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# Catalyst free, C-3 functionalization of imidazo[1,2-*a*]pyridines to rapidly access new chemical space for drug discovery efforts†

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**Multicomponent reactions (MCRs) are robust tools for the rapid synthesis of complex, small molecule libraries for use in drug discovery and development. By utilizing MCR chemistry, we developed a protocol to functionalize the C-3 position of imidazo[1,2-*a*]pyridine through a three component, decarboxylation reaction involving imidazo[1,2-*a*]pyridine, glyoxalic acid, and boronic acid.**

Multicomponent reactions (MCRs) facilitate the rapid generation of diverse, chemical libraries with complex form and function, which have vast use in drug discovery and development.[1] MCRs represent a powerful tool to expeditiously expand chemical diversity and to reach novel, chemical space. Because of their utility in medicinal chemistry, MCRs have become an essential tool to increase hit-to-lead efficiency while decreasing time exhausted in the medicinal chemistry iterative cycle.[2] The advantages of MCRs include one-pot synthesis, mild reaction conditions, and post-MCR functionalization to help constrain rotatable bonds and resolve stereochemistry.[3] In an effort to develop MCR chemistries to help expand drug chemotypes, we designed a novel decarboxylative, Petasis-like three component reaction to functionalize the C-3 position of imidazo[1,2-*a*]pyridine.

The imidazo[1,2-*a*]pyridine core is found in pharmaceuticals and natural products that possess a broad range of biological and pharmacological activities such as anticancer,[4] antibacterial,[5] anti-viral,[6] antifungal,[7] antiprotozoal,[8] anti-inflammatory and antiulcer.[9] Imidazo[1,2-*a*]pyridines such as alpidem, necopidem, and saripidem are marketed as anxiolytic drugs[10] and zolpidem is used to treat insomnia.[11] Another derivative, minodronic acid, is used to treat osteoporosis[12] and olprinone for heart failure.[13] In particular, imidazo[1,2-*a*]pyridine derivatives are important for exploratory drug discovery research, which has led to the identification of novel kinase inhibitors with activities against PI3K, p38, Nek2, and NFkB inducing kinase.[14] Owing to the biological importance of functionalized imidazo[1,2-*a*]pyridines, a variety of synthetic strategies have been developed to functionalize the heterocycle.[15] The strategies require metal catalysis, multiple steps, and molar equivalence of oxidants. Therefore, rapid, operationally-simplistic, and eco-friendly methods are still needed to functionalize imidazo[1,2-*a*]pyridines for use in drug discovery.

Because of the biological importance of C-3 substituted imidazo[1,2-*a*]pyridines and the nucleophilic nature of the C-3 carbon, numerous C–H functionalization reactions, such as sulfonylation, arylation, amination, carbonylation, annulation and oxidative homocoupling, have been developed in recent years to enhance C-3 diversity.[16] One-pot methods are available to construct 2,3-disubstituted imidazo[1,2-*a*]pyridines but all require metal catalysis.[15a,17] Direct arylomethylations have been disclosed but are relatively rare, and neither methodology is catalyst free (Fig. 1).[18] Accordingly, functionalizing imidazo[1,2-*a*]pyridines through an operationally-simplistic, catalyst free reaction from commercially available starting materials is highly warranted.

In the current protocol, we disclose an economical, catalyst free, eco-friendly MCR for the construction of aryl methane derivatives of imidazo[1,2-*a*]pyridine using commercially available boronic acids. The MCR was strategically designed to rapidly expand accessible chemotypes with an imidazo[1,2-*a*]pyridine core.

We began our investigation for arylomethylation with 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine **1a**, glyoxylic acid **2a**,

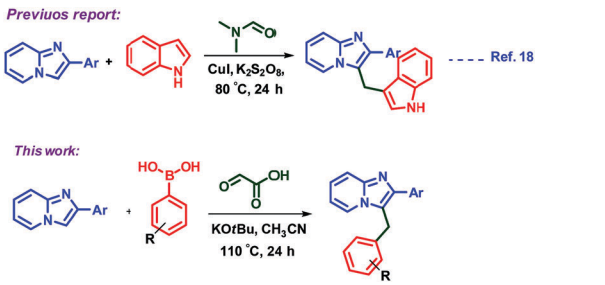


Fig. 1 Literature precedence for C-3 functionalization of imidazo[1,2-*a*]-pyridines.

