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# METAL-FREE C3-H HYDRAZINATION OF IMIDAZO[1,2-*a*]PYRIDINE WITH AZODIFORMATES IN WATER AT ROOM TEMPERATURE

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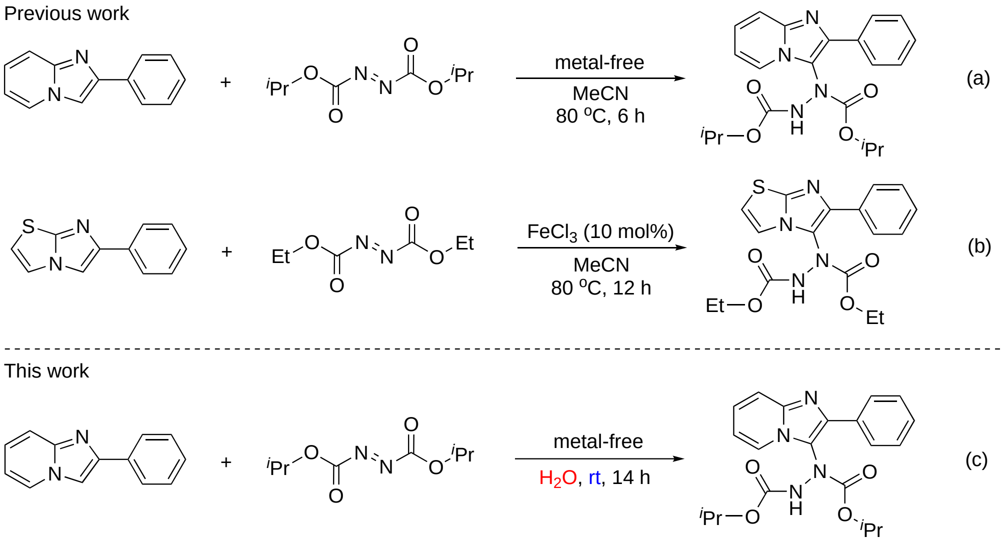
**Abstract** – An efficient synthesis of imidazo[1,2-*a*]pyridine-hydrazines was accomplished by making imidazo[1,2-*a*]pyridine substrates and azodiformates react in water phase. This reaction features mild and green conditions (proceeding without transition-metals and phase transfer catalyst in water under air at room temperature) as well as good tolerance of substrates. Note that electron-donating groups on the imidazo[1,2-*a*]pyridine substrates are benefit for this reaction, affording target products in excellent yields. Besides, this aqueous phase reaction could also tolerate the solid azodiformates.

## INTRODUCTION

Due to the unique biological and pharmacological properties,[1] such as anti-tumor,[2] anti-inflammatory,[3] anti-ulcer,[4] anti-microbial,[5] anti-fungal,[6] anti-viral,[7] and so on, imidazoheterocycles have wide applications in optoelectronics and pharmaceuticals. Among them, imidazo[1,2-*a*]pyridine derivatives could be also served as the key structures of many excellent natural products and marketed drugs, including alpidem, divalpon, DS-1, necopidem, olprinone, saripidem, zolpidem and zolimidine.[8] Therefore, developing the economical and environment-friendly routes to functionalized imidazo[1,2-*a*]pyridine derivatives has attracted increasing attentions of the chemists and medicinal chemists.

Recently, plentiful efforts have been devoted to develop new methodologies for direct C−H functionalizations of imidazo[1,2-*a*]pyridines, achieving greet progress in the transformations from C-H to C-C and C-heteroatom bonds (e.g. N, O, S, P, Cl, Se).[9-15] Among the rest, the C3-H hydrazinations could provide efficient protocols for C3 substituted imidazoheterocycles. For example, the pioneering work of C3−H hydrazination of imidazo[1,2-*a*]pyridines belongs to Li and co-workers, who developed a procedure of metal-free regioselective hydrazination of imidazo[1,2-*a*]pyridine with diethyl azodicarboxylate at 80 °C in 2015 (Scheme 1a).[16] Then, Tang's group developed an iron-catalyzed hydrazination of imidazoheterocycles at C3 position, which could afford a series of imidazoheterocycle-hydrazines (Scheme 1b).[17] Generally, these methods are useful and efficient, but both of them are operated at high temperature, which is difficult to conduct due to the necessary of water coolant and closed system. Meanwhile, employing organic solvents at high temperature could virtually increase the dangerousness of the experiment, due to the flammability and explosivity of many organic solvents. Beyond that, because of their responsibility for the toxicity issues (e.g. mutagenicity, teratogenicity, carcinogenicity and reprotoxicity) as well as environmental pollution, many organic solvents are not conforming to the demand of green chemistry.[18] As a result, the solvents of organic synthesis reactions have been the focus of environmental concerns.



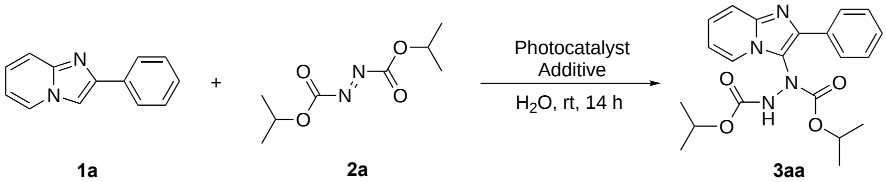
**Scheme 1.** The protocols for the preparation of imidazoheterocycle-hydrazines

The intelligent use of greener solvents, especially water, has been emerged as a reliable and robust tool in green chemistry practices. As known, water is a veritable green solvent, due to its unique advantages such as cheap, abundant, non-toxic, non-flammable, safe, environmentally friendly and so on. Besides, replacing organic solvents with water as the reaction medium could also benefit chemical processes by making reaction conditions mild, simplifying experimental operations, and occasionally even delivering unforeseen reactivities.[19] Although great progresses have been achieved, carrying out organic reactions in aqueous media is still fascinating and full of challenges.

The research interest of our group is to demonstrate a simple, efficient and environment-friendly reaction pattern for the preparation of imidazo[1,2-*a*]pyridine-hydrazines. Herein, we envisioned developing a protocol for the C3−H hydrazination of imidazo[1,2-*a*]pyridines in water at room temperature under air (Scheme 1c).

