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Novel Petasis boronic acid reactions with indoles: synthesis of indol-3-yl-aryl-acetic acids

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ABSTRACT

Indoles can serve as substrates for the Petasis boronic acid-Mannich reaction, providing a practical synthetic route for C–C bond formation in α-(N-substituted indole)carboxylic acids. The scope and limitations of this method have been examined.

In recent years the Petasis boronic acid-Mannich multicomponent reaction has been of considerable utility for the synthesis of α-amino acid derivatives in one step using a large variety of commercially available boronic acids and amines as building blocks in combinatorial chemistry and 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] hydroxylamine and sulfinamide,[6] and tertiary aromatic amines[7] can also participate. In earlier studies, it was shown that 1,3,5-trioxygenated benzenes can also participate in this reaction for the formation of two carbon-carbon bonds in α-(1,3,5-tri-oxygenated phenyl)carboxylic acids with four points of diversity,[8] whereas in the Petasis reaction, a carbon–carbon and a carbon–nitrogen bond are formed.[1a,b] To our knowledge, N-substituted indoles have not been studied previously as substrates for this reaction.[1–8] In this letter, we report a mild, practical, and novel method for the synthesis of two C–C bonds in α-(N-substituted indole)carboxylic acids using the Petasis-boronic acid-Mannich reaction.

Commercially available substrates **1** were subjected to standard Petasis boronic acid-Mannich reaction conditions, i.e., 1 equiv each of **1**, glyoxylic acid monohydrate and an organoboronic acid with stirring under reflux conditions in dioxane for 12 h (Table 1).[9]

The proposed mechanism for the reaction of *N*-methylindole with glyoxylic acid in the presence of *p*-methoxyphenylboronic acid is shown in Scheme 1.[3c,8,10] Initial studies involved reactions with *N*-methylindole and glyoxylic acid monohydrate affording the presumed intermediate **II** which might be formed *via* nucleophilic addition of **1** to glyoxylic acid in 1,4-dioxane under reflux conditions. The adduct **II** then reacted with *p*-methoxyphenylboronic acid to afford the desired product **2a**.

When R = Me, R^1 and R^2 = H and R^3 = aryl (**2a–2d**), the reactions proceeded quite well, affording the corresponding α-(N-substituted indole)carboxylic acids in yields ranging from 49% to 60% after HPLC purification. When R^3 = heterocyclic (**2e–2f**), the corresponding products were obtained in 47–51% yields after purification. It should be noted that when R^3 = aryl containing an electron-withdrawing group (**2g–2h**), the reaction afforded 42–48% yields of the desired products after HPLC purification. It is interesting to note that when R^2 = Me (**2i**) or Et (**2j**) these reactions also proceeded affording 41% and 39% yields of the products, respectively, after purification. When R = Me, Et, $-CH(Me)_2$, and R^1 = 6-Br and 5-Br, (**2k–2n**), the reactions proceeded to afford the corresponding α-(N-substituted indole)carboxylic acids ranging from 60% to 70% yields after purification. However, when R, R^1, R^2 = H, (**2o**) and R, R^1 = H, R^2 = Me (**2p**) the corresponding products were obtained in poor yields ranging from 26% to 30% after purification.

