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An expeditious approach to access 2-arylimidazo[1,2-*a*]pyridin-3-ol from 2-amino pyridine through a novel Petasis based cascade reaction

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ABSTRACT

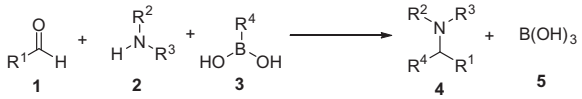
An expeditious cascade protocol for the synthesis of functionalized imidazo[1,2-*a*]pyridin-3-ols was developed based on the Petasis reaction. With the availability of commercial reagents and high efficiency in expanding molecule diversity, this methodology is superior to the existing procedures for the synthesis of imidazo-pyridin-3-ol analogues.

Multicomponent reactions (MCRs) are one of the most efficient methods to rapidly increase molecular complexity. MCRs feature abundant potential reagent combinations, inputs, and post-MCR modifications, which results in exceptionally high diversification power.[1] MCRs are known for atom economy, convergent character, operational simplicity, and structural diversity and complexity of the resulting molecules making MCR based chemistry extremely useful for the discovery and optimization of a lead molecule.[2] Among the various MCRs, the Petasis reaction (Petasis borono–Mannich reaction) has received much attention due to its power to produce various substituted amino acids and heterocyclic compounds.[3] The Petasis reaction results from the reaction between an aldehyde, an amine, and a boronic acid to form product **4** and boric acid **5** (Scheme 1).

In the past two decades, several modifications of the Petasis reaction have been reported. Naskar et al. took advantage of the Petasis reaction to prepare carboxylic acid using N-substituted indoles as an amine equivalent.[4] In another example of Petasis modification, Naskar et al. replaced the indoles with tertiary aromatic amines to afford substituted phenylacetic acid.[5] With α-hydroxy aldehyde used as a substrate, Pyne et al. utilized the Petasis reaction to furnish amino alcohols.[6] β-Amino alcohols can also be synthesized enantioselectively through the Petasis reaction.[7] However, the Petasis based cascade reaction has rarely been reported.[8]

In view of our continued interest in the synthesis of drug-like molecules through MCRs[9] for our high-throughput screening (HTS) program, we initially intended to perform a three-component Petasis reaction between 2-amino-5-methyl-pyridine (**6**), 4-methoxy phenyl boronic acid (**7**), and glyoxylic acid (**8**) to get amino acid **9** under microwave irradiation,[10] but we obtained a three-component Petasis reaction followed by a cascade cyclization, generating 2-(4-methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-ol (Compound **10**, Scheme 2).

Since imidazo[1,2-*a*]pyridin-3-ol with 2-aryl substituents display antifungal and anthelmintic activity,[11] two different procedures have been developed to synthesize these compounds.[12] One strategy is the condensation of 2-aminopyridine with substituted glyoxal,[12a,b] and the other is the reaction between pyridin-2-amine 1-oxides and phenacyl bromides.[12c,d] But, the two reported synthetic methods suffer from low efficiency in expanding molecular diversity because few substituted glyoxals and pyridin-2-amine 1-oxides are commercially available.



Scheme 1. The Petasis borono–Mannich reaction.

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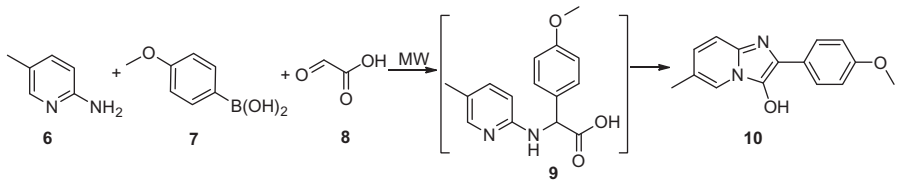
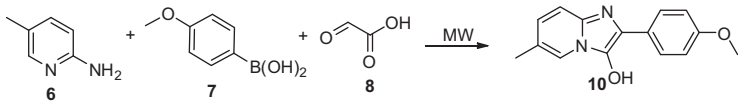


Scheme 2. The synthesis of Compound **10**.

