Microwave-Assisted One-Pot Synthesis of Substituted 3-Bromoimidazo [1,2-*a*]pyridines and Imidazoheterocycles

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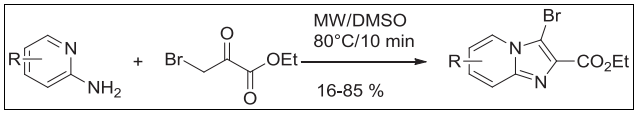

Herein, an efficient, one-pot microwave-assisted synthesis of a diverse set of 3-bromoimidazo[1,2-*a*]pyridines is being reported with good yields (40–85%). The method involves electrophilic aromatic bromination using bromodimethylsulfonium ion generated *in situ* via oxidation of HBr salt by DMSO. This methodology was also applied to the synthesis of related imidazoheterocycles. Copyright © 2014 HeteroCorporation

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INTRODUCTION

The imidazo[1,2-*a*]pyridine scaffold when functionalized appropriately is a starting point for preparation of a plethora of biologically active molecules [1]. Appropriately functionalized imidazo[1,2-*a*]pyridine is also an attractive building block for the synthesis of tricyclic heterocycles [2,3]. Many of the recently reported biologically active imidazo[1,2-*a*] pyridine scaffolds possess a key functional group in the 3-position. There are a number of synthesis of derivatized imidazo[1,2-*a*]pyridine in the literature, but an imidazo[1,2-*a*] pyridine functionalized with a reactive functionality in 3-position to enable further functionalization has a scope for further development. Herein, we report an efficient one-pot microwave-assisted synthesis of multifunctional 3-bromoimidazo [1,2-*a*]pyridine scaffold amenable for further functionalization.

As a part of a medicinal chemistry program to synthesize new chemical entities around a 3-functionalized imidazo [1,2-*a*]pyridine scaffold, it was imperative to have an efficient and easy synthesis of 3-bromoimidazo[1,2-*a*]pyridine scaffold. All reported literature procedures for the synthesis of 3-bromoimidazo[1,2-*a*]pyridine are at least two steps. Typically, the imidazo[1,2-*a*]pyridine ring is constructed in solvents such as ethanol [4], THF [5], and acetone [6] and a subsequent bromination step by using bromine [7], NBS [8], pyridinium hydrobromide perbromide [9], 1,2-dibromo-1,1,2,2-tetrafluoroethane [10], and so on and yields 3-bromoimidazo[1,2-*a*]pyridine scaffold.

Thus, an efficient one-pot synthesis of conveniently functionalized 3-bromoimidazo[1,2-*a*]pyridine derivatives would be an attractive addition to the synthetic methodologies already available for such synthesis. Recently, Kawano and Kato [11] reported a one-pot synthesis of 3-bromo-2-aryl imidazo[1,2-*a*]pyridine scaffold, but the reaction conditions used three equivalents of α-bromo ketones in DMSO and used prolonged reaction duration. The method was also restricted to very few simple examples. Thus, a need for improving the reagent economics along with reaction duration drove us to focus on microwave conditions for the one-pot ring construction and bromination. In brief, treatment of 2-aminopyridines in DMSO at 80°C with one equivalent α-bromocarbonyl compounds yielded 3-bromoimidazo[1,2-*a*]pyridine derivatives in good yields under microwave conditions.