## RESULTS AND DISCUSSION

**Table 1.** Screening optimal conditions[a]



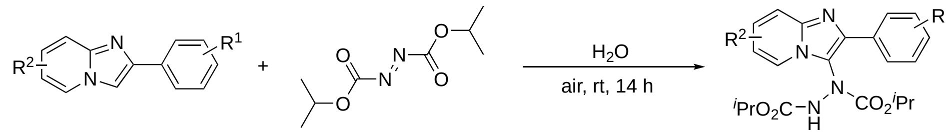
**1a** **2a** **3aa**

| Entry | Photocatalyst | Light source | Additive | Yield(%)[b] |
|---|---|---|---|---|
| 1 | eosin Y | white light | - | 71 |
| 2 | alizarin red S | white light | - | 71 |
| 3 | $Ru(bpy)_3Cl_2$ | white light | - | 71 |
| 4 | eosin B | white light | - | 70 |
| 5 | acid red 94 | white light | - | 71 |
| 6 | - | - | - | 71 |
| 7 | - | - | $Na_2CO_3$ | 25 |
| 8 | - | - | $NH_4Cl$ | 68 |
| 9 | - | - | $I_2$ | <5 |
| 10[c] | - | - | - | 85 |
| **11[d]** | **-** | **-** | **-** | **93** |
| 12[e] | - | - | - | 94 |
| 13[d,f] | - | - | - | 93 |
| 14[d,g] | - | - | - | 90 |

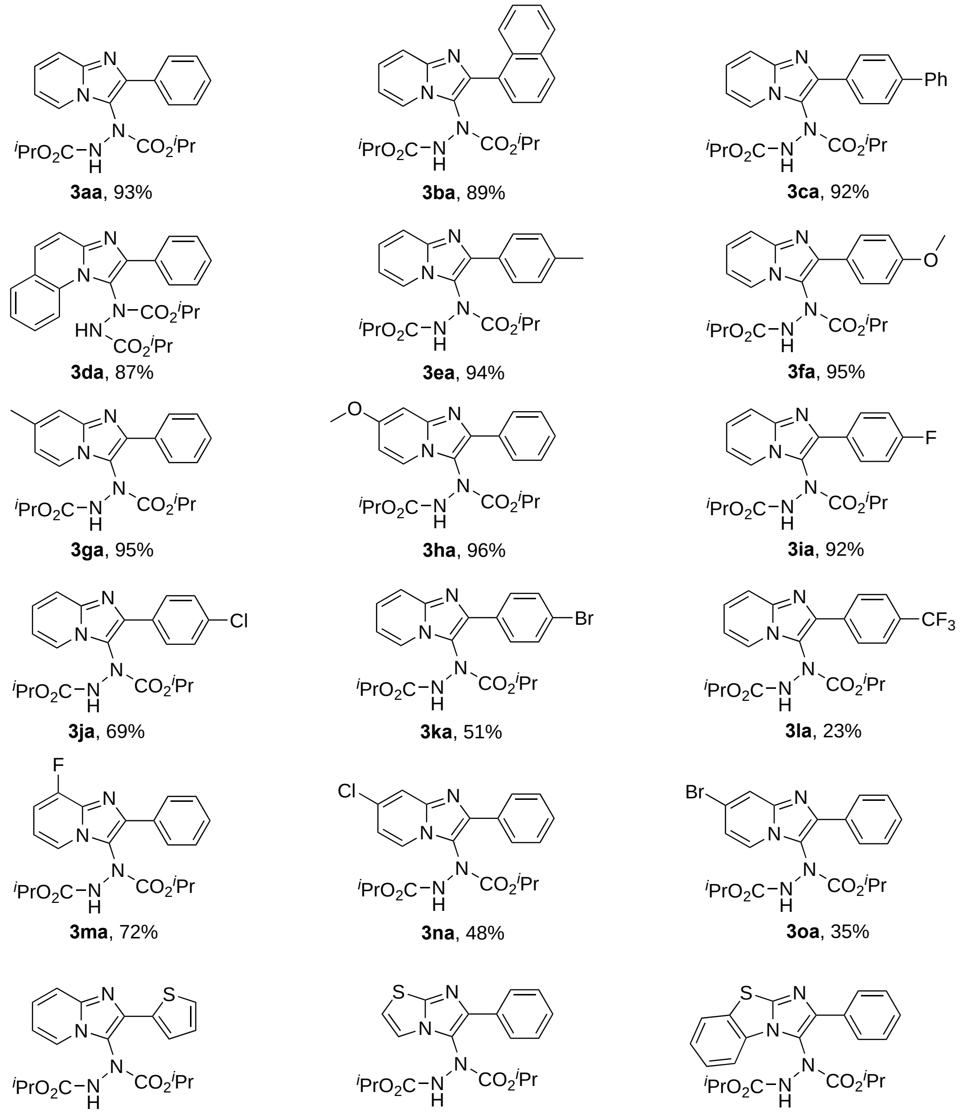
[a]Reaction conditions: **1a** (0.2 mmol, 38.8 mg), **2a** (0.4 mmol, 79.3 μL), photocatalyst (5 mol%), additive (0.5 mmol), $H_2O$ (1.5 mL), at room temperature under air for 14 h; [b]Isolated yield; [c]**2a** (0.5 mmol); [d]**2a** (0.6 mmol); [e]**2a** (0.7 mmol); [f]For 15 h; [g]For 13 h.

In 2020, Braga et al. reported a greener approach for the eosin Y catalyzed C3-H bond azo coupling of imidazo[1,2-*a*]pyridine under a photocatalytic system.[10d] Therefore, we tested the possibility of C3−H hydrazination of imidazo[1,2-*a*]pyridines by using a photocatalytic system at the beginning. We commenced our investigation by the reaction of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with diisopropyl (*E*)-diazene-1,2-dicarboxylate (**2a**) in $H_2O$ under the catalysis of eosin Y as the model reaction, and the target product **3aa** was obtained in 71% yield under the irradiation of white light (Table 1, entry 1). The molecular structure of **3aa** was unambiguously confirmed by single crystal X-ray diffraction study (CCDC 2103352). Then, other photocatalysts were also examined, including alizarin red S, $Ru(bpy)_3Cl_2$, eosin B, acid red 94, but the results had no obvious changes (Table 1, entries 2-5 *vs* entry 1). To our surprise, the desired product could be also formed in similar yield under the absence of photocatalyst and light irradiation (Table 1, entry 6), indicating that photocatalytic system has no evident effect on this reaction. Then, we examined various additives in the absence of photocatalytic system, and $K_2CO_3$, $NH_4Cl$, $I_2$ showed no effective influence on this hydrazination reaction (Table 1, entries 7-9). When the amount of **2a** was altered from 0.4 mmol to 0.5 mmol and 0.6 mmol, better results were observed and the coupling product were afforded in the yields of 85% and 93%, respectively (Table 1, entries 10-11).

