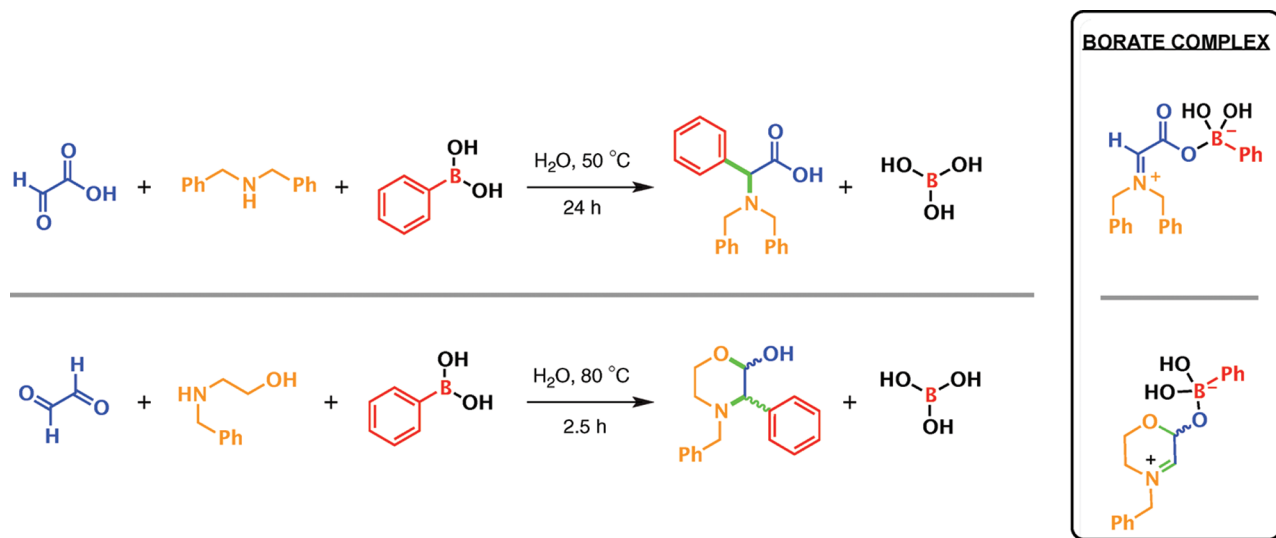
Boronic acids have recently drawn the attention of the scientific community due to their wide applications to organic synthesis, medicinal chemistry, and material sciences. Their stability toward air and water, low toxicity, and tolerance to several functional groups, together with their wide commercial

availability, make them a good subject for study in the organic teaching laboratory. These compounds are valuable partners in the formation of new C–C bonds in several metal-catalyzed reactions, but also in metal-free multicomponent reactions, such as the Petasis borono–Mannich (PBM).⁵

Multicomponent reactions (MCR) are a valuable tool in organic synthesis, namely in a green chemistry context, due to the incorporation of most atoms from the starting materials into the product.⁶ Boronic acids are ideal partners in MCR as they are generally stable and soluble in aqueous media. Furthermore, many different boronic acids are commercially available, facilitating the preparation of more specific molecules. The growing demands for new medicines, materials, and general products presents modern chemistry with the challenge of designing new processes to prepare any chemicals that may be required by society. Nevertheless, it is no longer acceptable that this large-scale production takes place at a high cost both to the environment or society. Therefore, future chemists will

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Scheme 1. The Petasis Borono–Mannich Reactions Studied in this Experiment



have to design processes in accordance with the guidelines for more sustainable chemistry.⁷ PBM multicomponent reaction fits into such guidelines, in which the use of volatile organic compounds is minimum, low or no toxicity of the side products is known, and no chromatography is needed, as in the case of the examples described herein.