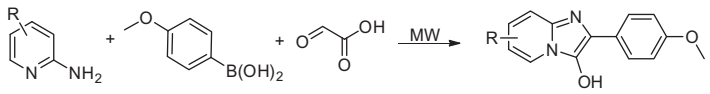
Table 1
Optimization of reaction conditions[a]

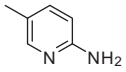
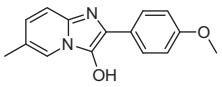
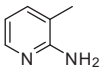
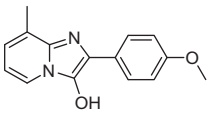
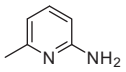
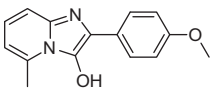
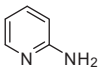
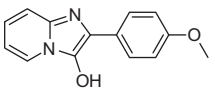
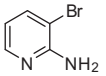
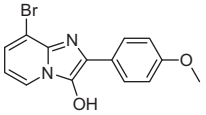
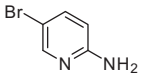
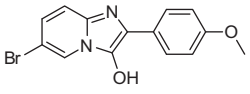
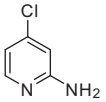
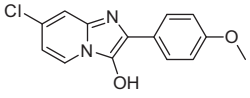


Entry	Solvent	Reaction condition	Yield[b] (%)
1	MeCN	20 min 100 °C	20
2	MeCN	30 min 100 °C	35
3	DMF–MeCN (1:1)	30 min 100 °C	38
4	DMF	30 min 100 °C	40
5	DMF	30 min 120 °C	48
6	DMF	30 min 140 °C	65
7	DMF	30 min 160 °C	80
8	EtOH	30 min 120 °C	30
9	CF_3CH_2OH	30 min 120 °C	50
10	$(CF_3)_2CHOH$	30 min 120 °C	75

[a] Unless noted, the reaction was conducted with 1 mmol **6**, 1 mmol **7**, and 1 mmol **8** in 3 mL solvent.
[b] Isolated yield.

Table 2
Substrate scope of aminopyridinel



Entry	Aminopyridine	Product	Yield[a] (%)
1			80
2			85
3			66
4			48
5			40
6			48
7			53

[a] Isolated yields obtained using 1 mmol aminopyridine, 1 mmol **7**, 1 mmol **8** in DMF at 160 °C for 30 min under microwave irradiation.

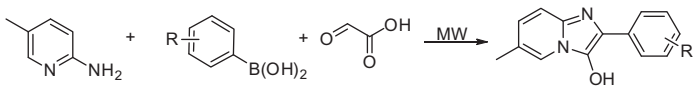
Therefore utilizing MCR-based chemistry, we developed a more practical method allowing for the expeditious access to imidazo[1,2-*a*]pyridine-3-ol from commercially available reagents. This facile procedure is in high demand permitting rapid structural diversification of imidazo[1,2-*a*]pyridin-3-ol. In this Letter we describe the synthesis of imidazo-pyridin-3-ol analogues through a Petasis based cascade reaction using 2-aminopyridine, glyoxylic acid, and boronic acid.