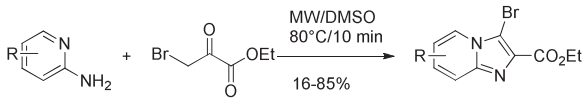
RESULTS AND DISCUSSION

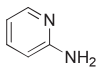
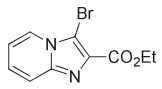
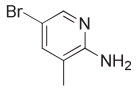
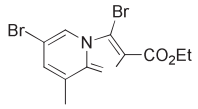
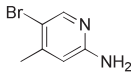
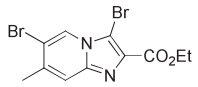
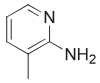
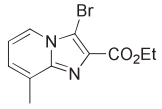
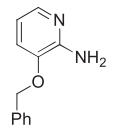
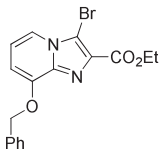
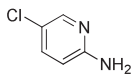
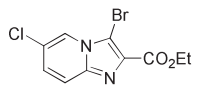
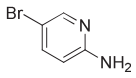
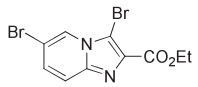
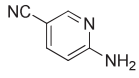
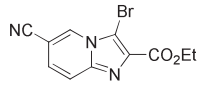
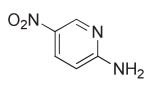
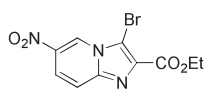
In our initial attempts, concentrated HNO_3 was used as an oxidant for the one-pot bromination. However, this method was not amenable to microwave conditions because the HNO_3 was added after 1 h of reaction at room temperature. Besides, HNO_3 is a harsh oxidizing agent, and thus, we decided to explore DMSO as an *in situ* mild oxidant. As an initial attempt, 2-aminopyridine and ethyl bromopyruvate in DMSO were stirred at 80°C for 6 h to yield the desired compound (Table 1, entry 1) in 62% yield. The job in hand was to further reduce the reaction time, and thus, we subjected the same substrates to microwave conditions and could achieve similar yields in 10 min. We extended this methodology to substituted pyridines (Table 1). As evident from the table, the cyclization reaction is dependent on the electronic nature of the substituted pyridine. The yields are good for electron donating groups (Table 1, entries 2–5) and poor for electron withdrawing groups such as cyano substituted pyridine (Table 1, entry 8). In case of a 5-nitro substituted substrate, we observed no cyclization to the imidazo[1,2-*a*]pyridine scaffold (Table 1, entry 9). In general, the yield of these reactions primarily depends on the cyclization step.

This methodology was further extended to the synthesis of 2-aryl substituted-3-bromoimidazo[1,2-*a*]pyridine scaffolds. Although an ester at 2-position is biologically significant, other aromatic substituents will enhance the scope of the reaction (Table 2). It was observed that these reactions resulted in better yields at 100°C as compared with 80°C. Yields

Table 1

One-pot synthesis of ethyl 3-bromoimidazo[1,2-*a*] pyridine-2-carboxylate scaffolds.



Entry	2-Aminopyridines	Product	Isolated yields (%)
1			62
2			85
3			82
4			70
5			80
6			70
7			72
8			16
9			No cyclisation

ranging from 30–80% have been observed for compounds with different substitution. In cases of 2-aryl substituted imidazo-pyridine core structure (Table 2), 3-methylthio derivative was observed in few cases as a minor side product. For example, entries 4, 5, 6, 7 and 8 (Table 2) yielded less than 15% of 3-methylthio derivative. It should be noted that in case of 3-bromoimidazo[1,2-a]pyridine-2-carboxylate scaffolds, no 3-methylthio product was observed (Table 1).

Upon successfully subjecting the one-pot microwave-assisted synthesis to various substituted imidazo[1,2-*a*] pyridine, we sought to extend this methodology to synthesize more complex pharmaceutically important imidazoheterocyclic scaffolds such as thiazolo-imidazoles (Table 3, entry 1), thiadiazolo-imidazoles (Table 3, entry 2), benzthiazolo-imidazoles (Table 3, entry 3), benzimidazolo-imidazoles (Table 3, entry 4), and pyrimido-imidazoles (Table 3, entry 5). In some cases (Table 3, entries 1 and 2), a nonbrominated imidazoheterocycles was isolated (<20%). In case of benzimidazolo-imidazole (Table 3, entry 4), a 3-methylthio derivative was observed as a minor product (<10%). In this endeavor, we were able to construct various diverse bromo substituted imidazoheterocycles for further functionalization with moderate to good yields.

Mechanistically, condensation of 2-aminopyridine with ethyl bromopyruvate produces 3-bromoimidazo[1,2-*a*]pyridine monohydrobromide (Scheme 1) [12]. Further reaction of HBr (generated *in situ*) with DMSO leads to formation of a bromodimethylsulfonium species [13]. This species probably participates in the electrophilic bromination of the imidazo [1,2-*a*]pyridine ring structure. As a proof of this hypothesis, we isolated 3-bromoimidazo[1,2-*a*]pyridine monohydrobromide and neutralized it thus removing HBr. As expected, reaction of the neutralized species with DMSO did not yield any bromo substituted product. Upon addition of one equivalent of HBr to the isolated neutral species of imidazo[1,2-*a*] pyridine in DMSO leads to 3-bromo substituted product in good yields. This implies that the source of the bromine is the HBr salt of the imidazo[1,2-*a*]pyridine moiety.

