Novel Petasis boronic acid reactions with 1,3,5-tri-oxygenated benzenes

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Abstract—1,3,5-tri-Oxygenated benzenes can serve as substrates for the Petasis boronic acid reaction, providing a practical synthetic route for the two C–C bond formation of α-(1,3,5-tri-oxygenated phenyl)carboxylic acids. The scope and limitations of this method have been examined.
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In recent years the Petasis boronic acid–Mannich multi-component reaction has been of considerable interest, since in one-step, commercially available boronic acids and amines can be used as building blocks in combinatorial chemistry to make many diverse α-amino acids for drug discovery.[1–4] 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,[1a,b] boronic acid esters,[1e,f] hydrazine[5] can also participate. In earlier studies, it was shown that tertiary aromatic amines can also participate in this reaction for the two carbon–carbon bond formation of α-(4-*N,N*-dialkylamino-2-alkyloxyphenyl)carboxylic acids with four points of diversity[6] where as in the Petasis reaction, a carbon–carbon and a carbon–nitrogen bond are formed.[1a,b] To our knowledge 1,3,5-tri-oxygenated benzenes have not previously been studied as substrates for this reaction.[1–6] In this letter, we report a mild, practical, and novel method for the synthesis of α-(1,3,5-tri-oxygenated phenyl)carboxylic acids using chemistry analogous to the Petasis boronic acid–Mannich reaction, but not incorporating an amine component.

Commercially available substrates **1** were mixed with one equivalent each of glyoxylic acid monohydrate and an organoboronic acid, stirred under reflux condition in dioxane for 12 h. As shown in Table 1, the reaction produces diphenyl acetic acids generally in 40–62% yields.[7]

The proposed mechanism of 1,3,5-tri-oxygenated benzene with glyoxylic acid in presence of *p*-methoxyphenylboronic acid is shown in Scheme 1.[3c,8] Initial studies involved reactions with 1,3,5-tri-methoxy benzene and glyoxylic acid monohydrate affording the presumed intermediate **II** which might be formed via nucleophilic aryl addition to the glyoxylic acid in *p*-dioxane under reflux condition. The solvent was removed and washed with DCM and dried under reduced pressure to afford the adduct **II** which was characterized by LCMS, 1H, ^{13}C NMR and HRMS.[9] Treatment of this adduct (**II**) with *p*-methoxy phenylboronic acid afforded the expected product **2a**.

When R^1, R^2, R^3 = Me and R^4 = aryl (**2a–e**), the reactions proceeded quite well, affording the corresponding α-(1,3,5-tri-methoxy phenyl)carboxylic acids ranging from 50 to 60% yield after HPLC purification. The reaction was relatively insensitive to R^4 substitution, electron withdrawing, donating and heterocyclic systems all gave comparable yields. When R^4 = heterocyclic (**2f**), and aryl containing electron withdrawing group (**2g**, **2h**), the corresponding product was obtained in 49–54% yields after purification. When R^4 = phenyl, naphthyl, these reactions also proceeded well affording 59–62% yield of the product. In the case studied, yields varied considerably with different R^1, R^2 and R^3 of the 1,3,5-tri-oxygenated benzene. When R^1 = H, R^2 and R^3 = Me (**2k–l**), the corresponding product was obtained in 48-49% yield. Similarly, when R^1, R^2 = H (**2m**), the corresponding product was obtained in 40% yield after purification. However, when R^1, R^2, R^3 = H, (**2n**), the corresponding product was obtained in

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Table 1. Boronic acid–glyoxylic acid reactions of 1,3,5-tri-oxygenated benzene

Compound	R^1	R^2	R^3	R^4	Time(h)	Yield[a]
2a	—Me	—Me	—Me	⟨⟩—OMe	12	50%
2b	—Me	—Me	—Me	benzodioxole	12	56%
2c	—Me	—Me	—Me	⟨⟩—OMe, OMe	12	45%
2d	—Me	—Me	—Me	styryl	12	60%
2e	—Me	—Me	—Me	⟨⟩—SMe	12	59%
2f	—Me	—Me	—Me	benzothiophene	12	54%
2g	—Me	—Me	—Me	⟨⟩—Br	12	54%
2h	—Me	—Me	—Me	⟨⟩—F	12	49%
2i	—Me	—Me	—Me	⟨⟩	12	59%
2j	—Me	—Me	—Me	naphthyl	12	62%
2k	—H	—Me	—Me	styryl	2	49%
2l	—H	—Me	—Me	benzothiophene	2	48%
2m	—H	—H	—Me	thiophene	1	40%
2n	—H	—H	—H	thiophene	1	10[b]%

