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Synthesis Design

Synthesis of 1,2,4-Triazolo[4,3-*a*]pyridines and Related Heterocycles by Sequential Condensation and Iodine-Mediated Oxidative Cyclization

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Abstract: A facile and efficient approach to access 1,2,4-triazolo[4,3-*a*]pyridines and related heterocycles has been accomplished through condensation of readily available aryl hydrazines with corresponding aldehydes followed by iodine-mediated oxidative cyclization. This transition-metal-free synthetic process is broadly applicable to a variety of aromatic, aliphatic, and α,β-unsaturated aldehydes, and can be conveniently conducted on the gram scale.

Introduction

Triazolopyridines are an important class of fused-ring heterocyclic compounds.[1] Among the various triazolopyridine derivatives, the 1,2,4-triazolo[4,3-*a*]pyridine skeleton widely exists in many compounds with diverse pharmaceutical properties, such as anti-inflammatory,[2] antithrombotic,[3] antiproliferative,[4] antidepressant/antipsychotic,[5] antibacterial,[6] and antiviral activities.[7] For example, selective p38a inhibitor **5** exhibited significant anti-inflammatory activity in a rat model of arthritis (Figure 1).[2c] As a positive allosteric modulator (PAM) of the

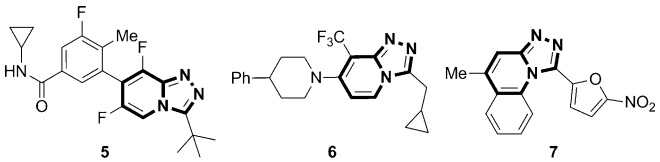

Figure 1. Representative bioactive 1,2,4-triazolo[4,3-*a*]pyridine derivatives.

metabotropic glutamate 2 receptor, compound **6** showed good antipsychotic activity in mice.[5a] 1,2,4-Triazolo[4,3-*a*]quinoline **7** was demonstrated to have good inhibitory activity against several bacterial strains.[6a] Moreover, 1,2,4-triazolo[4,3-*a*]pyridines can also be used as herbicidal agents in agriculture.[8] Owing to their excellent deep-blue emission and stability properties, 3-aryl[1,2,4]triazolo[4,3-*a*]pyridines could be potential candidates for applications in high-performance organic light-emitting diodes (OLEDs).[9]

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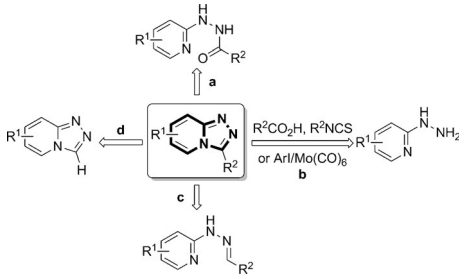
A survey of the literature indicated that 1,2,4-triazolo[4,3-*a*]pyridines could be prepared by the following strategies (Scheme 1): a) cyclodehydration of acylated 2-hydrazinopyri-



Scheme 1. Synthetic strategies for the preparation of 1,2,4-triazolo[4,3-*a*]pyridines.

dines in acetic acid under microwave irradiation[10] or by using Lawesson's reagent;[11] b) tandem/one-pot reaction of 2-hydrazinopyridines with carboxylic acids in the presence of reagents such as $POCl_3/PCl_5$,[12] polystyrene-bound triphenylphosphine (PS-PPh_3)/CCl_3CN,[13] and 1,1′-carbonyldiimidazole (CDI);[14] with isothiocyanates promoted by polymer-supported Mukaiyama's reagent;[15] or with aryl iodides through [$Mo(CO)_6$]-mediated carbonylation;[16] c) oxidative cyclization of 2-pyridylhydrazones with oxidants such as hypervalent iodine reagents,[17] *N*-bromosuccinimide (NBS),[18] chloramine T,[19] ceric ammonium nitrate (CAN),[20] and $CuCl_2$;[21] and d) Cu-catalyzed direct C–H (hetero)arylation of preformed 1,2,4-triazolo[4,3-*a*]pyridines.[9]

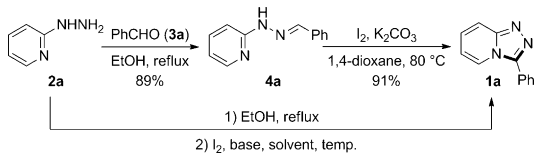
Nevertheless, there are still disadvantages associated with the existing methods due to harsh reaction conditions, the use of expensive and/or hazardous reagents, and limited substrate scope and/or scalability. Therefore, it is of great importance to develop practical and eco-friendly approaches to access this compound class. Previously, utilizing molecular iodine as the sole oxidant,[22] we have successfully constructed nitrogen-containing heterocyclic frameworks, such as pyrazoles, quinazolinones, and benzimidazoles, through oxidative C–N bond for-

mation.[23] Recently, we disclosed an I_2-mediated oxidative cyclization reaction of *N*-aryl amidines **8** to prepare 1,5-fused 1,2,4-triazoles **9**.[24] As a continuation of this research into the synthesis of fused 1,2,4-triazoles, herein we envisioned a sequential synthetic method for the preparation of 1,2,4-triazolo[4,3-*a*]pyridines and related heterocycles through condensation of aryl hydrazines and aldehydes followed by iodine-mediated oxidative cyclization.