In summary, we have developed a microwave assisted one-pot, atom-economical synthesis of 3-bromoimidazo[1,2-*a*]pyridine scaffold using equimolar 2-aminopyridines and α-bromocarbonyl compounds in the presence of DMSO as an oxidant. The reactions are typically completed in less than 30 min with moderate to excellent yields. The one-pot mild reaction condition has been implemented on a variety of substituted imidazo[1,2-*a*]pyridines. The methodology has also been extended to the formation of other heterocyclic ring structures. This methodology is presently being applied to other classes of heterocycles.

EXPERIMENTAL

Melting points were recorded on Labindia visual melting point apparatus (Mumbai, India). ^{1}H NMR spectra were recorded on 300 MHz Bruker FT-NMR (Avance DPX300) spectrometer (Faellandon, Switzerland) using tetramethylsilane as internal standard, and chemical shifts are reported in δ units. High resolution mass spectra were recorded using a Bruker Daltonics Micro TOF-Q spectrometer (ESI, N_2) (Bremen, Germany). HPLC purity was checked using Waters Alliance 2996 HPLC system. HPLC conditions used for checking purity were Ascentis C18 (50 × 4.6 mm, 3.5 μ) column; mobile phase: A: ACN, B: 0.01 M NH_4OAc + 0.5% TEA, pH 5.0 with AcOH (Time A/B%: 0/80, 6/20, 7/80, 10/80); flow rate: 1 mL/min. All chromatographic purifications were performed with silica gel (60–120 mesh), whereas all TLC (silica gel) development was performed on silica gel-coated (Merck Kiesel 60F_{254}, 0.2 mm thickness) sheets. All reagents and solvents were of commercial quality and were used as supplied unless otherwise stated. The microwave reactions were performed with a CEM microwave synthesizer using 10 mL sealed tube.

Typical reaction condition and representative spectroscopic data for compounds in Table 1

Ethyl-3,6-dibromo-8-methylimidazo[1,2-a]pyridine-2-carboxylate (Table 1, 2). In a 10 mL pyrex tube containing a Teflon-coated stir bar, a solution of 2-amino-5-bromo-3-methylpyridine (0.3 g, 1.6 mmol) in DMSO (3 mL) was added. Ethyl bromopyruvate, 90% (0.22 mL, 1.76 mmol) was added to this solution, and the reaction mixture was irradiated for 10 min in a CEM microwave synthesizer at 300 W at 80°C. Reaction mixture was diluted with water (20 mL), and pH was adjusted to 8–9. The reaction mass was then filtered, and it gave pure compound (0.49 g) (Table 1, 2).

Yield: 85%; pale yellow solid; mp 159–160°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.33 (t, *J* = 7.2 Hz, 3H), 2.51 (s, 3H), 4.35 (q, *J* = 7.2 Hz, 2H), 7.46 (s, 1H), 8.46 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 144.2, 133.9, 130.4, 128.9, 122.4, 109.8, 100.7, 61.7, 16.6, 14.4. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{11}Br_2N_2O_2$: 360.9182, found 360.9176; HPLC: 99.53%.

Ethyl 3-bromoimdazo[1,2-a]pyridine-2-carboxylate (Table 1, 1). Yield: 76%; yellow solid; mp 68°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (t, *J* = 7.2 Hz, 3H), 4.50 (q, *J* = 7.2 Hz, 2H), 7.01 (t, *J* = 6.9 Hz, 1H), 7.33 (t, *J* = 6.9 Hz, 1H), 7.71 (d, *J* = 9.3 Hz, 1H), 8.22 (d, *J* = 6.9 Hz, 1H); HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{10}H_{10}Br_1N_2O_2$: 268.9920, found 268.9910; HPLC: 98.37%.