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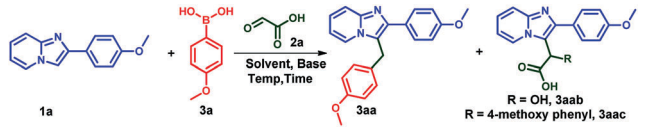
Table 1 Optimization of reaction conditions[a]




| S. no. | Solvent | Promoter | Tempe. (°C) | Time (h) | % of Yield[d] (3aa) | % of Yield[d] (3aab) | % of Yield[d] (3aac) |
|---|---|---|---|---|---|---|---|
| 1 | DMF | — | 100 | 12 | 10 | 50 | 15 |
| 2 | DMF | — | 120 | 24 | 30 | 60 | 20 |
| 3 | DMF | — | 110 | 24 | 40 | 50 | 30 |
| 4 | Dioxane | — | 110 | 24 | 30 | 25 | 40 |
| 5 | EtOH | — | 110 | 24 | — | 55 | 30 |
| 6 | $H_2O$ | — | 110 | 24 | — | 50 | 25 |
| 7 | $CH_3CN$ | — | 110 | 24 | 40 | 50 | — |
| 8 | $CH_3CN$ | *p*TSA | 110 | 24 | 20 | 50 | — |
| 9[b] | $CH_3CN$ | KO*t*Bu | 110 | 24 | 75 | 10 | — |
| 10 | DMF | KO*t*Bu | 110 | 24 | 60 | 20 | — |
| 11 | $CH_3CN$ | NaO*t*Bu | 110 | 24 | 65 | 30 | — |
| 12 | $CH_3CN$ | $Cs_2CO_3$ | 110 | 24 | 45 | 40 | — |
| 13 | $CH_3CN$ | KO*t*Bu | 110 | 12 | 50 | 40 | |
| 14[c] | $CH_3CN$ | KO*t*Bu | 110 | 24 | 60 | 40 | |
| 15 | DMF | PTSA | 110 | 24 | — | 50 | — |
| 16 | Toulene | KO*t*Bu | 110 | 24 | — | 40 | — |
| 17 | DCE | KO*t*Bu | 110 | 24 | — | 40 | — |

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), **3a** (1.5 mmol). [b] Base, 1 mmol. [c] Base, 1.5 mmol; solvent (4.0 mL). [d] Isolated yield.

and 4-methoxy phenylboronic acid **3a** in dimethyl formamide (DMF) as solvent at 100 °C for 12 h. With these conditions, only 10% of the desired product **3aa** was obtained, while the major products were a mixture of the imidazopyridine/glyoxylic acid adduct **3aab** and the non-decarboxylated form of the desired product **3aac** (Table 1, entry 1).

The yield of the desired product **3aa** increased to 30% when the reaction was extended to 24 hours and heated to 120 °C (Table 1, entry 2). This suggests that the desired decarboxylation of intermediate **3aac** could be achieved at higher temperatures with longer reaction durations. Even with more aggressive conditions, however, satisfactory yields of **3aa** were not obtained. Various solvents were investigated to help increase transformation but all failed to improve yield other than acetonitrile, which furnished **3aa** in 40% yield (Table 1, entry 7). Employment of *p*-toluenesulfonic acid to activate intermediate **3ab** did not have a positive impact on overall yield (Table 1, entry 8). Further investigation with various bases produced a dramatic improvement in yield (Table 1, entries 9–14). With 1 eq. of KO*t*Bu the isolated yield of the desired product **3aa** increased to 75% (Table 1, entry 9). Reaction optimization clearly indicated that a strong, non-nucleophilic base is necessary to promote reaction progression and, to efficiently decarboxylate intermediate **3aac**, an aprotic solvent is necessary.

With the optimized conditions in hand, we sequentially examined the substrate scope using commercially available boronic acids (Fig. 2).

