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Novel Petasis boronic acid–Mannich reactions with tertiary aromatic amines

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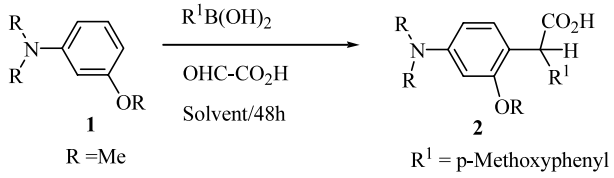
Abstract—Tertiary aromatic amines can serve as amine substrates for the Petasis boronic acid–Mannich reaction, providing a practical synthetic route for the C–C bond formation of α-(4-*N*,*N*-dialkylamino-2-alkyloxyphenyl)carboxylic acids. The scope and limitations of this method have been examined.

The Petasis boronic acid–Mannich reaction provides a powerful and convenient method for the preparation of α-amino acids.[1,2] Recently, it has been the subject of considerable attention for the synthesis of combinatorial libraries, because a wide variety of amines and aryl boronic acids can be readily condensed in a multi-parallel fashion on solid supports.[3] The Petasis boronic acid–Mannich reaction is ideally suited for combinatorial chemistry because: (1) it is a multi-component condensation;[4] (2) a large variety of boronic acids and amines are commercially available, and (3) the reaction proceeds at ambient temperature in a wide range of solvents. The reaction is most efficient with alkenyl and electron-rich aromatic boronic acids, secondary amines, and sterically hindered primary amines, although anilines, unprotected amino acids, and peptides can also participate.[1a,b] In our earlier studies, it was shown that hydrazines can also participate in this reaction.[5] To our knowledge, tertiary aromatic amines have not previously been studied as substrates for this reaction.[1–3] In this letter, we report a mild, practical, and novel method for the synthesis of C–C bond formation using the Petasis boronic acid–Mannich reaction.

Initially, our investigation on the Petasis reaction with tertiary aromatic amines was performed using *N*,*N*-dimethyl aniline in the presence of glyoxylic acid and boronic acid in DCM at ambient temperature, which afforded α-(4-*N*,*N*-dialkylamino-phenyl)carboxylic acids only in 8% yield (LCMS). However, when 3-methoxy-*N*,*N*-dimethyl aniline (**1**) was used in DCM at ambient temperature for 48 h, the product **2** was obtained in 28% yield after purification of the crude product by column chromatography (silica gel, EtOAc/hexane) (Scheme 1).

In order to find a suitable solvent for better yield of the dialkylaminocarboxylic acids, the reaction was performed in different solvents and monitored by LCMS (Table 1). Entry 8 was found to be the best condition for this reaction. Thus 3-methoxy-*N*,*N*-dimethylaniline was treated with *p*-methoxyphenyl boronic acid and glyoxylic acid in dioxane, refluxed for 24 h and monitored by LCMS. The solvent was removed and the residue was purified by preparative HPLC to afford 50% yield of the desired product.

Encouraged by these results, the scope of the reaction was explored further for an efficient synthesis of C–C bond formation by Petasis boronic acid–Mannich reaction. Commercially available substrates **3** were subjected to standard Petasis boronic acid–Mannich



Scheme 1.

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Table 1. Optimization of Petasis reaction with 3-methoxy-*N*,*N*-dimethylaniline

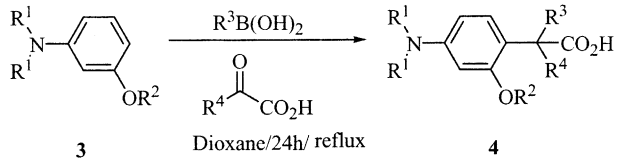
Entry	Solvent	Temp. (°C)	Yield (%)[a]
1	DCM	25	16
2	MeOH	25	0
3	DCE	25	17
4	$CHCl_3$	25	20
5	THF	25	17
6	Dioxane	25	24
7	CH_3CN	25	12
8	Dioxane	102	50

[a] All yields determined by LCMS.

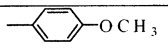
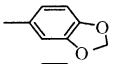
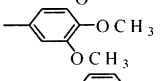
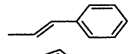
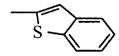
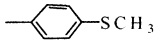
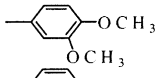
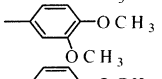
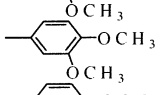
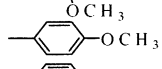
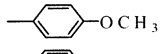
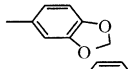
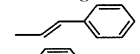
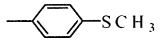
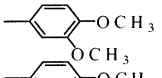
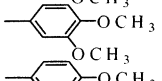
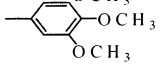
reaction conditions; i.e. one equivalent each of **3**, glyoxylic acid monohydrate, and an organoboronic acid stirred under reflux condition in dioxane for 24 h (Table 2).[6]