**Table 2.** Substrate scope of imidazo[1,2-*a*]pyridine derivatives[a,b]



**1** **2a** **3**



**3aa**, 93% **3ba**, 89% **3ca**, 92%

**3da**, 87% **3ea**, 94% **3fa**, 95%

**3ga**, 95% **3ha**, 96% **3ia**, 92%

**3ja**, 69% **3ka**, 51% **3la**, 23%

**3ma**, 72% **3na**, 48% **3oa**, 35%

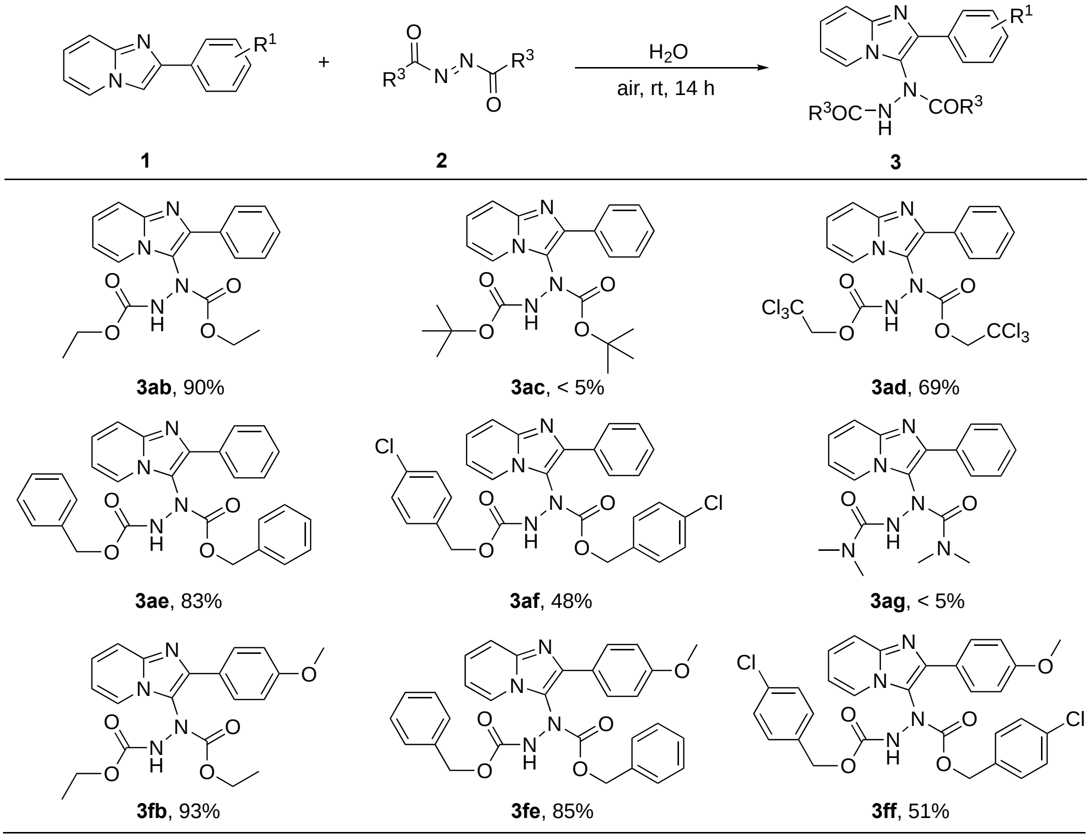
**3pa**, 95% **3qa**, 52% **3ra**, 48%

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol, 119.0 μL), $H_2O$ (1.5 mL), at room temperature under air for 14 h; [b]Isolated yield.

Encouraged by this result, we attempted to increase the amount of **2a** to 0.7 mmol, but the result showed no significantly improvement (Table 1, entry 12 *vs* entry 11). In addition, increasing the reaction time to 15 h or decreasing to 13 h led to the hydrazination product in no better yields (Table 1, entries 13-14 *vs* entry 11).

With the optimized reaction conditions in hand, the applicability of imidazo[1,2-*a*]pyridine derivatives was explored, and the results are summarized in Table 2. As shown, 2-phenylimidazo[1,2-*a*]pyridines bearing electronic neutral, electron-donating, or electron-withdrawing groups on the benzene ring are all well tolerated in this hydrazination reaction, and the target products could be afforded in 23% to 96% yields (**3aa-3oa**). Comparatively, electronic neutral substituents (**1a-1d**) and electron-donating substituents (**1e-1h**, e.g., Me and OMe) resulted in higher yields than those of the electron-withdrawing substituents (**1i-1o**, e.g., F, Cl, Br, and $CF_3$). According to the above, electron-donating groups on the substrates are benefit for this hydrazination reaction, generating the desired products in 94%-96% yields (**3ea-3ha**); but the electron-withdrawing groups could reduce the reactivity of this hydrazination reaction and result in the sharp decline of yields (**3ia-3oa**). In comparison, the electronic effect was more obvious

**Table 3.** Substrate scope of azodiformates[a,b]



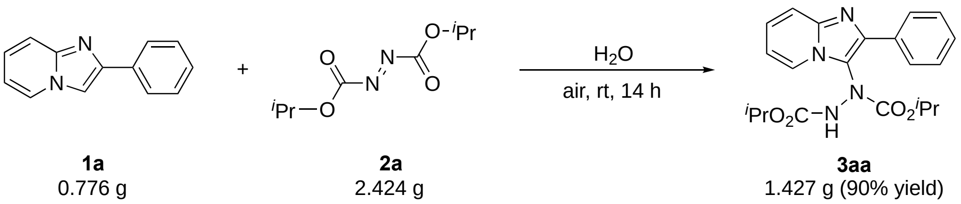
**3ab**, 90%
**3ac**, < 5%
**3ad**, 69%
**3ae**, 83%
**3af**, 48%
**3ag**, < 5%
**3fb**, 93%
**3fe**, 85%
**3ff**, 51%

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $H_2O$ (1.5 mL), at room temperature under air for 14 h; [b]Isolated yield.

on the pyridine ring of 2-phenylimidazo[1,2-*a*]pyridine than on the benzene ring. To our delight, other heterocyclic substrates (such as 2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine, 6-phenylimidazo[2,1-*b*]thiazole and 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole) could also participate in this coupling, producing the coupling products in 95%, 52% and 48% yields, respectively (**3pa-3ra**).