It was identified that electron donating boronic acids furnished good to excellent yields, while electron withdrawing boronic acids gave lower yields. However, strongly electron withdrawing boronic acids, such as $-NO_2$ and –CN, were unable

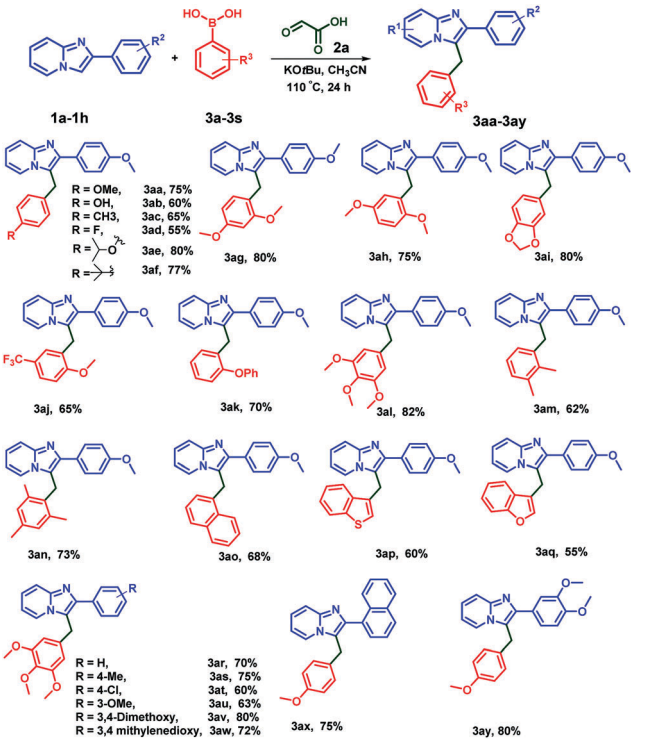



Fig. 2 Arylomethylation substrate scope with various boronic acids and imidazo[1,2-*a*]pyridines[a,b]. [a] Reactions were conducted with 1.0 mmol of **1a–1h**, 1.5 mmol of **2a**, 1.5 mmol of **3a–3s** and 1.0 mmol of KO*t*Bu in $CH_3CN$ at 110 °C for 24 h. [b] Isolated yields.

to produce the desired product. This suggests that electron density is important for product conversion, and the reaction is robust enough to handle mild electron withdrawing functionality. We further examined hetero aryl boronic acids for transformation, such as benzothiophene and benzofuran (Fig. 2, **3ap** and **3aq**). Both were successful in producing the desired product in good yields, but monocyclic hetero aryl boronic acids, such as pyridine, furan, and thiophene, did not furnish the desired product likely from delocalized electron density. The hindered substituted boronic acid **3an** exhibited good transformation suggesting that steric effects do not have a large impact on product conversion.

Further, we diversified the imidazo[1,2-*a*]pyridine core using both electron rich and deficient functionalities and, among them, electron donating groups furnished excellent to good yields compared to their electron deficient counterparts (Fig. 3). We expanded the imidazo[1,2-*a*]pyridine core to test transformation with more complex derivatives and observed excellent product conversion as seen with examples **4a–4n** (Fig. 3).

Based on previous reports[19] and control experiments, we proposed a mechanism for the arylomethylation reaction, which consists of a Petasis-like mechanism followed by decarboxylation to generate the desired product (Fig. 4). To support the mechanism, we completed extensive control experiments and identified molecular ion peaks that correspond to intermediates **3aab** and **3aac** (see ESI†). With this evidence, we proposed that the reaction initiates from the nucleophilic attack of glyoxylic acid by

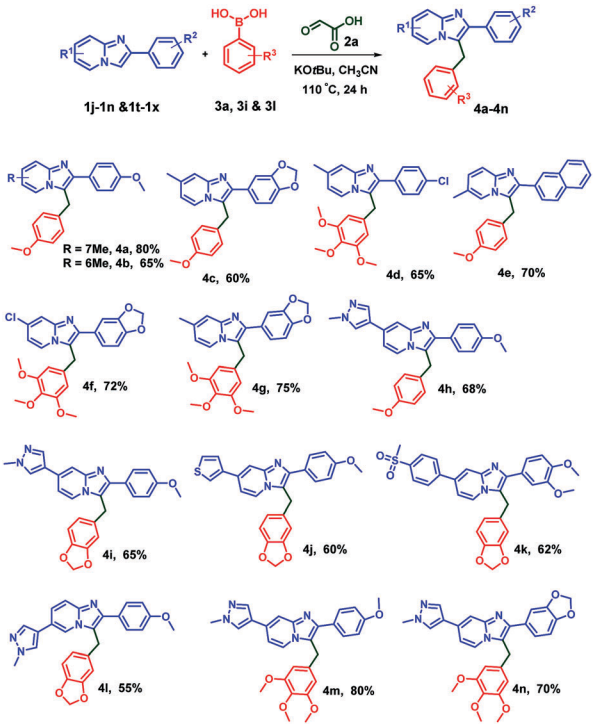



Fig. 3 More diverse imidazopyridines for arylomethylation.[a,b] [a] Reactions were conducted with 1.0 mmol of **1j–1n** & **1t–1x**, 1.5 mmol of **2a**, 1.5 mmol of **3a**, **3i** & **3l** and 1.0 mmol of KO*t*Bu in $CH_3CN$ at 110 °C for 24 h. [b] Isolated yields.