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

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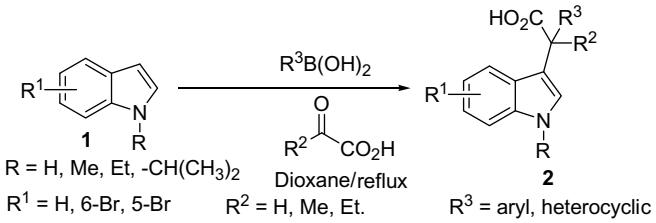
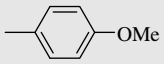
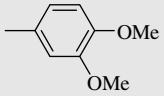
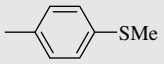
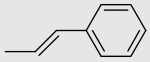
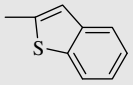
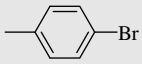
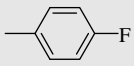
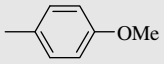
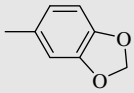
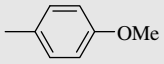
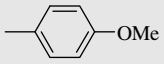
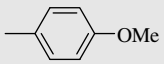
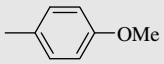
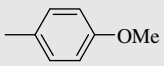
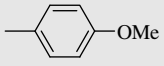
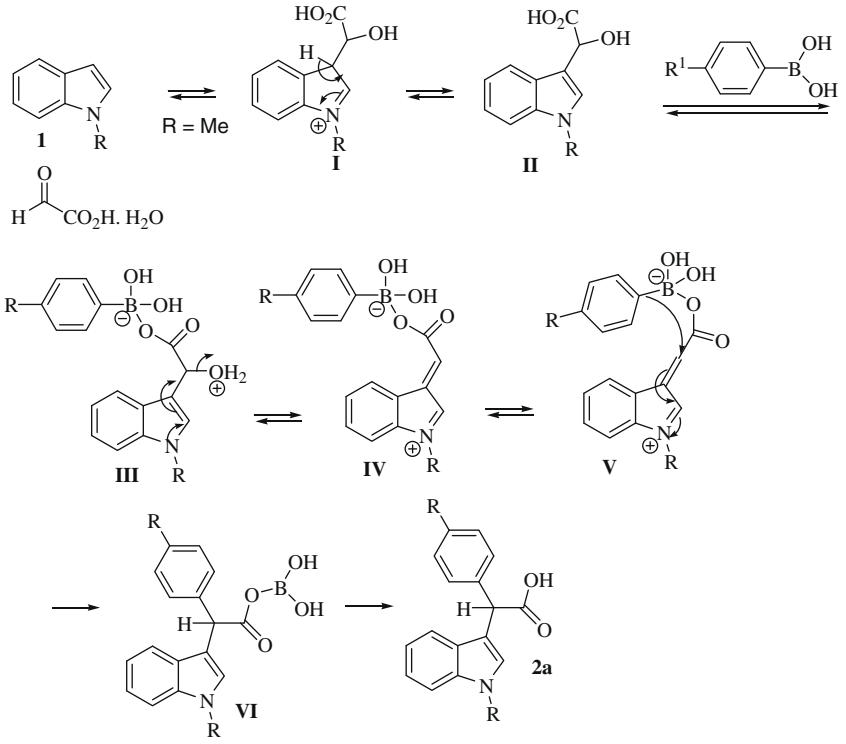
Table 1
Petasis boronic acid-Mannich reactions of indoles



Product	R	R^1	R^2	R^3	Yield[a] (%)	Mp (°C)
2a	Me	H	H		60	118–119
2b	Me	H	H		50	Liquid
2c	Me	H	H		49	132–133
2d	Me	H	H		51	121–122
2e	Me	H	H		47	Liquid
2f	Me	H	H		45	Liquid
2g	Me	H	H		48	93–94
2h	Me	H	H		42	Liquid
2i	Me	H	Me		41	164–165
2j	Me	H	Et		39	Liquid
2k	Me	6-Br	H		70	72–73
2l	Et	6-Br	H		68	71–72
2m		6-Br	H		60	153–154
2n	Me	5-Br	H		62	176–177
2o	H	H	H		30	168–169
2p	H	H	Me		26	141–142

[a] All yields refer to pure, isolated products. All compounds have been characterized by LC–MS, ^{1}H NMR, and ^{13}C NMR.



Scheme 1. Proposed mechanism for the reaction of *N*-methylindole with glyoxylic acid in the presence of *p*-methoxyphenylboronic acid.

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9. *General procedure for the Petasis boronic acid-Mannich reactions of N-methylindole* **2a**: To a stirred mixture of glyoxylic acid monohydrate (0.092 g, 1 mmol) in 1,4-dioxane (2 mL) was added *N*-methylindole (0.131 g, 1 mmol) followed by 4-methoxyphenylboronic acid (0.152 g, 1 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 μm particle size), mobile phase 0.1% aqueous TFA/CH_3CN linear gradient over 55 min, 60 mL/min] to give 0.171 g (60%) of **2a** as a reddish solid. mp: 118–119 °C; R_f = 0.26 (50% EtOAc–hexane); analytical HPLC: YMC-ODS-AQ (4.6 × 250 mm, 5 μm particle size), mobile phase 0.1% trifluoroacetic acid/CH_3CN linear gradient over 25 min, 0.8 mL/min, one peak detected by ELS and UV at t_R = 13.345 min, 99.657% purity. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77 (s, 3H), 3.80 (s, 3H), 5.23 (s, 1H), 6.85 (d, J = 8.8, 2H), 7.06 (m, 2H), 7.21–7.31 (m, 2H), 7.38 (d, J = 8.7, 2H), 7.46 (d, J = 8.0, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 32.81, 47.91, 55.26, 109.36, 111.55, 113.98, 119.14, 119.29, 121.92, 126.91, 127.94, 129.54, 130.17, 137.05, 158.89, 178.96; LCMS (UV): 296 ($M+H^+$); HRMS: 296.1294 [Calcd for $C_{18}H_{18}NO_3$ 296.1286 ($M+H^+$)].
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