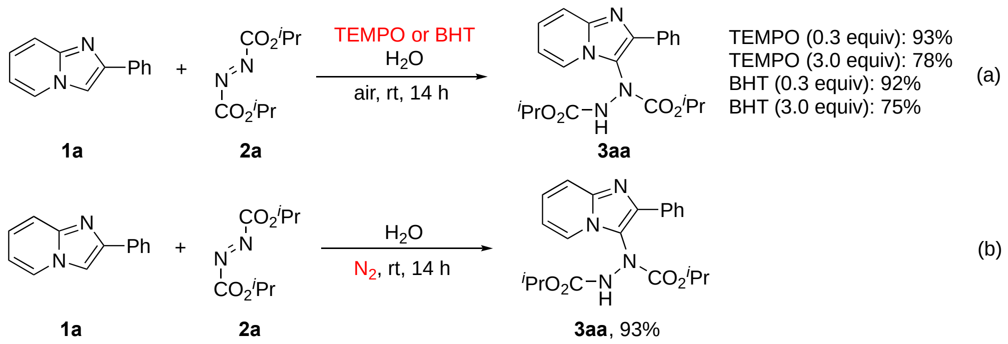
To further investigate the scope in this hydrazination reaction, a small range of azodiformates were examined under the standard reaction conditions (Table 3). Alkyl azodiformates and benzyl azodicarboxylates were all well applicable to this reaction system in moderate to excellent yields (**3ab**, **3ad-3af**), but di-*tert*-butyl azodicarboxylate showed low reactivity (**3ac**), which might be for the influence of steric hindrance of *tert*-butyl group. In particular, solid azodiformates were all well tolerated in the hydrazination reaction, and the target products could be afforded in moderate to good yields (**3ad-3af**, 69%, 83% and 48% yields, respectively). However, using azodicarbonamide as the hydrazination reagents resulted in almost no transformation on account of the low reactivity (**3ag**). Besides, whether liquid substrate or solid substrates could successfully react with 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (**1f**), generating the products in yields of 93% (**3fb**), 85% (**3fe**) and 51% (**3ff**), respectively.

To demonstrate the potential applicable value of this protocol in organic synthesis, a gram-scale reaction of **1a** with **2a** was executed (Scheme 2). This reaction could afford the target product **3aa** in an isolated yield of 90%.



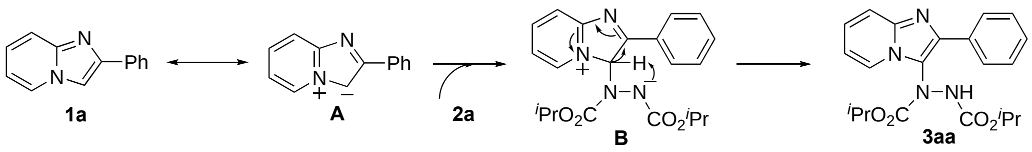
**Scheme 2.** The gram scale reaction

Next, we performed some control experiments to understand the probable reaction mechanism of this hydrazination reaction (Scheme 3). The addition of radical inhibitor 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-diisopropyl-4-methylphenol (BHT) could not suppress the reaction, indicating that this reaction might involve ionic mechanism (Scheme 3a). Performing the reaction under a nitrogen atmosphere instead of air resulted in a similar yield of **3aa**, which demonstrated that oxygen might have no effect on the hydrazination reaction (Scheme 3b).



**Scheme 3.** Control Experiments

Although the mechanism involved here remains unclear at present, a plausible mechanism (Scheme 4) of the reaction was proposed on the above-mentioned results and previous reports.[16,17] First, **1a** could undergo an interconversion process to afford the intermediate **A**. Subsequently, the carbanion of **A** could attack the N=N bond of **2a** through a pseudo-Michael reaction, forming an intermediate **B**. Finally, proton translocation and restoring conjugation of **B** provides the desired product **3aa**.



**Scheme 4.** Plausible mechanism

In summary, we have developed a mild and efficient protocol for the C3-H hydrazination of 2-phenylimidazo[1,2-*a*]pyridine with azodiformates, thus providing a facile, convenient and environment-friendly route to the C3-position imidazoheterocycle-hydrazine derivatives. The advantages of the present method include environmentally friendly conditions (avoiding the loading of transition metal salts, phase transfer catalyst, harmful solvents and high temperature) as well as good tolerance of substrates. Moreover, we indicate that imidazo[1,2-*a*]pyridine substrates bearing electron-withdrawing groups are not conducive to this reaction. Note that solid azodiformates could also be applicable to this aqueous phase reaction. Finally, a gram-scale C3-H hydrazination reaction is also successfully realized, which demonstrates its potential synthetic value.

## EXPERIMENTAL

### 1. General Information

$^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker DPX-400 spectrometer or Bruker DPX-600 spectrometer with $CDCl_3$ as the solvent and TMS as an internal standard. Melting points were measured using a WC-1 microscopic apparatus and are uncorrected. Mass spectra were measured on an LC-MSD-Trap-XCT instrument. Elemental analysis was determined by Elementar Vario EL. All solvents were used directly without further purification. Dichloromethane, ethyl acetate, and hexane were used for column chromatography. The commercials were obtained from commercial sources and used as-received without further purification unless otherwise noted.

## 2. Typical Procedure for the Products

(a) A 10 mL reaction tube was equipped with a magnetic stir bar and charged with imidazo[1,2-*a*]pyridine derivatives **1** (0.2 mmol), azodiformates **2** (0.6 mmol, 3 equiv), and $H_2O$ (1.5 mL). The resulting mixture was stirred under air at room temperature for 14 h. Upon completion, $CH_2Cl_2$ (20 mL) was added to the reaction system, which was extracted with $H_2O$ (20 mL), and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$ and filtered. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (200–300 mesh) using hexane-EtOAc as an eluent to afford the pure product **3**.

