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Catalyst-free Petasis-type reaction: Three-component decarboxylative coupling of boronic acids with proline and salicylaldehyde for the synthesis of alkylaminophenols

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ABSTRACT

A simple method is reported for the synthesis of alkylaminophenols in moderate to good yields *via* a three-component, catalyst-free decarboxylative coupling of proline with salicylaldehyde and boronic acids.

The Petasis Borono-Mannich reaction, a three-component coupling reaction of an amine, an aldehyde, and a boronic acid, is an attractive method for the synthesis of various biologically interesting nitrogen-containing molecules, including α-arylglycines,[1] α-aminoalcohols,[2] alkylaminophenols,[3] allyl amines,[4] tetrahydroisoquinoline-1-carboxylic acids,[4] tertiary amines and α-amino acids.[5]

The classical Petasis reaction is a three component coupling reaction between aldehydes containing a boron-activating hydroxyl group, such as salicylaldehydes, amines and alkylboronic acids, to give alkylaminophenol derivatives.[1] The reaction with salicylaldehyde proceeds *via* the formation of an activated boronate complex (Scheme 1).[6] Various variants of the Petasis reaction have also been developed to overcome the substrate limitations of the classical reaction,[6] leading to the development of various catalytic systems including CuBr, $BF_3{\cdot}OEt_2$, $InBr_3$, $Yb(OTf)_3$, $CoFe_2O_4$ and protonated trititanate nanotubes.[7] Green approaches using microwave irradiation and ionic liquids are also employed to accelerate the Petasis reaction.[8] However, the drawbacks of many of the reported catalytic systems, such as their sensitivity to air, high cost, and toxicity, limit their application in organic synthesis. Therefore, the development of the Petasis reaction under catalyst-free conditions is highly desirable from both environmental and economical points of views.

On the other hand, the functionalization of α-amino acids adjacent to nitrogen *via* decarboxylation processes are of increased interest for the modification of α-amino acids, since this reaction leads to the facile preparation of amine compounds by replacing the carboxyl group of natural α-amino acids with a variety of functional groups (Scheme 2).[9] This strategy has been applied to the transformation of α-amino acids into α-aminophosphonic acids and the arylation of α-amino acids *via* photoredox processes (Scheme 2).[10]

With increasing demand for environmentally friendly methods, and as part of our efforts to introduce novel methods for the synthesis of organic compounds,[11] we recently reported the decarboxylative functionalization of α-amino acids with a phosphonate functional group under catalyst-free conditions (Scheme 3).[12]

In the decarboxylative coupling reaction of proline with various benzaldehyde and diethylphosphite, among an equilibrium mixture of azomethine ylides **A** and **B** generated by decarboxylation, ylide **B** selectively reacted with the phosphonate to give the phosphonate analog of proline in high yield *via* betaine **C** (Scheme 3).[12]

On the basis of these findings, we speculated that the azomethine ylides generated from the reaction between salicylaldehyde and proline would activate the hydroxyl group on the phenyl nuclei to form a reactive boronate complex. However, to the best

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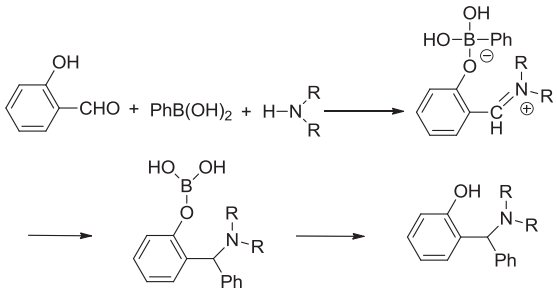
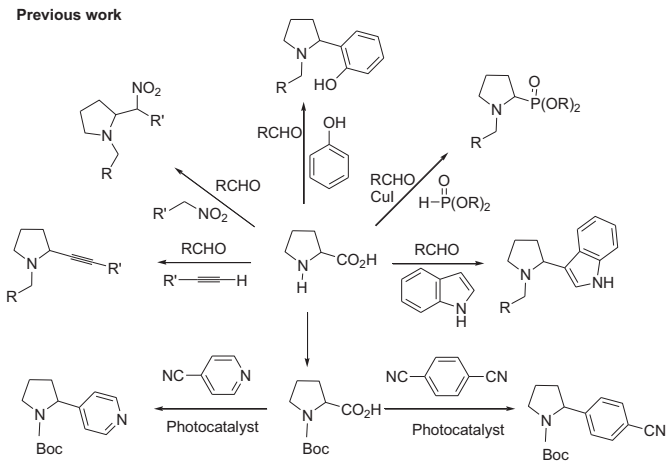
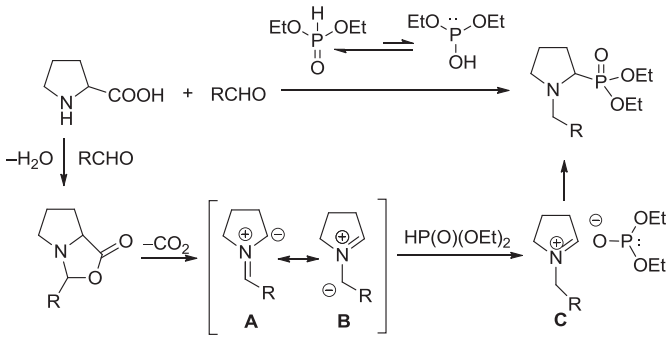


Scheme 1. Schematic illustration of the Petasis reaction.