Ethyl 3,6-dibromo-7-methylimidazo [1,2-a]pyridine-2-carboxylate (Table 1, 3). Yield: 82%; white solid; mp 176–178°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (t, *J* = 7.2 Hz, 3H), 2.51 (s, 3H), 4.51 (q, *J* = 7.2 Hz, 2H), 7.55 (s, 1H), 8.39 (s, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{11}Br_2N_2O_2$: 360.9182, found 360.9177. HPLC: 99.53%.

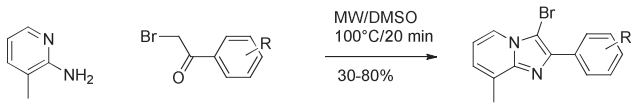
Ethyl 3-bromo-8-methylimidazo [1,2-a]pyridine-2-carboxylate (Table 1, 4). Yield: 70%; brown solid; mp 68–71°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (t, *J* = 7.2 Hz, 3H), 2.69 (s, 3H), 4.53 (q, *J* = 7.2 Hz, 2H), 6.95 (t, *J* = 6.9 Hz, 1H), 7.16 (d, *J* = 6.9 Hz, 1H), 8.11 (d, *J* = 6.9 Hz, 1H). HRMS (ESI+) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{12}Br_1N_2O_2$: 283.0077, found 283.0083. HPLC: 99.28%.

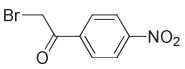
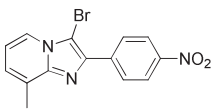
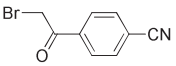
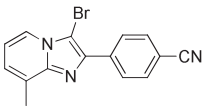
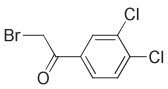
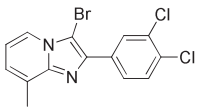
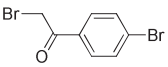
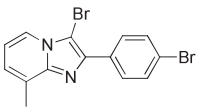
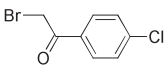
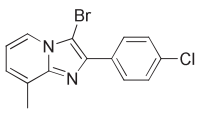
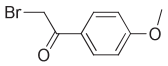
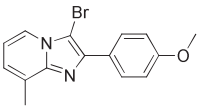
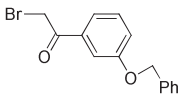
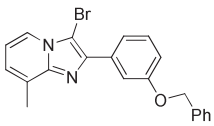
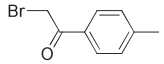
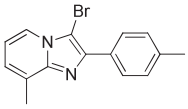
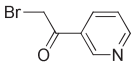
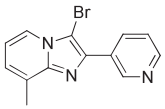
Ethyl 8-(benzyloxy)-3-bromoimidazo[1,2-a]pyridine-2-carboxylate (Table 1, 5). Yield: 80%; white solid; mp 144–145°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.2 Hz, 3H), 4.49 (q, *J* = 7.2 Hz, 2H), 5.36 (s, 2H), 6.58 (d, *J* = 7.2 Hz, 1H), 6.83 (t, *J* = 7.2 Hz, 1H), 7.37 (m, 3H), 7.49 (bd, 2H), 7.84 (d, *J* = 7.2 Hz, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{17}H_{16}Br_1N_2O_3$: 375.0339, found 375.0326. HPLC: 98.06%.

Ethyl 3-bromo-6-chloroimidazo[1,2-a]pyridine-2-carboxylate (Table 1, 6). Yield: 70%; off white solid; mp 147–148°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (t, *J* = 7.2 Hz, 3H), 4.50 (q, *J* = 7.2 Hz, 2H), 7.30 (d, *J* = 9.6 Hz, 1H), 7.69 (d, *J* = 9.6 Hz, 1H), 8.28 (s, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{10}H_9Br_1Cl_1N_2O_2$ $[M+H]^+$ 302.9530, found 302.9530. HPLC: 98.21%.

Table 2

One-pot synthesis of 3-bromo-2-aryl substituted imidazo[1,2-*a*]pyridine scaffold with various substitution on the aryl group.