**Diisopropyl 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3aa)** (Known compound)[20]: Obtained as a white solid in 93% yield (73.7 mg) (hexane/EtOAc, 2:1); Mp 162-163 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.70 (s, 1H), 7.79 (d, *J* = 7.4 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.30-7.27 (m, 1H), 7.09-7.00 (m, 1H), 6.89 (t, *J* = 6.7 Hz, 1H), 5.14-4.94 (m, 2H), 1.30-1.02 (m, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 156.4, 154.7, 143.0, 139.3, 132.9, 128.8, 128.2, 126.8, 125.7, 124.6, 118.6, 117.2, 112.3, 72.1, 70.5, 21.9, 21.8, 21.6, 21.5.

**Diisopropyl 1-(2-(naphthalen-1-yl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ba)**: Obtained as an orange solid in 89% yield (79.5 mg) (hexane/EtOAc, 2:1); Mp 127-128 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.75 (s, 1H), 8.34 (s, 1H), 7.96-7.88 (m, 4H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.55-7.53 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.11-7.02 (m, 1H), 6.94 (t, *J* = 5.8 Hz, 1H), 5.21-4.99 (m, 2H), 1.31-1.08 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 156.4, 154.8, 143.2, 139.3, 133.6, 133.2, 130.3, 128.8, 128.5, 127.7, 126.5, 126.2, 126.0, 124.7, 124.2, 119.0, 117.3, 112.5, 72.3, 70.7, 22.0, 21.8, 21.7. MS (ESI+) $[M+H]^+$ *m/z*: 447.3. Anal. Calcd for $C_{25}H_{26}N_4O_4$: C, 67.25; H, 5.87; N, 12.55. Found: C, 67.27; H, 5.85; N, 12.58.

**Diisopropyl 1-(2-([1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ca)**: Obtained as an orange solid in 92% yield (86.9 mg) (hexane/EtOAc, 2:1); Mp 135-136 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.74 (s, 1H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 3H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.32-7.27 (m, 2H), 6.92 (t, *J* = 6.2 Hz, 1H), 5.17-4.97 (m, 2H), 1.32-1.06 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 156.6, 154.8, 143.1, 141.1, 140.0, 139.0, 131.9, 128.9, 127.6, 127.5, 127.2, 127.0, 125.9, 124.7, 118.7, 117.3, 112.5, 72.3, 70.7, 22.0, 21.9, 21.7, 21.6. MS

(ESI+) [M+H]$^+$ *m/z*: 473.1. Anal. Calcd for $C_{27}H_{28}N_4O_4$: C, 68.63; H, 5.97; N, 11.86. Found: C, 68.67; H, 5.96; N, 11.85.

**Diisopropyl 1-(2-phenylimidazo[1,2-*a*]quinolin-1-yl)hydrazine-1,2-dicarboxylate (3da)**: Obtained as an orange solid in 87% yield (77.7 mg) (hexane/EtOAc, 2:1); Mp 117-118 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 9.07 (s, 1H), 7.82 (d, $J$ = 7.6 Hz, 1H), 7.78-7.77 (m, 2H), 7.71 (t, $J$ = 7.4 Hz, 1H), 7.62-7.58 (m, 2H), 7.54-7.50 (m, 3H), 7.44 (t, $J$ = 7.4 Hz, 1H), 6.89-6.76 (m, 1H), 5.25-4.94 (m, 2H), 1.29-1.00 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 155.5, 155.3, 142.4, 133.5, 133.2, 129.3, 128.8, 128.7, 128.5, 127.9, 127.0, 125.1, 124.4, 123.0, 117.2, 72.7, 70.4, 22.0, 21.9, 21.8, 21.7. MS (ESI+) [M+H]$^+$ *m/z*: 447.4. Anal. Calcd for $C_{25}H_{26}N_4O_4$: C, 67.25; H, 5.87; N, 12.55. Found: C, 67.24; H, 5.88; N, 12.59.

**Diisopropyl 1-(2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ea)**: Obtained as an orange solid in 94% yield (77.2 mg) (hexane/EtOAc, 2:1); Mp 152-153 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.70 (s, 1H), 7.70 (d, $J$ = 7.6 Hz, 2H), 7.63 (d, $J$ = 8.9 Hz, 1H), 7.28-7.27 (m, 3H), 7.11-7.03 (m, 1H), 6.70 (t, $J$ = 6.4 Hz, 1H), 5.15-4.98 (m, 2H), 2.41 (s, 3H), 1.31-1.05 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 156.5, 154.8, 143.0, 139.4, 138.3, 130.1, 129.7, 126.7, 125.7, 124.6, 118.4, 117.2, 112.3, 72.1, 70.6, 22.0, 21.9, 21.7, 21.6, 21.3. MS (ESI+) [M+H]$^+$ *m/z*: 411.3. Anal. Calcd for $C_{22}H_{26}N_4O_4$: C, 64.37; H, 6.38; N, 13.65. Found: C, 64.38; H, 6.39; N, 13.63.

**Diisopropyl 1-(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3fa)**: Obtained as an orange solid in 95% yield (81.0 mg) (hexane/EtOAc, 3:2); Mp 140-141 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.67 (s, 1H), 7.73 (d, $J$ = 8.7 Hz, 2H), 7.59 (d, $J$ = 9.0 Hz, 1H), 7.25-7.23 (m, 2H), 6.97 (d, $J$ = 8.8 Hz, 2H), 6.87 (t, $J$ = 6.7 Hz, 1H), 5.12-4.95 (m, 2H), 3.84 (s, 3H), 1.29-1.03 (m, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 159.7, 156.5, 154.9, 143.0, 139.3, 128.1, 125.7, 125.5, 124.6, 117.9, 117.1, 114.4, 112.2, 72.1, 70.6, 55.3, 22.0, 21.9, 21.7, 21.6. MS (ESI+) [M+H]$^+$ *m/z*: 427.4. Anal. Calcd for $C_{22}H_{26}N_4O_5$: C, 61.96; H, 6.15; N, 13.14. Found: C, 61.97; H, 6.18; N, 13.12.