[a]All yields refer to pure, isolated products. All compounds have been characterized by LC-MS, HNMR, and CNMR. [b]LCMS Yield.
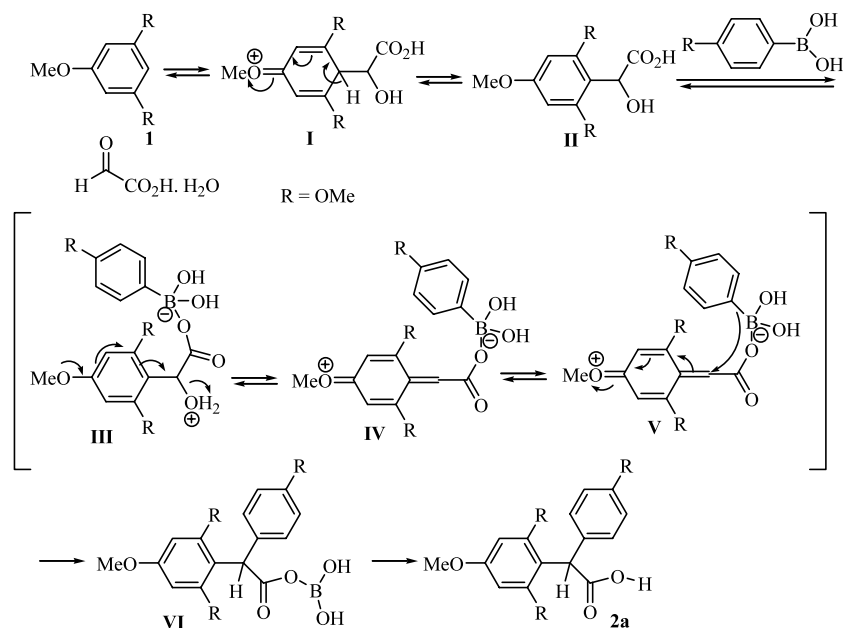
Scheme 1. Hypothetical mechanism of the reaction of 1,3,5-tri-methoxy benzene with glyoxylic acid in presence of *p*-methoxyphenylboronic acid.

reduced (10%) yield (LCMS) after heating for 1 h, further heating did not improve the yield of the product.

In summary, 1,3,5-tri-oxygenated benzene adds to glyoxylic acid and boronic acids in a process similar to boronic acid–Mannich reaction, yielding products in which two carbon–carbon bonds are formed in the multicomponent condensation. To the best of our knowledge these compounds have not been synthesized earlier.

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7. **General procedure for boronic acid–glyoxylic acid reactions of 1,3,5-tri-oxygenated benzene 2a**: To a stirred mixture of glyoxylic acid monohydrate (0.184 mg, 2 mmol) in *p*-dioxane (6 mL) was added 1,3,5-trimethoxybenzene (0.336 mg, 2 mmol) followed by 4-methoxyphenylboronic acid (0.304 mg, 2 mmol). The resulting mixture was refluxed for 12 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$_3$CN linear gradient over 55 min, 60 mL/min] to give 0.316 mg (50%) of **2a** as a white solid. Mp: 178–179°C; R_f=0.45 (50% EtOAc:hexane); analytical HPLC: Polaris C18 column (4.6×250 mm, 3 micron particle size), mobile phase 0.1% aqueous phosphoric acid/CH$_3$CN linear gradient over 30 min, 1 mL/min, one peak detected by ELS and UV at 215 nm, t_R=5.02 min; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.78 (s, 3H), 3.82 (s, 6H), 3.83 (s, 3H), 5.36 (s, 1H), 6.18 (s, 2H), 6.84 (d, 2H), 7.29 (d, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 45.39, 55.55, 55.74, 56.14, 92.02, 109.99, 113.79, 130.67, 131.02, 158.54, 158.69, 160.95, 180.11; LCMS (ELSD): 332 (M+H$^+$); HRMS: 333.135017 [calcd for C$_{18}$H$_{20}$O$_6$ 333.133814 (M+H)$^+$].

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9. ^{1}H NMR (CD$_3$OD, 300 MHz): δ 3.83 (s, 6H), 3.84 (s, 3H), 5.53 (s, 1H), 6.25 (s, 2H); ^{13}C NMR (CD$_3$OD, 75 MHz): δ 55.83, 56.23, 64.63, 91.90, 94.70, 110.09, 160.66, 163.33, 177.92; LCMS (ELSD): 241 (M−H$^+$); HRMS: 243.085709 [calcd for C$_{11}$H$_{15}$O$_6$ 243.086863 (M+H)$^+$].