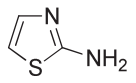
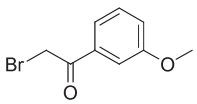
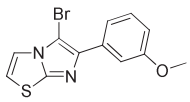
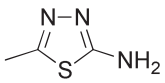
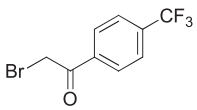
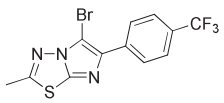
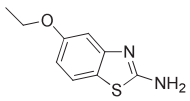
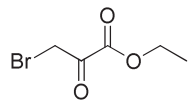
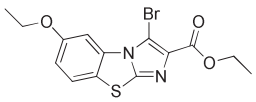
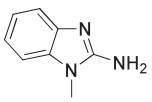
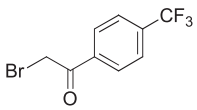
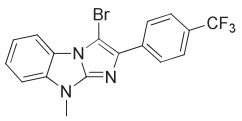
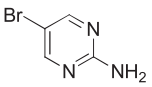
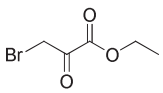
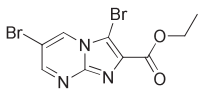


Entry	Alphabromoacetophenones	Product	Isolated yields (%)
1			76[a]
2			72[a]
3			82[a]
4			55[b]
5			55[b]
6			40[b]
7			70[b]
8			63[b]
9			No reaction

[a]Corresponding 3-methylthio derivatives were observed in trace quantity on TLC (not isolated) and confirmed by LCMS.
[b]Corresponding 3-methylthio derivatives were isolated in yield of 10–20% (data included in experimental section).

Table 3

Synthesis of 3-bromo imidazoheteroaryl scaffolds.

Entry	Amino heterocyclics	α-Bromocarbonyls	Product	Isolated yields (%)
1				65[a]
2				55[a]
3				48
4				30[b]
5				30

Reaction condition: MW/DMSO/100°C/20 min.
[a]Corresponding imidazoheterocyclic derivatives were isolated without bromination at 3-position (<20%).
[b]Corresponding 3-methylthio derivative was observed in trace quantity on TLC (not isolated) and confirmed by LCMS.

Ethyl 3,6-dibromoimidazo[1,2-a]pyridine-2-carboxylate (Table 1, 7). Yield: 72%; yellow solid; mp 166–168°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (t, *J* = 7.2 Hz, 3H), 4.50 (q, *J* = 7.2 Hz, 2H), 7.43 (d, *J* = 9.6 Hz, 1H), 7.63 (d, *J* = 9.6 Hz, 1H), 8.38 (s, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{10}H_9Br_2N_2O_2$: 346.9025, found 346.9026. HPLC: 98.29%.

Ethyl 3-bromo-6-cyanoimidazo[1,2-a]pyridine-2-carboxylate (Table 1, 8). Yield: 16%; pale yellow; mp 195–197°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (t, *J* = 7.2 Hz, 3H), 4.52 (q, *J* = 7.2 Hz, 2H), 7.44 (dd, *J* = 9.3 Hz, 1.5 Hz, 1H), 7.81 (d, *J* = 9.3 Hz, 1H), 8.67 (d, *J* = 1.5 Hz, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_9BrN_3O_2$: 293.9873, found 293.9852. HPLC: 99.10%.

Typical reaction condition and representative spectroscopic data for compounds in Table 2 and 3

3-Bromo-8-methyl-2-(4-nitrophenyl)imidazo[1,2-a]pyridine (Table 2, 1). In a 10 mL pyrex tube containing a Teflon-coated stirring bar, 2-amino-3-methylpyridine (0.33 g, 3.05 mmol) and 2-bromo-4′-nitroacetophenone (0.75 g, 3.08 mmol) were mixed in DMSO (3 mL). The mixture was irradiated for 20 min in a CEM microwave system at 300 W at 100°C. Upon diluting the reaction mixture with ethanol (5 mL), on filtration, it gave pure compound (0.75 g) (Table 2, 1).

Yield: 76%; light yellow solid; mp 201–202°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3H), 6.93 (t, *J* = 6.9 Hz, 1H), 7.15 (d, *J* = 6.9 Hz, 1H), 8.11 (d, *J* = 6.9 Hz, 1H), 8.36 (d, *J* = 9 Hz, 2H), 8.41 (d, *J* = 9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$ + drop DMSO-d_6): δ = 147.1, 146.1, 139.7, 139.6, 128.3, 128.1, 124.6, 123.7, 121.9, 113.7, 93.6, 77.1, 40.1, 16.5. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{11}Br_1N_3O_2$: 332.0029, found 332.0027. HPLC: 89.8%.