**Diisopropyl 1-(7-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ga)**: Obtained as an orange solid in 95% yield (78.0 mg) (hexane/EtOAc, 2:1); Mp 141-143 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.58 (s, 1H), 7.79 (d, $J$ = 7.3 Hz, 2H), 7.45 (t, $J$ = 7.6 Hz, 2H), 7.38-7.35 (m, 2H), 7.13-7.08 (m, 1H), 6.73 (d, $J$ = 6.5 Hz, 1H), 5.14-4.98 (m, 2H), 2.44 (s, 3H), 1.31-1.04 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 156.5, 154.9, 143.5, 139.0, 136.9, 133.1, 129.0, 128.2, 126.8, 123.8, 118.2, 115.7, 115.0, 72.1, 70.6, 22.0, 21.9, 21.7, 21.6, 21.4. MS (ESI+) [M+H]$^+$ *m/z*: 411.3. Anal. Calcd for $C_{22}H_{26}N_4O_4$: C, 64.37; H, 6.38; N, 13.65. Found: C, 64.36; H, 6.40; N, 13.68.

**Diisopropyl 1-(7-methoxy-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ha)**: Obtained as a white solid in 96% yield (81.9 mg) (hexane/EtOAc, 3:2); Mp 132-134 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.53 (s, 1H), 7.76 (d, $J$ = 7.5 Hz, 2H), 7.45-7.41 (m, 2H), 7.36-7.32 (m, 1H), 7.15-7.06 (m, 1H), 6.89 (d, $J$ = 2.0 Hz, 1H), 6.60 (dd, $J$ = 7.2, 1.7 Hz, 1H), 5.11-4.95 (m, 2H), 3.88 (s, 3H), 1.29-1.02 (m, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.9, 156.5, 154.9, 144.7, 138.7, 133.1, 128.9, 128.2, 126.6, 125.2, 117.8, 107.3, 94.6, 72.1, 70.6, 55.6, 22.0, 21.9, 21.8, 21.6. MS (ESI+) [M+H]$^+$ *m/z*: 427.1. Anal. Calcd for $C_{22}H_{26}N_4O_5$: C, 61.96; H, 6.15; N, 13.14. Found: C, 61.93; H, 6.17; N, 13.17.

**Diisopropyl 1-(2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ia)**: Obtained as a white solid in 92% yield (76.2 mg) (hexane/EtOAc, 2:1); Mp 173-174 °C. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.71 (s, 1H), 7.78 (dd, $J$ = 5.5, 8.5 Hz, 2H), 7.62 (d, $J$ = 8.9 Hz, 1H), 7.31-7.29 (m, 1H), 7.22 (s, 1H), 7.14 (t, $J$ = 8.5 Hz, 2H), 6.91 (t, $J$ = 6.3 Hz, 1H), 5.14-4.98 (m, 2H), 1.31-1.04 (m, 12H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 162.8 (d, $J$ = 248.7 Hz), 156.5, 154.7, 143.0, 138.6, 129.2, 128.7, 126.0, 124.7, 118.4, 117.3, 116.0 (d, $J$ = 21.5 Hz), 112.5, 72.3, 70.7, 22.0, 21.9, 21.7, 21.6. MS (ESI+) [M+H]$^+$ *m/z*: 415.5. Anal. Calcd for $C_{21}H_{23}FN_4O_4$: C, 60.86; H, 5.59; N, 13.52. Found: C, 60.87; H, 5.60; N, 13.55.

**Diisopropyl 1-(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ja)**: Obtained as a white solid in 69% yield (59.4 mg) (hexane/EtOAc, 2:1); Mp 167-168 °C. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.71 (s, 1H), 7.75 (d, $J$ = 8.4 Hz, 2H), 7.63 (d, $J$ = 8.9 Hz, 1H), 7.44 (d, $J$ = 8.5 Hz, 2H), 7.31 (t, $J$ = 7.4 Hz, 1H), 7.13-7.04 (m, 1H), 6.92 (t, $J$ = 6.4 Hz, 1H), 5.14-4.97 (m, 2H), 1.32-1.05 (m, 12H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 156.6, 154.7, 143.1, 138.3, 134.3, 131.5, 129.2, 128.1, 126.1, 124.7, 118.7, 117.3, 112.6, 72.4, 70.8, 22.0, 21.9, 21.7, 21.6. MS (ESI+) [M+H]$^+$ *m/z*: 431.0. Anal. Calcd for $C_{21}H_{23}ClN_4O_4$: C, 58.54; H, 5.38; N, 13.00. Found: C, 58.56; H, 5.39; N, 13.02.

**Diisopropyl 1-(2-(4-bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ka)** (Known compound)[20]: Obtained as a white solid in 51% yield (48.4 mg) (hexane/EtOAc, 2:1); Mp 163-165 °C. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.71 (s, 1H), 7.68-7.67 (m, 2H), 7.62 (d, $J$ = 8.9 Hz, 1H), 7.55 (d, $J$ = 8.3 Hz, 2H), 7.46-7.21 (m, 2H), 6.91 (d, 1H), 5.13-4.97 (m, 2H), 1.28-1.03 (m, 12H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 156.6, 154.6, 143.1, 138.3, 132.0, 131.9, 128.4, 126.1, 124.7, 122.5, 118.7, 117.3, 112.6, 72.3, 70.7, 22.0, 21.9, 21.7, 21.6.

**Diisopropyl 1-(2-(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3la)**: Obtained as a white solid in 23% yield (21.4 mg) (hexane/EtOAc, 2:1); Mp 177-178 °C. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.73 (s, 1H), 7.94 (d, $J$ = 8.0 Hz, 2H), 7.72 (d, $J$ = 8.2 Hz, 2H), 7.65 (d, $J$ = 8.9 Hz, 1H), 7.33 (t, $J$ = 7.5 Hz, 1H), 7.19-7.06 (m, 1H), 6.94 (t, $J$ = 6.0 Hz, 1H), 5.15-4.99 (m, 2H), 1.33-1.04 (m, 12H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 156.6, 154.5, 143.2, 137.9, 136.5, 130.1 (q, $J$ = 31.5 Hz), 127.0, 126.3, 125.9, 124.8, 124.1 (q, $J$ = 270.3 Hz), 119.3, 117.5, 112.8, 72.4, 70.9, 21.9, 21.8, 21.7, 21.6. MS (ESI+) [M+H]$^+$ *m/z*: 465.4. Anal. Calcd for $C_{22}H_{23}F_3N_4O_4$: C, 56.89; H, 4.99; N, 12.06. Found: C, 56.87; H, 5.02; N, 12.09.