Results and Discussion

First, we investigated the oxidative cyclization of the purified hydrazone **4a**, obtained in 89% yield through the condensation of 2-hydrazinopyridine (**2a**) and benzaldehyde (**3a**). Treatment of **4a** with molecular iodine in the presence of K_2CO_3 in 1,4-dioxane at 80 °C resulted in the desired triazolopyridine (**1a**) in 91% yield (Table 1, entry 1). Next, we attempted to probe the feasibility of the sequential synthesis of triazolopyridine **1a** without purification of intermediate **4a**. Upon completion of the first condensation step, the solvent was removed and the resulting crude product **4a** was directly subjected to the above oxidative cyclization conditions; this gave product **1a** in equally good yield (Table 1, entry 2). Raising the reaction temperature accelerated the conversion rate and did not affect the yield (Table 1, entry 3). Further screening of a series of commonly used laboratory solvents (Table 1, entries 3–8) suggested that CH_2Cl_2 was the optimal solvent for the cyclization step. By taking the synthesis of **1a** as an example, the reaction was conveniently carried out on a gram scale (6 mmol; Table 1, entry 8). Replacement of K_2CO_3 with either an organic base (Table 1, entry 9) or a weaker inorganic base (Table 1, entry 10) decreased the yield of the product.

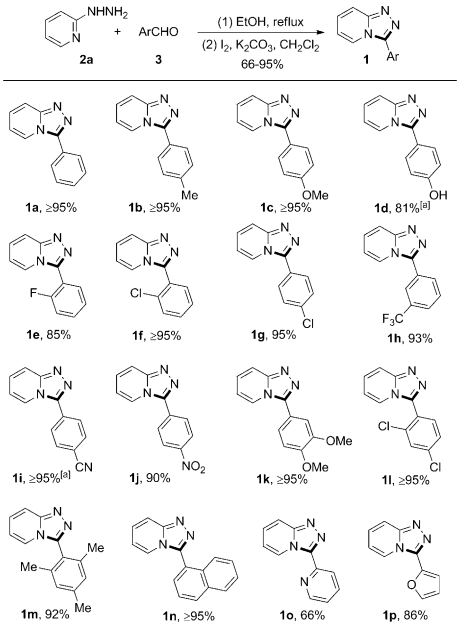
Table 1. Optimization of the reaction conditions for the synthesis of 3-phenyl[1,2,4]triazolo[4,3-*a*]pyridine (**1a**).[a]



Entry	Substrate	Base	Solvent	*T*	*t*	Yield[b] [%]
1	**4a**	K_2CO_3	1,4-dioxane	80 °C	5 h	91
2	**2a**+**3a**	K_2CO_3	1,4-dioxane	80 °C	5 h	90
3	**2a**+**3a**	K_2CO_3	1,4-dioxane	reflux	2 h	90
4	**2a**+**3a**	K_2CO_3	DMSO	100 °C	1 h	81
5	**2a**+**3a**	K_2CO_3	DMF	100 °C	10 min	71
6	**2a**+**3a**	K_2CO_3	EtOH	RT	1 h	89
7	**2a**+**3a**	K_2CO_3	MeCN	RT	3 h	69
8	**2a**+**3a**	K_2CO_3	CH_2Cl_2	RT	1 h	≥95[c]
9	**2a**+**3a**	DBU[d]	CH_2Cl_2	RT	30 min	82
10	**2a**+**3a**	$NaHCO_3$	CH_2Cl_2	RT	1 h	24

[a] Optimal reaction conditions: 1) **2a** (0.5 mmol), **3a** (0.5 mmol), EtOH, reflux; 2) I_2 (0.6 mmol), K_2CO_3 (1.5 mmol), CH_2Cl_2, RT. [b] Yields of products isolated are given. [c] Yields for both 0.5 and 6 mmol scale reactions. [d] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

With the optimal reaction conditions (Table 1, entry 8) in hand, we sought to examine the scope and generality of this sequential synthesis. Condensation of **2a** with substituted benzaldehydes **3**, followed by I_2-mediated oxidative cyclization, produced a series of 3-aryl[1,2,4]triazolo[4,3-*a*]pyridines (**1b**–**m**) in good to excellent yields (Scheme 2). This synthetic method