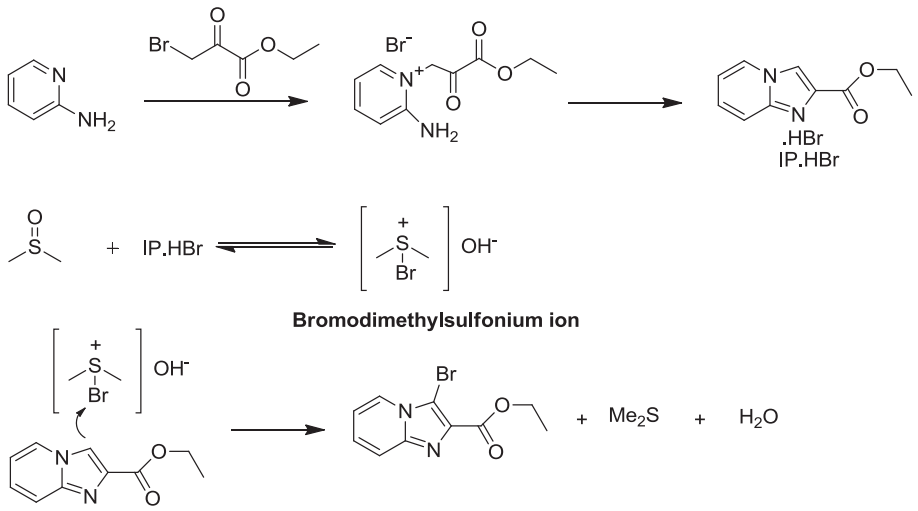
4-(3-Bromo-8-methylimidazo[1,2-a]pyridin-2-yl)benzonitrile (Table 2, 2). Yield: 65%; yellow solid; mp 187–188°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 3H), 6.89 (t, *J* = 6.9 Hz, 1H), 7.11 (d, *J* = 6.9 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 6.9 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 2H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{15}H_{11}Br_1N_3$: 312.0131, found 312.0135. HPLC: 95.50%.

3-Bromo-2-(3,4-dichlorophenyl)-8-methylimidazo[1,2-a]pyridine (Table 2, 3). Yield: 80%; off white solid; mp 149°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 3H), 6.87 (t, *J* = 6.9 Hz, 1H), 7.09 (d, *J* = 6.9 Hz, 1H), 7.55 (d, *J* = 6.9 Hz, 1H), 8.00 (dd, *J* = 8.7 Hz, 1.8 Hz, 1H), 8.05 (d, *J* = 8.7 Hz, 1H), 8.28 (d, *J* = 1.8 Hz, 1H). HMRS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{10}Br_1Cl_2N_2$: 354.9399, found 354.9389. HPLC: 98.21%.

3-Bromo-2-(4-bromophenyl)-8-methylimidazo[1,2-a]pyridine (Table 2, 4). Yield: 55%; yellow solid; mp 132–133°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 3H), 6.86 (t, *J* = 6.9 Hz, 1H), 7.08 (d, *J* = 6.9 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 2H), 8.05 (d, *J* = 6.9 Hz, 1H). HMRS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{11}Br_2N_2$: 364.9283, found 364.9267. HPLC: 98.48%.

2-(4-Bromophenyl)-8-methyl-3-(methylthio)imidazo[1,2-a]pyridine (Table 2, 4b). Yield: 12%; off white solid; mp 104°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H), 2.68 (s, 3H), 6.88 (t, *J* = 6 Hz, 1H), 7.13 (d, *J* = 6 Hz, 1H), 7.63 (d, *J* = 9 Hz, 2H), 8.23 (d, *J* = 9 Hz, 2H), 8.37 (d, *J* = 6 Hz, 1H).

Scheme 1. Plausible mechanism of 3-bromo imidazo[1,2-*a*]pyridine formation.



HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{15}H_{14}Br_1N_2S_1$: 333.0056, found 333.0048. HPLC: 99.83%.