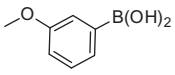
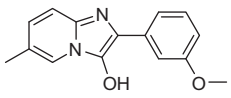
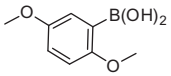
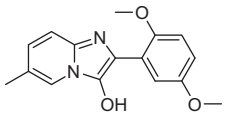
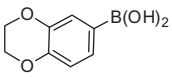
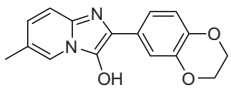
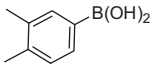
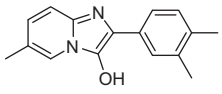
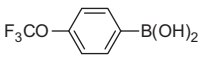
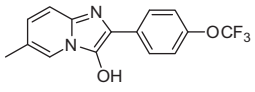
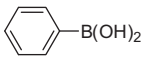
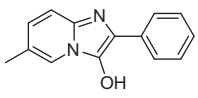
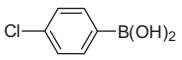
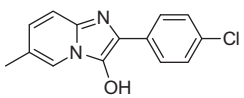
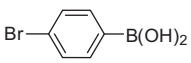
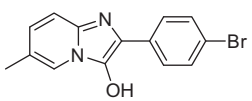
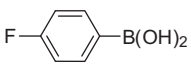
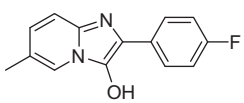
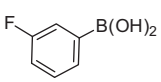
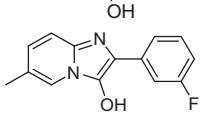
To establish efficient and appropriate reaction conditions, we first selected **6**, **7**, and **8** as substrates and examined time, solvent, and temperature effects on the overall yield for the reaction (Table 1). First, we carried out a reaction in MeCN at 100 °C under microwave irradiation for 20 min, but only trace amount of product **10** was detected (in 20% yield, entry 1). The yield was increased to 35% with a longer reaction time (entry 2). We further optimized the reaction by varying the reaction solvents. When DMF was used as solvent at 100 °C for 30 min, about 40% of product was isolated (entry 4). Increasing the temperature from 100 °C to 120 °C in the same solvent, the yield was slightly improved to 48% (entry 5). A high yield of 80%, (entry 7) in DMF was obtained with a temperature of 160 °C. Interestingly, a good yield (75%, entry 10) was also achieved with hexafluoro-2-propanol[13] used as solvent under more mild conditions (120 °C for 30 min).

With the optimized reaction condition in hand, we evaluated the scope and limitations of the reaction. We initially assessed the reactions of various substituted aminopyridines with **7** (Table 2). As shown in Table 2, various aminopyridines were reacted with **7** with DMF used as solvent at 160 °C for 30 min, and the corresponding substituted 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-ol were obtained in moderate to good yields.[14] We also found electron-rich pyridines gave higher yields than electron-deficient pyridines. This was especially true with methyl substituted aminopyridines (entries 1–3), which afforded much higher yields than aminopyridines with halide substituents (entries 5–7).

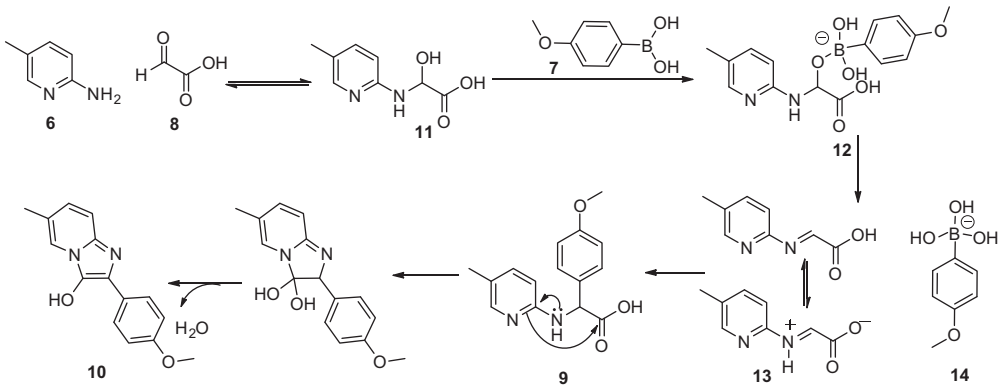
To further examine the efficiency of this reaction and to rapidly expand our unique compound collection, reaction diversity was

Table 3
Substrate scope of phenylboronic acid



Entry	Boronic acid	Product	Yield[a] (%)
1			78[b]
2			67[b]
3			69[b]
4			65[b]
5			61[b]
6			60[b]
7			51[c]
8			55[c]
9			54[c]
10			45[c]

[a] Isolated yield.
[b] DMF, microwave, 160 °C, 30 min.
[c] Hexafluoroisopropanol, microwave, 120 °C, 30 min.