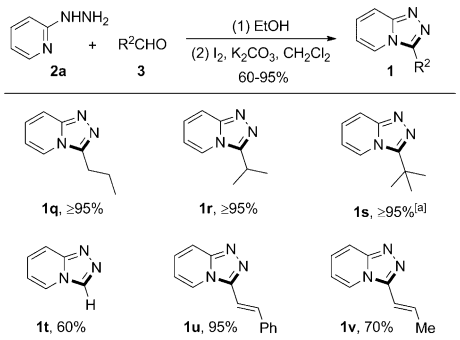


Scheme 2. Scope of aromatic aldehydes tested. Optimal reaction conditions: 1) **2a** (0.5 mmol), **3** (0.5 mmol), EtOH, reflux; 2) I_2 (0.6 mmol), K_2CO_3 (1.5 mmol), CH_2Cl_2, RT (isolated yields are given). [a] The second step was performed at reflux.

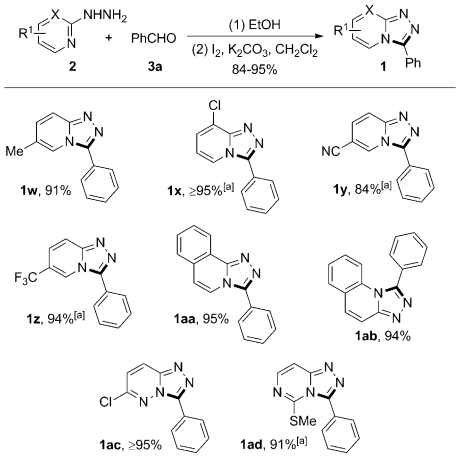
is compatible with both electron-donating and -withdrawing groups (EDGs and EWGs, respectively) at the *para*, *meta*, and *ortho* positions of the benzene ring of the aldehydes (**3b**–**m**). It is worth mentioning that good functional group tolerance allows the preparation of the product containing a phenolic hydroxy group (**1d**). Additionally, α-naphthylaldehyde, pyridine-2-aldehyde, and 2-furaldehyde were converted into the expected triazolopyridines (**1n**–**p**) in satisfactory yields as well.

In light of these encouraging results, we further explored the substrate scope by replacing the aromatic aldehydes with aliphatic ones (**3q**–**s**; Scheme 3). The desired products (**1q**–**s**) were obtained in good yields under the optimal reaction conditions. The reaction of paraformaldehyde with **2a** gave the unsubstituted 1,2,4-triazolo[4,3-*a*]pyridine (**1t**) in 60% yield. This synthetic process also worked well with α,β-unsaturated aldehydes (**3u**,**v**), which afforded products **1u** and **1v**, respectively. Furthermore, triazolopyridines containing both EDGs and EWGs on the pyridine ring (**1w**–**z**) and other 4,3-fused 1,2,4-triazoles (**1aa**–**ad**) were prepared in excellent yields by using the corresponding aryl hydrazines (Scheme 4).

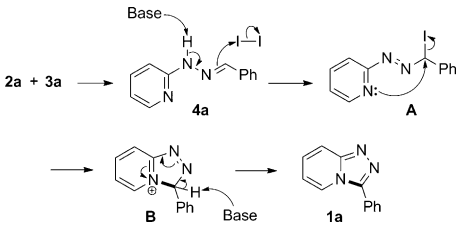
A plausible reaction mechanism for the formation of 1,2,4-triazolo[4,3-*a*]pyridine is proposed (Scheme 5). Taking the formation of **1a** as an example, the base-promoted oxidative iodination of hydrazone **4a** produces a plausible iodo species **A**.[25] Then, the pyridine nitrogen attacks the iodo-substituted



Scheme 3. Scope of aliphatic and α,β-unsaturated aldehydes tested. Optimal reaction conditions: 1) **2a** (0.5 mmol), **3** (0.5 mmol), EtOH, reflux; 2) I_2 (0.6 mmol), K_2CO_3 (1.5 mmol), CH_2Cl_2, RT (isolated yields are given). [a] The second step was performed at reflux.



Scheme 4. Scope of hydrazines tested. Optimal reaction conditions: 1) **2** (0.5 mmol), **3** (0.5 mmol), EtOH, reflux; 2) I_2 (0.6 mmol), K_2CO_3 (1.5 mmol), CH_2Cl_2, RT (isolated yields are given). [a] The second step was performed at reflux.