3-Bromo-2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine (Table 2, 5). Yield: 55%; off white solid; mp 139–140°C. ^{1}H NMR (300 MHz, CDCl3): δ = 2.68 (s, 3H), 6.88 (t, *J* = 6.9 Hz, 1H), 7.10 (d, *J* = 6.9 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 8.07 (d, *J* = 6.9 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 2H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{11}Br_1Cl_1N_2$: 320.9789, found 320.9798. HPLC: 97.77%.

2-(4-Chlorophenyl)-8-methyl-3-(methylthio)imidazo[1,2-a]pyridine (Table 2, 5b). Yield: 15%; off white solid; mp 102°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H), 2.68 (s, 3H), 6.88 (t, *J* = 6 Hz, 1H), 7.12 (d, *J* = 6 Hz, 1H), 7.48 (d, *J* = 9 Hz, 2H), 8.29 (d, *J* = 9 Hz, 2H), 8.37 (d, *J* = 6 Hz, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{15}H_{14}Cl_1N_2S_1$ 289.0561, found 289.0534. HPLC: 99.28%.

3-Bromo-2-(4-methoxyphenyl)-8-methylimidazo[1,2-a]pyridine (Table 2, 6). Yield: 40%; brown solid; mp 113–115°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 3H), 3.87 (s, 3H), 6.83 (t, *J* = 6.9 Hz, 1H), 6.99–7.48 (m, 3H), 8.02–8.09 (m, 3H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{15}H_{14}Br_1N_2O_1$: 317.0284, found 317.0282. HPLC: 99.56%.

2-(4-Methoxyphenyl)-8-methyl-3-(methylthio)imidazo[1,2-a] pyridine (Table 2, 6b). Yield: 17%; colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H), 2.73 (s, 3H),), 3.89 (s, 3H), 6.85 (t, *J* = 6 Hz, 1H), 7.05 (d, *J* = 9 Hz, 2H), 7.10 (d, *J* = 6 Hz, 1H), 8.25 (d, *J* = 9 Hz, 2H), 8.36 (d, *J* = 6 Hz, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{16}H_{17}N_2O_1S_1$: 285.1056, found 285.1066. HPLC: 99.45%.

2-(3-(Benzyloxy)phenyl)-3-bromo-8-methyl imidazo[1,2-a] pyridine (Table 2, 7). Yield: 30%; dark brown semisolid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67 (s, 3H), 5.18 (s, 2H), 6.85 (t, *J* = 6.9 Hz, 1H), 7.02 (dd, *J* = 7.8 Hz, 2.4 Hz, 1H), 7.07 (d, *J* = 6.9 Hz, 1H), 7.30–7.42 (m, 4H), 7.48 (bs, 1H), 7.50 (d, *J* = 6.9 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.77 (bs, 1H), 8.06 (d, *J* = 6.9 Hz, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{21}H_{18}Br_1N_2O_1$: 393.0597, found 393.0590. HPLC: 99.13%.

2-(3-(Benzyloxy)phenyl)-8-methyl-3-(methylthio)imidazo[1,2-a] pyridine (Table 2, 7b). Yield: 11%; brown semisolid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3H), 2.69 (s, 3H), 5.21 (s, 2H), 6.87 (t, *J* = 6 Hz, 1H), 7.04 (dd, *J* = 9 Hz, 3 Hz, 1H), 7.11 (d, *J* = 6 Hz, 1H), 7.35–7.44 (m, 4H), 7.50 (d, *J* = 6 Hz, 2H), 7.93 (d, *J* = 9 Hz, 1H), 8.00 (bs, 1H), 8.38 (d, *J* = 6 Hz, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{22}H_{21}N_2O_1S_1$: 361.1369, found 361.1356. HPLC: 99.06%.

3-Bromo-8-methyl-2-(p-tolyl)imidazo[1,2-a]pyridine (Table 2, 8). Yield: 70%; dark brown solid; mp 75–76°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 2.67 (s, 3H), 6.84 (t, *J* = 6.9 Hz, 1H), 7.05 (d, *J* = 6.9 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 8.02 (d, *J* = 8.1 Hz, 2H), 8.06 (d, *J* = 6.9 Hz, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{15}H_{14}Br_1N_2$: 301.0335, found 301.0324. HPLC: 99.73%.