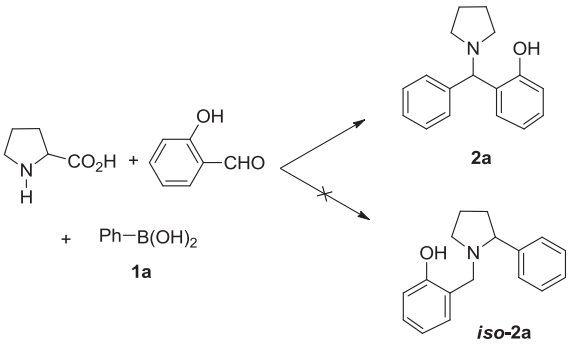
Scheme 2. Representative decarboxylative coupling reactions of proline.



Scheme 3. Decarboxylative coupling of proline with aldehydes and diethyl phosphite.

of our knowledge, there are no reports regarding catalyst-free Petasis type reactions activated by azomethine ylides.

Initially, the decarboxylative reaction of proline in the presence of salicylaldehyde and phenylboronic acid **1a** was examined as a model reaction (Scheme 4 and Table 1). Heating an equimolar mixture of phenylboronic acid **1a**, salicylaldehyde, and proline in toluene at reflux for 24 h afforded the desired coupling product **2a** in 20% yield (Table 1, entry 1). The structure of **2a** was deduced by ^{1}H NMR and ^{13}C NMR analysis. The yield of **2a** slightly increased upon increasing the reaction time to 48 h (Entry 2). The reaction in 1,4-dioxane at ambient temperature failed to give **2a** (Entry 3) even after 48 h, while heating at 50° C for 24 h gave the desired product **2a** in 26% yield (Entry 4). When the reaction was carried out in 1,4-dioxane at 70 °C for 24 h, the yield increased slightly to 33% (Entry 5). Compound **2a** was obtained in 50% yield when



Scheme 4. Decarboxylative three-component reaction of proline with salicylaldehyde and phenylboronic acid.

the reaction temperature was increased to reflux (Entry 6). The yield of **2a** did not increase upon increasing the reaction time to 48 h (Entry 7). In these reactions, the possible regioisomer *iso*-**2a** was not detected.

It should be noted that the use of water, CH_3CN and EtOH did not afford the desired product **2a** (Entries 8–10). A mixture of unknown compounds was obtained upon conducting the reaction in DMF at reflux (Entry 11).

With the optimal conditions established, we next examined the scope and limitation of the three-component decarboxylative coupling reaction. Initial investigations were focused on the use of various boronic acids. As illustrated in Table 2, the use of *para*-substituted phenylboronic acids bearing electron-withdrawing and -donating groups gave the corresponding products **2b-d** in moderate to good yields (Entries 1–4). The phenylboronic acid bearing a formyl group in the *para* position gave a mixture of unknown products (Entry 5). *meta*-Substituted phenylboronic acids produced the corresponding products **2e-g** in moderate yields (Entries 6–8). Whereas *p*-chlorophenylboronic acid provided the corresponding alkylaminophenol **2b** in 75% yield (Entry 2), *o*-chlorophenylboronic acid gave unidentified products without formation of the desired product (Entry 9). *ortho*-Fluorophenylboronic acid produced the corresponding product **2 h** in moderate yield (Entry 10). This method was also applicable to the decarboxylative coupling of proline with α- and β-naphthylboronic acids in the presence of salicylaldehyde. α-Naphthylboronic acid gave the corresponding alkylaminophenol **2i** in 64% yield and β-naphthylboronic acid produced the corresponding product **2j** in 70% yield (Entries 11 and 12). Whereas benzofuran-2-ylboronic acid provided the corresponding alkylaminophenol **2 k** in 45% yield (Entry 13), the decarboxylative coupling of 2-thiophenylboronic acid failed to give the corresponding product (Entry 14). Finally, the reaction of styrylboronic acid gave unidentified products without formation of the desired product (Entry 15).

The coupling reaction of l-phenyl alanine with salicylaldehyde and phenylboronic acid was also studied under the standard conditions (1,4-dioxane, reflux, 32 h). However, the reaction gave only a known[13] polar boronate complex **3** in 46% yield (Scheme 5).

The coupling reaction of (*S*)-(−)-*trans*-4-hydoxyproline with salicylaldehyde and phenylboronic acid in 1,4-dioxane or a mixture of dioxane:ethanol at reflux for 32 h also failed to give any product (Scheme 6).

Finally, the analogous three-component coupling reactions of proline and phenylboronic acid were carried out under the standard conditions (reflux, 32 h, 1,4-dioxane), where the salicylaldehyde component was replaced with various aldehydes including benzaldehyde, *p*-methoxybenzaldehyde, *m*-nitrobenzaldehyde, *m*-hydroxybenzaldehyde, *p*-hydroxybenzaldehyde, 2-furanecarboxaldehyde and 2-thiophenecarboxaldehyde. However these