Scheme 5. Proposed mechanism for the formation of 1,2,4-triazolo[4,3-*a*]pyridine **1a**.

carbon in **A** to generate intermediate **B** through a S_N2'-type cyclization, which forms a new C–N bond. Finally, the subsequent deprotonation and rearomatization by a base affords the 1,2,4-triazolo[4,3-*a*]pyridine framework **1a**.

Conclusion

We have developed a practical and environmentally benign approach for the synthesis of 1,2,4-triazolo[4,3-*a*]pyridine derivatives through I_2-mediated oxidative C–N bond formation. Under the optimal sequential reaction conditions, readily available aryl hydrazines and the corresponding aldehydes were smoothly converted into the desired triazolopyridines without purification of the condensation intermediates. This operationally simple synthetic process is broadly applicable to a variety of aromatic, aliphatic, and α,β-unsaturated aldehydes; this allows the efficient and scalable preparation of a variety of 1,2,4-triazolo[4,3-*a*]pyridines and related heterocycles.

Experimental Section

General

^1H and ^{13}C NMR spectra were recorded on a 400 MHz (100 MHz for ^{13}C NMR spectroscopy) spectrometer. Chemical shift values are given in ppm with tetramethylsilane (TMS) as an internal standard. The resonance patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets. The coupling constants (*J*) are reported in Hz. Melting points were determined on a micromelting point apparatus without corrections. High-resolution mass spectra were obtained on a Q-TOF mass spectrometer equipped with an ESI source operated in positive mode. Flash column chromatography was performed over silica gel 200–300 mesh by using a mixture of EtOAc and petroleum ether (PE) (or MeOH and EtOAc) as the eluent.

General procedure for the synthesis of 1,2,4-triazolo[4,3-*a*]-pyridines 1

A mixture of the hydrazine (**2**; 0.5 mmol) and aldehyde (**3**; 0.5 mmol) in EtOH (6 mL) was heated at reflux for 30 min (TLC indicated that condensation was complete). Then, the solvent was evaporated under reduced pressure, and the resulting residue was redissolved in CH_2Cl_2 (6 mL), followed by the sequential addition of K_2CO_3 (207 mg, 1.5 mmol) and iodine (152 mg, 0.6 mmol). The reaction mixture was stirred at room temperature (for the synthesis of products **1d**, **1i**, **1s**, **1x**, and **1ab**, the reaction was performed at reflux) until TLC indicated the total consumption of intermediate **4** (0.5–4 h). Upon completion of the reaction, it was quenched with 5% $Na_2S_2O_3$ (15 mL), and then extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated. The given residue was purified by column chromatography through silica gel to afford pure product **1**.

Compound 1a: Yield: 94 mg, ≥ 95% (0.5 mmol scale); 1.15 g, ≥ 95% (6 mmol scale); off-white solid, m.p. 171–173 °C (lit.[19] m.p. 172–174 °C); R_f = 0.3 (EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 7.2 Hz, 1H), 7.85–7.81 (m, 3H), 7.61–7.55 (m, 3H), 7.31–7.27 (m, 1H), 6.88 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 146.7, 130.2, 129.3, 128.2, 127.1, 126.6, 122.6, 116.8, 114.2; HRMS (*m/z*) $[M+H]^+$ calcd for $C_{12}H_{10}N_3$, 196.0869; found: 196.0874.

Compound 1b: Yield: 102 mg, ≥95%; white solid; m.p. 162–164 °C (lit.[6a] m.p. 157 °C); R_f = 0.3 (EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.81 (d, *J* = 9.6 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.29–7.25 (m, 1H), 6.86 (td, *J* = 6.8, 0.8 Hz, 1H), 2.46 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 146.9, 140.5, 130.0, 128.2, 127.0, 123.7, 122.7, 116.8, 114.1, 21.5 ppm; HRMS: *m/z* calcd for $C_{13}H_{12}N_3$ $[M+H]^+$: 210.1026; found: 210.1031.

Compound 1c: Yield: 111 mg, ≥95%; off-white solid; m.p. 121–123 °C (lit.[19] m.p. 123–125 °C); R_f = 0.3 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 6.8 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 10.0, 7.2 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 6.85 (t, J = 6.8 Hz, 1H), 3.90 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 150.4, 146.7, 129.7, 126.9, 122.6, 118.8, 116.8, 114.8, 114.1, 55.5 ppm; HRMS: m/z calcd for $C_{13}H_{12}N_3O$ $[M+H]^+$: 226.0975; found: 226.0980.

Compound 1d: Yield: 86 mg, 81%; off-white solid; m.p. 247–249 °C (lit.[21] m.p. 249–250 °C); R_f = 0.4 (MeOH/CH_2Cl_2 5:95); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.06 (s, 1H), 8.48 (d, J = 7.2 Hz, 1H), 7.81 (d, J = 9.6 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.39 (dd, J = 9.2, 6.4 Hz, 1H), 7.01–6.97 ppm (m, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 159.1, 149.7, 146.3, 129.8, 127.7, 123.9, 117.1, 116.1, 115.6, 114.2 ppm; HRMS: m/z calcd for $C_{12}H_{10}N_3O$ $[M+H]^+$: 212.0818; found: 212.0820.