Scheme 3. Proposed mechanism for the reaction.

completed by varying the phenylboronic acid input. As demonstrated in Table 3, with the same reaction conditions (DMF, 160 °C, 30 min), the reaction of phenylboronic acids containing electron-donating groups with **6** underwent smoothly to afford the corresponding products in good yields (entries 1–5). When phenylboronic acid was used as substrate, a good yield (60%, entry 6) was also obtained. It is noteworthy that the reactivity of electron-deficient phenylboronic acids was slightly worse than electron-rich phenylboronic acids. The reaction of phenylboronic acids containing electron-withdrawing groups with **6** produced the desired products only in hexafluoroisopropanol. In hexafluoroisopropanol at 120 °C for 30 min, the reaction yield with the electron-deficient phenylboronic acids was optimized to 45–55% (entries 7–10). Importantly, utilizing hexafluoroisopropanol as solvent allows for significantly more mild conditions, which permits the use of sensitive functional groups without sacrificing yield.

The plausible mechanistic pathway for the formation of **10** through three-component, one pot, domino reaction is depicted in Scheme 3. Compound **9** was formed through the standard Petasis reaction mechanism. Then compound **9** undergoes intramolecular nucleophile cyclization followed by dehydroxylation and aromatization to generate the thermodynamically stable compound **10**. To validate the proposed mechanism, we prepared compound **9** and then converted it to compound **10**. Under milder reaction conditions (oil bath, 80 °C, DMF, 1 h), the three-component Petasis reaction between **6**, **7**, and **8** proceeded smoothly and compound **9** was isolated in 90% yield. Then compound **9** was dissolved in DMF (concentration 0.5 M) and irradiated under microwaves (160 °C, 30 min), which resulted in an 89% isolated yield of compound **10**. Additionally, Follmann et al.[10c] reported that the three-component reaction between 2-aminopyridine with **7** and **8** gave the normal Petasis reaction product 2-(4-methoxyphenyl)-2-(pyridin-2-ylamino)acetic acid.

In conclusion, we have developed an expeditious protocol employing a Petasis based cascade reaction to access imidazo[1,2-*a*]pyridin-3-ol in a one pot operation in moderate to good yields. In addition, low cost, availability of reagents, and high efficiency in expanding molecule diversity make the developed methodology operationally superior over existing protocols. Further, efforts to screen the antifungal and anticancer activity of the synthesized compounds are currently underway and will be reported in due course. Studies are also in progress to utilize the functionalized imidazo[1,2-*a*]pyridin-3-ols for use as kinase inhibitors in anticancer therapies.

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References and notes

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14. Experimental procedure for the synthesis of **9**: In a 10 mL microwave tube 2-amino-5-methylpyridine (1 mmol), (4-methoxyphenyl)boronic acid (1 mmol), and Glyoxylic acid (1 mmol, 50%) solution in water were taken in 5 mL DMF and the tube was sealed with a pressure cap. The tube was irradiated in a CEM Explorer microwave for 30 min at 160 °C. After cooling to room temperature, the solvent was removed under vacuum to get the crude product, which is purified by silica chromatography (DCM/MeOH = 10:1). Yellow solid (82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (s, 1H), 7.89 (d, J = 8 Hz, 2H), 7.34 (d, J = 12 Hz, 1H), 6.97 (d, J = 8 Hz, 2H), 6.92 (d, J = 8 Hz, 1H), 3.81 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.81, 168.20, 162.00, 161.45, 148.24, 148.19, 137.93, 130.65, 130.60, 129.48, 127.45, 115.14, 113.82, 55.84, 17.75; LCMS: m/z = 255 [M+1]$^+$.