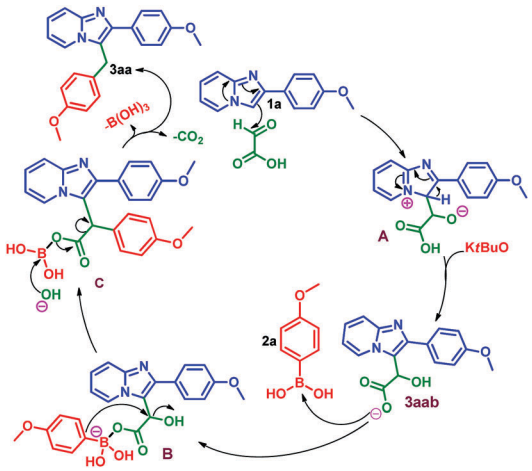



Fig. 4 Proposed reaction mechanism.

imidazo[1,2-*a*]pyridine to afford the stable intermediate **3aab** through A. Under high temperature and basic conditions, the boronic acid can complex with intermediate **3aab** to generate B. The resulting adduct is converted to intermediate C through phenyl migration to the benzylic position of imidazo[1,2-*a*]-pyridine. The final step is decarboxylation of C to generate the desired arylomethylated product. It is important to note that intermediate **3aab** can be isolated and converted to the desired product with addition of base and boronic acid, supporting the proposed mechanism (see ESI†).

Table 2 Antiproliferative activity and selectivity of **3aa**, **4g**, and **4d**[a]

| | Cell $GI_{50}$ (μM) | | |
|---|---|---|---|
| Comp. | H460 | HCC827 | LC-2/ad |
| **3aa** | >1 | >1 | >1 |
| **4g** | 0.15 ± 0.01 | 0.60 ± 0.18 | 0.063 ± 0.029 |
| **4d** | 0.39 ± 0.07 | 2.03 ± 0.56 | 0.28 ± 0.040 |

[a] $GI_{50}$ values are expressed in μM units and are the results of three independent experiments.

Products from the arylomethylation were screened against cancer cell lines to help identify novel chemotypes that impair cancer cell growth (Table 2). The cell lines employed for the studies were HCC827 (EGFR-driven), LC-2/ad (RET-driven), and H460 (non-oncogene). We identified that **3aa**, which was the first compound synthesized, did not exhibit strong activity against any cell line tested ($GI_{50}$ > 1 μM). From screening the entire library of the arylomethylation series, it was identified that compounds **4g** and **4d** were able to potently inhibit cancer cell growth and exhibited sub-micromolar growth inhibition ($GI_{50}$) values. The most active compound, **4g**, exhibited a $GI_{50}$ on LC-2/ad cells of 0.063 ± 0.029 μM. The compound exhibited some selectivity between H460 and LC-2/ad, suggesting **4g** may be more active against RET-driven cell lines. Further studies are underway to determine the exact mechanism by which **4g** and **4d** elicit antiproliferative effects.

In conclusion, we have developed an innovative, catalyst free route to access distinctly substituted, C-3 arylomethylation derivatives of imidazo[1,2-*a*]pyridines. For ease of use, the method was developed to utilize commercially available boronic acids and glyoxylic acid, through a three component Petasis-like reaction followed by decarboxylation in one pot. The current protocol improves on prior methods, which all require the use of a metal catalyst and oxidizing agents. By using this methodology, we have achieved broad substrate scope with 39 variously substituted analogues, and we also evaluated antiproliferative activity in cancer cell lines. From the study, **4g** and **4d** were identified as promising hit, anticancer candidates, which support the use of this new methodology to identify novel, bioactive molecules.

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## Conflicts of interest

There are no conflicts to declare.

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