Compound 1e: Yield: 90 mg, 85%; white solid; m.p. 108–109 °C; R_f = 0.4 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.95 (m, 1H), 7.87–7.82 (m, 2H), 7.61–7.55 (m, 1H), 7.41–7.27 (m, 3H), 6.92–6.88 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8 (d, J(C,F) = 249.0 Hz), 150.7, 143.0, 132.6 (d, J(C,F) = 8.3 Hz), 132.4 (d, J(C,F) = 2.8 Hz), 127.4, 125.3 (d, J(C,F) = 3.4 Hz), 123.6 (d, J(C,F) = 7.0 Hz), 116.5, 116.3 (d, J(C,F) = 20.8 Hz), 114.7 (d, J(C,F) = 14.3 Hz), 114.1 ppm; HRMS: m/z calcd for $C_{12}H_9FN_3$ $[M+H]^+$: 214.0775; found: 214.0778.

Compound 1f: Yield: 110 mg, ≥95%; off-white solid; m.p. 123–125 °C (lit.[19] m.p. 125–127 °C); R_f = 0.4 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (dt, J = 9.6, 1.2 Hz, 1H), 7.81 (dt, J = 6.8, 1.2 Hz, 1H), 7.69 (dd, J = 7.6, 1.6 Hz, 1H), 7.61–7.46 (m, 3H), 7.34 (ddd, J = 9.2, 6.8, 1.2 Hz, 1H), 6.89 ppm (td, J = 6.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 145.0, 134.1, 133.3, 132.0, 130.2, 127.5, 127.4, 125.9, 123.5, 116.6, 113.9 ppm; HRMS: m/z calcd for $C_{12}H_9ClN_3$ $[M+H]^+$: 230.0480; found: 230.0468.

Compound 1g: Yield: 109 mg, 95%; off-white solid; m.p. 199–201 °C (lit.[19] m.p. 198–199 °C); R_f = 0.4 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, J = 7.2 Hz, 1H), 7.84 (d, J = 9.6 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.31 (dd, J = 8.8, 6.8 Hz, 1H), 6.91 ppm (t, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 145.8, 136.4, 129.7, 129.5, 127.2, 125.1, 122.4, 117.0, 114.6 ppm; HRMS: m/z calcd for $C_{12}H_8ClN_3Na$ $[M+Na]^+$: 252.0299; found: 252.0292.

Compound 1h: Yield: 123 mg, 93%; light yellow solid; m.p. 154–155 °C; R_f = 0.5 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, J = 7.2 Hz, 1H), 8.14 (s, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.83–7.73 (m, 2H), 7.35 (ddd, J = 9.2, 6.4, 0.8 Hz, 1H), 6.96 ppm (td, J = 7.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8, 145.4, 131.9 (q, J(C,F) = 32.8 Hz), 131.4 (d, J(C,F) = 11.3 Hz), 130.0, 127.6, 127.5, 126.9 (q, J(C,F) = 3.7 Hz), 125.0 (q, J(C,F) = 3.7 Hz), 122.2, 117.1, 114.9 ppm; HRMS: m/z calcd for $C_{13}H_9F_3N_3$ $[M+H]^+$: 264.0743; found: 264.0747.

Compound 1i: Yield: 108 mg, ≥95%; off-white solid; m.p. 261–262 °C (lit.[19] m.p. 258–260 °C); R_f = 0.3 (MeOH/CH_2Cl_2 2:98); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, J = 7.2 Hz, 1H), 8.04–8.02 (m, 2H), 7.91–7.89 (m, 3H), 7.37 (ddd, J = 9.2, 6.4, 0.8 Hz, 1H), 6.99 ppm (td, J = 6.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 145.0, 133.1, 131.1, 128.5, 127.7, 122.3, 118.1, 117.2, 115.2, 113.8 ppm; HRMS: m/z calcd for $C_{13}H_8N_4Na$ $[M+Na]^+$: 243.0641; found: 243.0636.

Compound 1j:[19] Yield: 108 mg, 90%; brown solid; m.p. >300 °C; R_f = 0.4 (MeOH/CH_2Cl_2 2:98); ^{1}H NMR (400 MHz, CF_3CO_2D): δ = 8.98 (d, J = 6.8 Hz, 1H), 8.84–8.81 (m, 2H), 8.50–8.38 (m, 4H), 7.91 ppm (td, J = 7.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, CF_3CO_2D): δ = 150.1, 145.5, 145.0, 139.0, 130.3, 128.1, 124.9, 119.9, 111.3 ppm; HRMS: m/z calcd for $C_{12}H_9N_4O_2$ $[M+H]^+$: 241.0720; found: 241.0722.