When R^1 = Me, R^2 = Me, R^3 = aryl and R^4 = H (**4a–d**), the reactions proceeded well, affording the corresponding α-(4-*N*,*N*-dialkylamino-2-alkyloxyphenyl)carboxylic acids ranging from 51 to 54% yield after HPLC purification. When R^3 = heterocyclic (**4e**), the corresponding product was obtained in reduced (25%) yield (LCMS). It is also to be noted that when R^3 = thioanisole (**4f**), the reaction afforded 48% yield of the desired product after purification. Interestingly, when α keto acids were used (R^4 = Me, Et, Bn; **4g**, **4h**, **4j**), products containing an α-quaternary center were formed in 41–52% yield. However, when R^4 = Ph, the yield dropped significantly, affording only 12% yield (**4i**) after purification. In the

Table 2. Petasis boronic acid–Mannich reactions of tertiary aromatic amine



3 **4**

Compound	R^1	R^2	R^3	R^4	Yield[a]
4a	—Me	—Me		—H	50%
4b	—Me	—Me		—H	52%
4c	—Me	—Me		—H	54%
4d	—Me	—Me		—H	51%
4e	—Me	—Me		—H	25%
4f	—Me	—Me		—H	48%
4g	—Me	—Me		—Me	52%
4h	—Me	—Me		—Et	49%
4i	—Me	—Me		—Ph	12%
4j	—Me	—Me		—Bn	41%
4k	—Et	—Et		—H	51%
4l	—Et	—Et		—H	53%
4m	—Et	—Et		—H	52%
4n	—Et	—Et		—H	50%
4o	—Et	—Et		—Me	44%
4p	—Et	—Et		—Et	46%
4q	—Et	—Et		—Bn	49%

[a]All yields refer to pure, isolated products. All compounds have been characterized by LC-MS, HNMR, and CNMR.

cases studied, yields varied considerably with different R^1 and R^2 groups on the amine. When R^1 and $R^2 = Et$, $R^3 =$ aryl and $R^4 = H$ (**4k**–**n**), the corresponding product was obtained in 50–53% yield after purification by HPLC. As in the case of R^1 and $R^2 = Et_3$, varying the α-keto acid (**4o**–**p**, $R^4 =$ Me and Et) furnished 44–46% yields, respectively. Remarkably, when $R^4 =$ Bn (**4q**), the desired product was obtained in 49% yield after HPLC purification.

In summary, tertiary aromatic amines can replace the amine component in the Petasis boronic acid–Mannich reaction, yielding products in which two carbon–carbon bonds have been formed in the multicomponent condensation. The resulting α-(4-*N*,*N*-dialkylamino-2-alkyloxyphenyl)carboxylic acid products (**4**) contain four points of diversity. To the best of our knowledge these compounds have not been synthesized earlier.

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6. **General procedure for the Petasis boronic acid–Mannich reactions of tertiary aromatic amine 4a**: To a stirred mixture of glyoxylic acid monohydrate (0.184 g, 2 mmol) in *p*-dioxane (6 mL) was added 3-dimethylaminoanisole (0.302 mg, 2 mmol) followed by 4-methoxyphenylboronic acid (0.304 g, 2 mmol). The resulting mixture was refluxed for 24 h and after this time, the dioxane was removed under reduced pressure. The residue was purified by preparative HPLC [Polaris C18 column (250×500 mm, 10 micron particle size), mobile phase 0.1% aqueous TFA/CH_3CN linear gradient over 55 min, 60 mL/min] to give 0.316 g (50%) of **4a** as a white solid. Mp: 46–47°C; $R_f = 0.14$ (50% EtOAc:hexane); analytical HPLC: Polaris C18 column (4.6×250 mm, 3 micron particle size), mobile phase 0.1% aqueous phosphoric acid/CH_3CN linear gradient over 30 min, 1 mL/min, one peak detected by ELS and UV at 215 nm, $t_R = 7.44$ min; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.97 (s, 6H), 3.82 (s, 3H), 3.85 (s, 3H), 5.18 (s, 1H), 6.30 (br.d, $J = 8.4$, 2H), 6.87–6.92 (m, 3H), 7.27 (d, $J = 9$, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 41.15, 49.99, 55.65, 55.77, 96.61, 105.12, 114.29, 116.37, 129.91, 130.34, 130.50, 151.69, 158.02, 159.04, 179.59; LCMS (ELSD): 316 ($M+H^+$); HRMS: 316.154798 [calcd for $C_{18}H_{21}NO_4$ 316.154883 $(M+H)^+$].