8-Methyl-3-(methylthio)-2-(p-tolyl)imidazo[1,2-a]pyridine (Table 2, 8b). Yield: 10%; semisolid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H), 2.44 (s, 3H), 2.69 (s, 3H), 6.84 (t, *J* = 6 Hz, 1H), 7.10 (d, *J* = 6 Hz, 1H), 7.30 (d, *J* = 9 Hz, 2H), 8.19 (d, *J* = 9 Hz, 2H), 8.37 (d, *J* = 6 Hz, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{16}H_{17}N_2S_1$: 269.1107, found 269.1119. HPLC: 99.82%.

Imidazoheterocycle sacaffold (Table 3)

5-Bromo-6-(3-methoxyphenyl)imidazo[2,1-b]thiazole (Table 3, 1). Yield: 65%; brown solid; mp 98°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3H), 6.91 (dd, *J* = 8.1 Hz, 2.4 Hz, 1H), 6.95 (d, *J* = 4.5 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 4.5 Hz, 1H), 7.60 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{10}Br_1N_2O_1S_1$: 308.9692, found 308.9686. HPLC: 99.21%.

6-(3-Methoxyphenyl)imidazo[2,1-b]thiazole (Table 3, 1a). Yield: 15%; off white solid; mp 153°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3H), 6.85 (bd, *J* = 6 Hz, 1H), 6.88 (dd, *J* = 9 Hz, 3 Hz, 1H), 7.32 (t, *J* = 9 Hz, 1H), 7.41 (d, *J* = 3 Hz, 1H), 7.44 (d, *J* = 6 Hz, 1H), 7.45 (d, *J* = 9 Hz, 1H), 7.76 (s, 1H). MS (ESI) *m/z* $[M+H]^+$ 231.0; HPLC: 99.55%.

5-Bromo-2-methyl-6-(4-(trifluoromethyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (Table 3, 2). Yield: 55%; white solid; mp156–157°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.80 (s, 3H), 7.72 (d, *J* = 8.4 Hz, 2H), 8.19 (d, *J* = 8.4 Hz, 2H). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_8Br_1F_3N_3S_1$: 361.9569, found 361.9554. HPLC: 97.5%.

2-Methyl-6-(4-(trifluoromethyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (Table 3, 2a). Yield: 18%; yellow solid; mp 218–220°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.75 (s, 3H), 7.68 (d,

$J = 9$ Hz, 2H), 7.95 (d, $J = 9$ Hz, 2H), 8.05 (s, 1H). MS (ESI) *m/z* $[M + H]^+$ 284.0; HPLC: 97.72%.

Ethyl 3-bromo-6-ethoxybenzo[d]imidazo[2,1-b]thiazole-2-carboxylate (Table 3, 3). Yield: 48%; brown solid; mp 208–210°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (m, $J = 7.2$ Hz, 6H), 4.08 (q, $J = 7.2$ Hz, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 7.15 (dd, $J = 9$ Hz, 2.4 Hz, 1H), 7.70 (d, $J = 2.4$ Hz, 1H), 8.29 (d, $J = 9$ Hz, 1H). HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{14}H_{14}Br_1N_2O_3S_1$: 368.9903, found 368.9887. HPLC: 99.00%.

3-Bromo-9-methyl-2-(4-(trifluoromethyl)phenyl)-9H-benzo[d]imidazo[1,2-a]imidazole (Table 3, 4). Yield: 30%; white solid; mp 179°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 7.24–7.34 (m, 2H), 7.41 (d, $J = 8.1$ Hz, 1H), 7.72 (d, $J = 8.4$ Hz, 2H), 8.07 (d, $J = 8.1$ Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 2H). HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{17}H_{12}Br_1F_3N_3$: 394.0161, found 394.0161. HPLC: 98.83%.

Ethyl 3,6-dibromoimidazo[1,2-a]pyrimidine-2-carboxylate (Table 3, 5). Yield: 30%; pale yellow solid; mp 108°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.47$ (t, $J = 7.2$ Hz, 3H), 4.50 (q, $J = 7.2$ Hz, 2H), 8.71 (d, $J = 2.1$ Hz, 1H), 9.78 (d, $J = 2.1$ Hz, 1H). HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_9H_8Br_2N_3O_2$: 347.8978, found 347.8966. HPLC: 96.57%.

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