Compound 1k: Yield: 126 mg, ≥95%; off-white solid; m.p. 157–159 °C; R_f = 0.3 (MeOH/EtOAc 5:95); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 7.2 Hz, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.35–7.26 (m, 2H), 7.06–7.04 (m, 1H), 6.87 (t, J = 6.8 Hz, 1H), 3.98 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 150.4, 149.8, 146.7, 127.0, 122.7, 120.3, 119.1, 116.8, 114.1, 111.8, 111.3, 56.2, 56.1 ppm; HRMS: m/z calcd for $C_{14}H_{13}N_3O_2Na$ $[M+Na]^+$: 278.0900; found: 278.0895.

Compound 1l: Yield: 131 mg, ≥95%; off-white solid; m.p. 134–136 °C (lit.[26] m.p. 137 °C); R_f = 0.5 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dt, J = 9.2, 1.2 Hz, 1H), 7.79 (dt, J = 7.2, 1.2 Hz, 1H), 7.65–7.63 (m, 2H), 7.48 (dd, J = 8.4, 2.4 Hz, 1H), 7.36 (ddd, J = 9.2, 6.4, 1.2 Hz, 1H), 6.92 ppm (td, J = 6.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4, 144.1, 137.7, 134.8, 134.1, 130.2, 128.0, 127.5, 124.6, 123.3, 116.7, 114.1 ppm; HRMS: m/z calcd for $C_{12}H_7Cl_2N_3Na$ $[M+Na]^+$: 285.9909; found: 285.9909.

Compound 1m:[10] Yield: 110 mg, 92%; off-white solid; m.p. 142–144 °C; R_f = 0.5 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, J = 9.2 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.31–7.27 (m, 1H), 7.03 (s, 2H), 6.82–6.78 (m, 1H), 2.38 (s, 3H), 1.99 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 145.8, 140.6, 139.1, 128.7, 127.0, 122.4, 122.2, 116.6, 113.9, 21.3, 19.6 ppm; HRMS: m/z calcd for $C_{15}H_{15}N_3Na$ $[M+Na]^+$: 260.1158; found: 260.1159.

Compound 1n:[9] Yield: 121 mg, ≥95%; off-white solid; m.p. 120–121 °C; R_f = 0.5 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.0 Hz, 1H), 7.97–7.95 (m, 1H), 7.89–7.86 (m, 1H), 7.77–7.75 (m, 2H), 7.69–7.67 (m, 1H), 7.65–7.61 (m, 1H), 7.58–7.54 (m, 1H), 7.50–7.46 (m, 1H), 7.33–7.28 (m, 1H), 6.80–6.76 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 145.8, 133.9, 131.5, 131.1, 129.0, 128.7, 127.5, 127.3, 126.7, 125.3, 125.0, 123.5, 123.0, 116.6, 114.0 ppm; HRMS: m/z calcd for $C_{16}H_{11}N_3Na$ $[M+Na]^+$: 268.0845; found: 268.0834.

Compound 1o:[11] Yield: 65 mg, 66%; black solid; m.p. 117–119 °C; R_f = 0.5 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (d, J = 7.2 Hz, 1H), 8.63–8.62 (m, 1H), 8.45 (d, J = 8.4 Hz, 1H), 7.82–7.77 (m, 2H), 7.31–7.26 (m, 2H), 6.89 ppm (t, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 148.7, 148.3, 144.4, 137.1, 128.0, 127.1, 123.7, 122.6, 116.0, 114.3 ppm; HRMS: m/z calcd for $C_{11}H_9N_4$ $[M+H]^+$: 197.0822; found: 197.0830.

Compound 1p: Yield: 80 mg, 86%; light brown solid; m.p. 92–94 °C (lit.[26] m.p. 92 °C); R_f = 0.4 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, J = 6.8 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.67 (s, 1H), 7.32–7.26 (m, 2H), 6.94 (t, J = 6.8 Hz, 1H), 6.65 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 143.6, 142.9, 139.6, 127.4, 124.2, 116.5, 114.5, 112.1, 111.0 ppm; HRMS: m/z calcd for $C_{10}H_8N_3$ $[M+H]^+$: 186.0662; found: 186.0665.