**Diisopropyl 1-(8-fluoro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ma)**: Obtained as a white solid in 72% yield (59.7 mg) (hexane/EtOAc, 2:1); Mp 159-160 °C. $^1$H NMR (600

MHz, $CDCl_3$): *δ* 8.57 (s, 1H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.1 Hz, 1H), 7.20 (s, 1H), 6.99 (t, *J* = 8.9 Hz, 1H), 6.82 (d, *J* = 4.1 Hz, 1H), 5.14-4.96 (m, 2H), 1.30-1.02 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$): *δ* 156.5, 154.5, 151.2 (d, *J* = 253.7 Hz), 139.9, 135.6 (d, *J* = 29.3 Hz), 132.4, 129.0, 128.6, 127.0, 121.0, 120.0, 111.3, 108.3 (d, *J* = 16.0 Hz), 72.4, 70.8, 21.9, 21.8, 21.7, 21.6. MS (ESI+) $[M+H]^+$ *m/z*: 415.3. Anal. Calcd for $C_{21}H_{23}FN_4O_4$: C, 60.86; H, 5.59; N, 13.52. Found: C, 60.85; H, 5.61; N, 13.53.

**Diisopropyl 1-(7-chloro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3na)**: Obtained as a white solid in 48% yield (41.3 mg) (hexane/EtOAc, 2:1); Mp 170-171 ºC. $^1$H NMR (600 MHz, $CDCl_3$): *δ* 8.69 (s, 1H), 7.77 (d, *J* = 7.3 Hz, 2H), 7.62 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.0 Hz, 1H), 7.27-7.20 (m, 1H), 6.88 (t, *J* = 6.7 Hz, 1H), 5.14-4.98 (m, 2H), 1.30-1.03 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$): *δ* 156.6, 154.6, 142.8, 140.2, 132.6, 129.1, 128.7, 127.1, 126.8, 125.1, 118.9, 116.2, 114.1, 72.4, 70.9, 22.0, 21.8, 21.7, 21.6. MS (ESI+) $[M+H]^+$ *m/z*: 431.5. Anal. Calcd for $C_{21}H_{23}ClN_4O_4$: C, 58.54; H, 5.38; N, 13.00. Found: C, 58.53; H, 5.41; N, 12.99.

**Diisopropyl 1-(7-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3oa)**: Obtained as a white solid in 35% yield (33.2 mg) (hexane/EtOAc, 2:1); Mp 165-166 ºC. $^1$H NMR (600 MHz, $CDCl_3$): *δ* 8.63 (s, 1H), 7.81 (s, 1H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.46-7.45 (m, 2H), 7.39 (s, 1H), 7.21-7.11 (m, 1H), 7.00 (d, *J* = 6.3 Hz, 1H), 5.14-4.98 (m, 2H), 1.32-1.04 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$): *δ* 156.6, 154.6, 143.1, 140.0, 132.5, 129.0, 128.7, 127.1, 126.8, 125.1, 120.0, 119.5, 116.4, 72.4, 70.8, 22.0, 21.8, 21.7, 21.6. MS (ESI+) $[M+H]^+$ *m/z*: 475.2. Anal. Calcd for $C_{21}H_{23}BrN_4O_4$: C, 53.06; H, 4.88; N, 11.79. Found: C, 53.03; H, 4.89; N, 11.80.

**Diisopropyl 1-(2-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3pa)**: Obtained as a brown solid in 95% yield (76.4 mg) (hexane/EtOAc, 2:1); Mp 119-121 ºC. $^1$H NMR (400 MHz, $CDCl_3$): *δ* 8.71 (s, 1H), 7.60-7.54 (m, 4H), 7.36 (d, *J* = 4.7 Hz, 1H), 7.29-7.25 (m, 2H), 7.13 (dd, *J* = 3.7, 4.9 Hz, 1H), 6.88 (t, *J* = 6.5 Hz, 1H), 5.12-4.94 (m, 2H), 1.32-1.02 (m, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$): *δ* 156.6, 154.6, 143.2, 135.3, 135.1, 128.0, 126.2, 125.9, 125.1, 124.7, 117.6, 117.1, 112.6, 72.3, 70.7, 22.0, 21.9, 21.7, 21.6. MS (ESI+) $[M+H]^+$ *m/z*: 403.4. Anal. Calcd for $C_{19}H_{22}N_4O_4S$: C, 56.70; H, 5.51; N, 13.92. Found: C, 56.71; H, 5.50; N, 13.91.

**Diisopropyl 1-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)hydrazine-1,2-dicarboxylate (3qa)** (Known compound)[17]: Obtained as a white solid in 52% yield (41.9 mg) (hexane/EtOAc, 3:1); Mp 160-161 ºC. $^1$H NMR (600 MHz, $CDCl_3$): *δ* 7.92 (s, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.17-7.11 (m, 1H), 6.82 (s, 1H), 5.11-4.98 (m, 2H), 1.30-1.07 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$): *δ* 156.4, 154.6, 148.0, 140.7, 133.1, 128.8, 127.8, 126.2, 120.3, 119.3, 112.0, 72.2, 70.6, 21.9, 21.7, 21.7, 21.6.

**Diisopropyl 1-(2-phenylbenzo[d]imidazo[2,1-*b*]thiazol-3-yl)hydrazine-1,2-dicarboxylate (3ra)**: Obtained as a light yellow solid in 48% yield (43.4 mg) (hexane/EtOAc, 3:1); Mp 167-169 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.35 (s, 1H), 7.71 (d, $J$ = 7.4 Hz, 3H), 7.52-7.48 (m, 3H), 7.40-7.37 (m, 2H), 7.00 (s, 1H), 5.15-4.94 (m, 2H), 1.40-1.07 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 155.4, 155.0, 146.5, 140.2, 133.0, 132.5, 129.8, 129.2, 128.1, 126.1, 125.0, 123.6, 122.5, 115.6, 72.7, 70.4, 22.0, 21.9, 21.7. MS (ESI+) $[M+H]^+$ *m/z*: 453.3. Anal. Calcd for $C_{23}H_{24}N_4O_4S$: C, 61.05; H, 5.35; N, 12.38. Found: C, 61.04; H, 5.39; N, 12.37.