If one brings these three desirable features together, the use of boronic acids, multicomponent reactions, as well as the use of water as a reaction medium, it is possible to develop an environmentally friendly protocol for the construction of libraries of compounds associated to a diminished waste generation. The PBM reaction employs three components—an amine, an aldehyde, and a boronic acid—to synthesize a new amine derived from a C–C bond-forming reaction (Scheme 1).⁸ Despite the robustness of this reaction, there are some constraints regarding activation of the boronic acid. The determinant step of this reaction is the migration of the boronic acid substituent to the carbon of an iminium ion intermediate and can be promoted by using high temperatures. However, the presence of an OH group in either the aldehyde or amine component will activate the boronic acid by formation of a boron tetrahedral intermediate. Nevertheless, the PBM reaction is a very useful tool for the preparation of small libraries of compounds, such as α -amino acids^{8b,9} amino alcohols,^{8c,10} 2H-chromenes,¹¹ or 2-hydroxymorpholines.¹² To demonstrate the utility of this reaction, the preparation of two different types of tertiary amines by different modes of activation of the boronic acid are reported. In the first case, in which the borate intermediate complex is formed by coordination of the boronic acid onto the O–H of glyoxylic acid, a procedure was developed for the aqueous preparation of phenylglycine, resulting in the easy isolation of the product in good purity by a simple filtration.¹³ In the second case, the boronic acid moiety is activated by coordination onto the iminium intermediary of the reaction, and the product is obtained in good diastereoselectivity after extraction of the reaction medium.^{13,14}

EXPERIMENT OVERVIEW

This laboratory experiment is appropriate for upper-division undergraduate students currently learning advanced organic

chemistry. The overall experiment needs only one session of 4 h and less than 30 min on the day before to set up the preparation of the amino acid. All reagents were used as obtained from Sigma-Aldrich. The two reactions are easily performed and the products, *N,N*-dibenzylphenylglycine and 4-benzyl-3-phenylmorpholin-2-ol, are obtained in good purity after simple workup procedures, making this experiment suitable for classes with more than 20 students (58–80% range of yields for the preparation of *N,N*-dibenzylphenylglycine and 55–97% for the preparation of 4-benzyl-3-phenylmorpholin-2-ol, in which the product is obtained as a *cis:trans* 0.2:1 diastereoisomeric mixture). Both reactions are performed in a parallel manner, such that the workup of *N,N*-dibenzylphenylglycine is done while morpholin-2-ol is being prepared. *N,N*-Dibenzylphenylglycine is purified by a simple filtration of the aqueous reaction mixture, and morpholin-2-ol is purified by extraction of the aqueous reaction mixture with diethyl ether.

HAZARDS

Phenylboronic acid may be harmful if inhaled and may cause respiratory tract irritation. It is harmful if absorbed through skin and it may cause skin irritation. Glyoxylic acid and *N,N*-dibenzylamine are extremely destructive to some tissues such as mucous membranes and upper respiratory tract as well as it can cause skin burns. Glyoxal and 2-benzylaminoethanol cause respiratory tract irritation by inhalation and can cause skin and eyes irritation. Diethyl ether is extremely flammable and its vapors may cause drowsiness and dizziness.

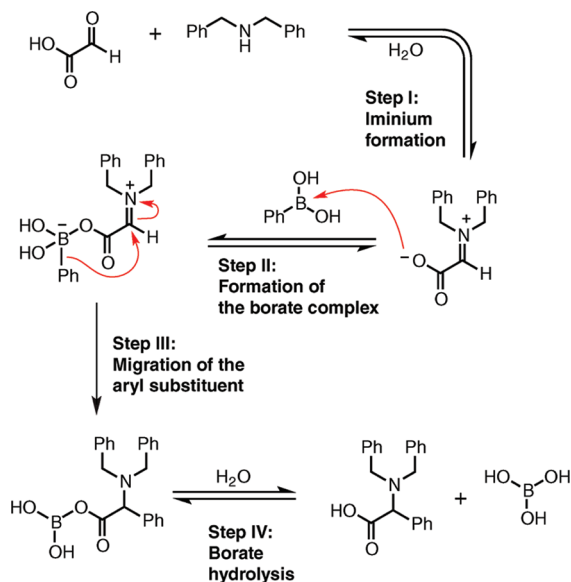
DISCUSSION

This experiment gave students practical experience with multicomponent reactions and demonstrates the utility of these reactions to build small libraries of compounds and, additionally, showed the simplicity of experimental procedures regarding multicomponent reactions. Furthermore, it introduced boronic acids as a useful class of compounds in organic synthesis and their wide commercial availability. In a green chemistry context, the use of water as a solvent for both reactions (Scheme 1) generated almost no waste, apart from that resulting from the purification of the product. Moreover,

boric acid was the only byproduct of the reaction, displaying low toxicity as it is used in several medicinal and industrial applications, such as eyewash solutions or antiseptic. These experiments were intended to alert students to the heterogeneous nature of these reactions. Although the use of water as a reaction medium made efficient stirring of the reaction mixture difficult, the diffusion and mass transfer phenomena were sufficient to promote the reaction to completion at the scale described herein. The second experiment in this protocol was also suitable to emphasize the ^1H NMR characterization of a mixture of diastereoisomers and to determine the cis:trans ratio of the same mixture.