Compound 1q:[27] Yield: 78 mg, ≥95%; light brown oil; R_f=0.2 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.92 (d, J=7.2 Hz, 1H), 7.74 (d, J=9.2 Hz, 1H), 7.26–7.22 (m, 1H), 6.86 (t, J=6.8 Hz, 1H), 3.07 (t, J=7.4 Hz, 2H), 1.95 (sext, J=7.4 Hz, 2H), 1.08 ppm (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.7, 146.7, 126.6, 121.9, 116.6, 113.5, 26.4, 20.0, 13.9 ppm; HRMS: m/z calcd for $C_9H_{12}N_3$ $[M+H]^+$: 162.1026; found: 162.1026.

Compound 1r:[10] Yield: 80 mg, ≥95%; light brown oil; R_f=0.2 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.95–7.93 (m, 1H), 7.75 (td, J=9.2, 1.2 Hz, 1H), 7.22 (ddd, J=9.2, 6.4, 1.2 Hz, 1H), 6.86–6.82 (m, 1H), 3.39 (heptet, J=6.8 Hz, 1H), 1.54 ppm (d, J=6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.3, 150.1, 126.5, 122.0, 116.9, 113.4, 25.3, 20.3 ppm; HRMS: m/z calcd for $C_9H_{11}N_3Na$ $[M+Na]^+$: 184.0845; found: 184.0845.

Compound 1s:[10] Yield: 87 mg, ≥95%; off-white solid; m.p. 90–95 °C; R_f=0.4 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.20 (d, J=7.2 Hz, 1H), 7.77 (d, J=9.2 Hz, 1H), 7.23–7.19 (m, 1H), 6.81 (t, J=6.8 Hz, 1H), 1.62 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.0, 151.0, 126.1, 123.9, 117.1, 113.1, 32.5, 27.88 ppm; HRMS: m/z calcd for $C_{10}H_{14}N_3$ $[M+H]^+$: 176.1182; found: 176.1187.

Compound 1t:[9] Yield: 36 mg, 60%; light brown oil; R_f=0.2 (MeOH/EtOAc 5:95); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.87 (s, 1H), 8.19 (d, J=6.8 Hz, 1H), 7.81 (d, J=9.6 Hz, 1H), 7.32–7.28 (m, 1H), 6.89 ppm (t, J=6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.4, 135.6, 127.8, 123.5, 116.5, 114.3 ppm; HRMS: m/z calcd for $C_6H_6N_3$ $[M+H]^+$: 120.0556; found: 120.0539.

Compound 1u: Yield: 105 mg, 95%; yellow solid; m.p. 185–187 °C (lit.[27] m.p. 185–187 °C); R_f=0.5 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.17 (d, J=6.8 Hz, 1H), 7.89 (d, J=16.4 Hz, 1H), 7.78 (d, J=9.2 Hz, 1H), 7.60–7.58 (m, 2H), 7.43–7.33 (m, 3H), 7.26 (m, 1H, overlapped with the chloroform signal), 7.16 (d, J=16.0 Hz, 1H), 6.92 ppm (t, J=6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=150.2, 145.2, 135.8, 135.4, 129.2, 129.0, 127.2, 127.0, 122.1, 116.9, 114.3, 109.4 ppm; HRMS: m/z calcd for $C_{14}H_{11}N_3Na$ $[M+Na]^+$: 244.0845; found: 244.0840.

Compound 1v: Yield: 56 mg, 70%; off-white solid; m.p. 143–145 °C; R_f=0.2 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (d, J=7.2 Hz, 1H), 7.74 (d, J=9.6 Hz, 1H), 7.25–7.21 (m, 1H), 7.06–6.97 (m, 1H), 6.86 (t, J=6.6 Hz, 1H), 6.56 (d, J=15.6 Hz, 1H), 2.05 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.8, 145.0, 134.9, 126.7, 122.1, 116.8, 113.9, 113.7, 19.2 ppm; HRMS: m/z calcd for $C_9H_9N_3Na$ $[M+Na]^+$: 182.0689; found: 182.0698.

Compound 1w: Yield: 96 mg, 91%; light yellow solid; m.p. 184–186 °C (lit.[27] m.p. 187–188 °C); R_f=0.3 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.05 (s, 1H), 7.83 (d, J=6.8 Hz, 2H), 7.74 (d, J=9.2 Hz, 1H), 7.61–7.53 (m, 3H), 7.15 (d, J=9.2 Hz, 1H), 2.34 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=150.0, 146.4, 130.6, 130.1, 129.3, 128.3, 126.9, 124.2, 119.6, 116.1, 18.3 ppm; HRMS: m/z calcd for $C_{13}H_{11}N_3Na$ $[M+Na]^+$: 232.0845; found: 232.0842.