**Diethyl 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ab)** (Known compound)[17]: Obtained as an orange solid in 90% yield (66.3 mg) (hexane/EtOAc, 2:1); Mp 141-143 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.71 (s, 1H), 7.81 (d, $J$ = 7.5 Hz, 2H), 7.64 (d, $J$ = 8.9 Hz, 1H), 7.47 (t, $J$ = 7.5 Hz, 2H), 7.39 (t, $J$ = 7.4 Hz, 1H), 7.31-7.29 (m, 1H), 6.92 (t, $J$ = 6.5 Hz, 1H), 6.62 (s, 1H), 4.24-4.20 (m, 4H), 1.27-1.11 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 156.8, 155.2, 143.1, 139.4, 132.8, 129.0, 128.4, 126.8, 125.9, 124.6, 118.4, 117.3, 112.5, 64.0, 62.2, 14.4, 14.3.

**Bis(2,2,2-trichloroethyl) 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ad)**: Obtained as a white solid in 69% yield (78.9 mg) (hexane/EtOAc, 2:1); Mp 187-188 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.77-8.32 (m, 2H), 7.80-7.76 (m, 2H), 7.64 (d, $J$ = 9.0 Hz, 1H), 7.37-7.30 (m, 4H), 6.93 (t, $J$ = 6.5 Hz, 1H), 5.01-4.64 (m, 4H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 155.3, 153.6, 143.4, 140.6, 132.3, 128.9, 128.7, 127.1, 126.4, 124.7, 117.5, 117.4, 112.9, 94.4, 94.0, 76.1, 75.4. MS (ESI+) $[M+H]^+$ *m/z*: 572.9. Anal. Calcd for $C_{19}H_{14}Cl_6N_4O_4$: C, 39.69; H, 2.45; N, 9.74. Found: C, 39.70; H, 2.43; N, 9.73.

**Dibenzyl 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ae)**: Obtained as an orange solid in 83% yield (81.7 mg) (hexane/EtOAc, 2:1); Mp 158-159 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.68 (s, 1H), 7.71 (d, $J$ = 6.8 Hz, 2H), 7.63 (d, $J$ = 8.7 Hz, 1H), 7.48-6.87 (m, 16H), 5.40-5.04 (m, 4H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 156.7, 155.2, 143.2, 139.7, 135.0, 134.9, 132.6, 129.0, 128.6, 128.5, 128.2, 126.9, 126.1, 124.7, 118.1, 117.3, 112.6, 69.4, 68.3. MS (ESI+) $[M+H]^+$ *m/z*: 493.4. Anal. Calcd for $C_{29}H_{24}N_4O_4$: C, 70.72; H, 4.91; N, 11.38. Found: C, 70.70; H, 4.93; N, 11.39.

**Bis(4-chlorobenzyl) 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3af)**: Obtained as an orange solid in 48% yield (53.8 mg) (hexane/EtOAc, 2:1); Mp 170-171 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.65 (s, 1H), 7.68-7.54 (m, 4H), 7.34-7.00 (m, 12H), 6.88 (s, 1H), 5.31-4.99 (m, 4H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 156.6, 155.0, 143.2, 139.7, 134.5, 133.6, 133.3, 132.5, 129.6, 128.9, 128.8, 128.7, 128.6, 126.8, 126.1, 124.5, 117.9, 117.4, 112.7, 68.6, 67.4. MS (ESI+) $[M+H]^+$ *m/z*: 561.1. Anal. Calcd for $C_{29}H_{22}Cl_2N_4O_4$: C, 62.04; H, 3.95; N, 9.98. Found: C, 62.07; H, 3.93; N, 9.99.

**Diethyl 1-(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3fb)** (Known compound)[17]: Obtained as an orange solid in 93% yield (74.1 mg) (hexane/EtOAc, 3:2); Mp 114-115 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.68 (s, 1H), 7.75 (d, $J$ = 8.6 Hz, 2H), 7.62 (d, $J$ = 8.9 Hz, 1H), 7.29-7.27 (m, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 6.90 (t, *J* = 6.5 Hz, 1H), 4.24-4.22 (m, 4H), 3.87 (s, 3H), 1.27-1.12 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 159.8, 156.9, 155.3, 143.0, 139.4, 128.1, 125.8, 125.4, 124.6, 117.7, 117.1, 114.5, 112.4, 64.0, 62.6, 55.3, 14.3.

**Dibenzyl 1-(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3fe)**: Obtained as an orange solid in 85% yield (88.8 mg) (hexane/EtOAc, 3:2); Mp 132-133 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.65 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.56-7.10 (m, 12H), 6.87 (d, *J* = 8.3 Hz, 3H), 5.39-5.05 (m, 4H), 3.83 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 159.8, 156.7, 155.3, 143.1, 139.7, 135.1, 135.0, 128.6, 128.5, 128.2, 125.9, 125.2, 124.6, 117.4, 117.1, 114.4, 112.4, 69.4, 68.2, 55.3. MS (ESI+) $[M+H]^+$ *m/z*: 523.1. Anal. Calcd for $C_{30}H_{26}N_4O_5$: C, 68.95; H, 5.02; N, 10.72. Found: C, 68.93; H, 5.03; N, 10.75.

**Bis(4-chlorobenzyl) 1-(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (3ff)**: Obtained as an orange solid in 51% yield (60.2 mg) (hexane/EtOAc, 3:2); Mp 139-141 ºC. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.63 (s, 1H), 7.61-7.59 (m, 3H), 7.38-7.02 (m, 10H), 6.87 (s, 3H), 5.32-5.00 (m, 4H) , 3.85 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 159.9, 156.5, 155.1, 143.1, 139.7, 134.5, 133.6, 133.4, 129.7, 129.5, 128.8, 128.7, 128.1, 126.0, 125.0, 124.4, 117.2, 114.4, 112.5, 68.5, 67.4, 55.3. MS (ESI+) $[M+H]^+$ *m/z*: 591.3. Anal. Calcd for $C_{30}H_{24}Cl_2N_4O_5$: C, 60.92; H, 4.09; N, 9.47. Found: C, 60.95; H, 4.10; N, 9.45.

(b) For the gram scale reaction: A 100 mL reaction tube was equipped with a magnetic stir bar and charged with imidazo[1,2-*a*]pyridine **1a** (4 mmol, 0.776 g), diisopropyl (*E*)-diazene-1,2-dicarboxylate **2a** (12 mmol, 2.424 g), and $H_2O$ (30 mL). The resulting mixture was stirred under air at room temperature for 14 h. Upon completion, the mixture was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$ and filtered. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (200-300 mesh) using hexane-EtOAc (hexane/EtOAc, 2:1) as an eluent to afford the pure product **3aa** (1.427 g, 90% yield).

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