The experiment was suitable to highlight iminium formation mechanisms and topics related with boron chemistry, such as its electrophilic aptitude and geometry. The reactions proceeded through two different, but closely related mechanisms. Both reactions started by the nucleophilic addition of the amine to the aldehyde, to form the iminium species (step I). In the preparation of phenylglycine (Scheme 2), the second step

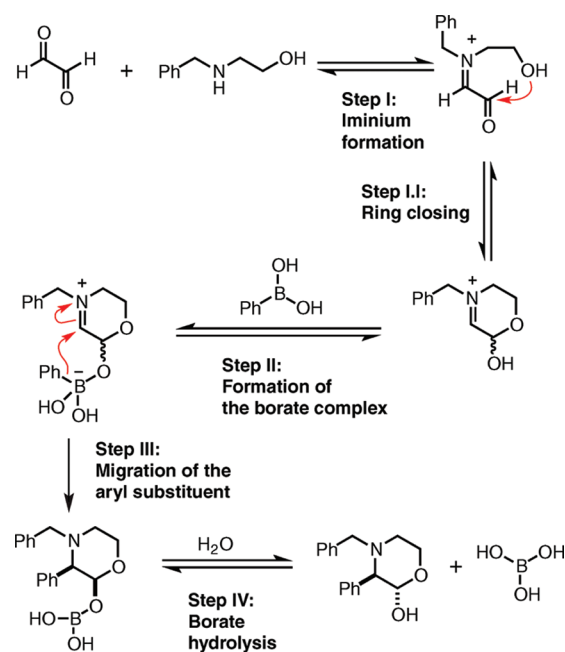
Scheme 2. Proposed Mechanism of the PBM Reaction in the Formation of *N,N*-Dibenzylphenylglycine



was activation of the boronic acid due to nucleophilic attack by the carboxylate on the boron of the boronic acid to form a negatively charged borate intermediate, which further reacted by aryl substituent migration to the iminium's electro-deficient carbon (step III). Final hydrolysis of the borate provided boric acid together with the desired product.

Regarding the mechanism to form morpholin-2-ol (Scheme 3), there was one additional step due to the more favorable intramolecular nucleophilic attack of the hydroxyl to the aldehyde (Step I.I), followed by subsequent formation of a borate complex. Because of the formation of a stereogenic center in the ring-closing step, the subsequent migration of the aryl substituent can be diastereoselective. Under the reaction conditions herein described (50 °C, 2.5 h), a diastereoselectivity toward the formation of the trans isomer was determined by ^1H NMR (cis:trans 0.2:1). It is expectable that this migration step was cis diastereoselective; however, it is probable that the cis diastereomer epimerizes to the more stable trans diastereomer under thermodynamic control.

Scheme 3. Proposed Mechanism of the PBM Reaction in the Formation of 4-Benzyl-3-phenylmorpholin-2-ol



Several reaction conditions for the preparation of the morpholin-2-ol derivative were screened in a research environment, and the complete consumption of the starting materials was achieved at room temperature for 24 h or at 50 °C for 5 h.

SUMMARY

With these experiments, boronic acids, multicomponent reactions, and the use of water as a reaction solvent were introduced to advanced organic chemistry students in a green chemistry context. The experiments were carried out in less than 4 h using commercially available reagents and this simple protocol allowed students to become familiar with multicomponent reactions in a chemical sustainable perspective. The experiments described were developed in a research laboratory (*N,N*-dibenzylphenylglycine was obtained in 80% yield and 4-benzyl-3-phenylmorpholin-2-ol in 97%) and tested in a classroom by four students (average yields were 54% (50–58% range) for preparation of *N,N*-dibenzylphenylglycine and 73% average yield (55–90% range) for preparation of 4-benzyl-3-phenylmorpholin-2-ol). Topics of discussion include mechanistic considerations for the Petasis borono–Mannich reaction, synthetic utility of boronic acids, heterogeneous reactions, and green chemistry.

ASSOCIATED CONTENT

Supporting Information

Student handout, spectral data, and notes for the instructor. This material is available via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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