Compound 1x: Yield: 113 mg, ≥95%; off-white solid; m.p. 157–159 °C (lit.[19] m.p. 152–154 °C); R_f=0.5 (MeOH/CH_2Cl_2 2:98); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.22 (d, J=6.8 Hz, 1H), 7.82–7.80 (m, 2H), 7.62–7.55 (m, 3H), 7.35 (d, J=6.8 Hz, 1H), 6.84 ppm (t, J=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=148.6, 148.3, 130.6, 129.4, 128.5, 126.2, 125.9, 123.0, 121.4, 114.0 ppm; HRMS: m/z calcd for $C_{12}H_8ClN_3Na$ $[M+Na]^+$: 252.0299; found: 252.0296.

Compound 1y: Yield: 92 mg, 84%; white solid; m.p. 193–195 °C; R_f=0.4 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.73 (s, 1H), 7.92 (dd, J=9.6, 0.4 Hz, 1H), 7.83–7.80 (m, 2H), 7.68–7.64 (m, 3H), 7.36 ppm (dd, J=9.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.0, 147.8, 131.2, 129.9, 129.7, 128.4, 126.4, 125.1, 118.3, 115.5, 101.2 ppm; HRMS: m/z calcd for $C_{13}H_8N_4Na$ $[M+Na]^+$: 243.0641; found: 243.0642.

Compound 1z: Yield: 124 mg, 94%; white solid; m.p. 93–95 °C; R_f=0.5 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.61 (s, 1H), 7.95 (d, J=9.6 Hz, 1H), 7.84–7.82 (m, 2H), 7.67–7.62 (m, 3H), 7.42 ppm (dd, J=9.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.9, 148.0, 130.9, 129.7, 128.4, 125.6, 123.0 (q, J(C,F)=2.2 Hz), 122.9 (q, J(C,F)=270.0 Hz), 122.2 (q, J(C,F)=6.0 Hz), 119.0 (q, J(C,F)=34.2 Hz), 118.1 ppm; HRMS: m/z calcd for $C_{13}H_8F_3N_3Na$ $[M+Na]^+$: 286.0563; found: 286.0566.

Compound 1aa: Yield: 109 mg, 89%; light yellow solid; m.p. 180–183 °C (lit.[19] mp181–183 °C); R_f=0.3 (MeOH/CH_2Cl_2 2:98); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.80–8.78 (m, 1H), 7.98 (d, J=7.6 Hz, 1H), 7.85–7.83 (m, 2H), 7.75–7.66 (m, 3H), 7.62–7.54 (m, 3H), 7.08 ppm (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.3, 148.7, 130.4, 130.2, 129.9, 129.4, 129.3, 128.7, 127.2, 126.8, 124.3, 121.8, 119.7, 115.6 ppm; HRMS: m/z calcd for $C_{16}H_{11}N_3Na$ $[M+Na]^+$: 268.0845; found: 268.0845.

Compound 1ab: Yield: 115 mg, 94%, light yellow solid; m.p. 134–136 °C (lit.[19] m.p. 135–137 °C); R_f=0.5 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.80 (dd, J=7.6, 0.8 Hz, 1H), 7.71–7.69 (m, 3H), 7.64–7.54 (m, 5H), 7.46 (t, J=7.6 Hz, 1H), 7.36–7.32 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=150.0, 149.1, 132.0, 130.6, 130.0, 129.8, 129.7, 129.4, 129.2, 129.0, 126.2, 124.7 ppm; HRMS: m/z calcd for $C_{16}H_{11}N_3Na$ $[M+Na]^+$: 268.0845; found: 268.0838.

Compound 1ac: Yield: 114 mg, ≥95%; off-white solid; m.p. 197–199 °C (lit.[19] m.p. 199–201 °C); R_f=0.4 (MeOH/CH_2Cl_2 2:98); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.47–8.44 (m, 2H), 8.16 (d, J=9.6 Hz, 1H), 7.60–7.52 (m, 3H), 7.16 ppm (d, J=9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.5, 148.2, 143.8, 130.8, 129.0, 127.8, 126.8, 125.6, 122.0 ppm; HRMS: m/z calcd for $C_{11}H_7ClN_4Na$ $[M+Na]^+$: 253.0251; found: 253.0252.

Compound 1ad: Yield: 110 mg, 91%; off-white solid; m.p. 169–171 °C (lit.[19] m.p. 169–171 °C); R_f=0.4 (MeOH/CH_2Cl_2 2:98); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.82 (d, J=6.8 Hz, 1H), 7.63–7.60 (m, 3H), 7.53–7.49 (m, 2H), 7.44 (d, J=6.4 Hz, 1H), 2.53 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.5, 150.1, 146.3, 140.4, 131.8, 131.0, 127.9, 127.0, 106.5, 15.2 ppm; HRMS: m/z calcd for $C_{12}H_{10}N_4SNa$ $[M+Na]^+$: 265.0518; found: 265.0506.

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