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Palladium-catalyzed oxidation of amine in air: an efficient approach to *H*-pyrazolo[5,1-*a*]-isoquinolines

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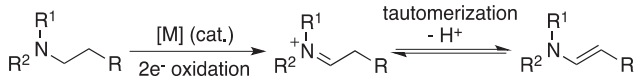
ABSTRACT

An efficient approach to *H*-pyrazolo[5,1-*a*]isoquinolines through a reaction of *N*′-(2-alkynylbenzylidene) hydrazide with amine in the presence of a cooperative catalysis under mild conditions is reported. The palladium-catalyzed oxidation of amine in air leading to the formation of enamine is the key step during the transformation.

1. Introduction

Continuous interests have been appeared for the transition metal catalyzed formation of iminium ions from tertiary amines. This process usually proceeds through a cross-dehydrogenative coupling involving selective C–H activation of adjacent α-protons of nitrogen atom.[1–3] A tautomerization would happen from iminium ion toward enamine via two-electron oxidation if the amine possesses more than two carbons on alkyl chains (Scheme 1). Compared with the conventional methods for the synthesis of enamines,[4] this approach is much more attractive, which would generate the enamine in a practical way.Currently, the rapid generation of natural product-like small molecules is in high demand for the studies of chemical genetics.[5] As a privileged scaffold, *H*-pyrazolo[5,1-*a*]isoquinoline derivatives display promising biological activities toward the inhibition against PTP1B (protein tyrosine phosphatase 1 B), CDC25, and cervical carcinoma.[6] With an expectation to get more active compounds, we need to develop a facile route for the effective construction of such kind of framework and its related library. Recently, silver(I)-catalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazide has been applied broadly for the construction of *N*-heterocycles.[7] The role of silver(I) catalyst was demonstrated to promote the 6-*endo* cyclization of *N*′-(2-alkynylbenzylidene)hydrazide, which would produce the key intermediate isoquinolinium-2-yl amide. Encouraged by these results and the advancement of the transition metal catalyzed oxidation reaction of amines as mentioned above, we envisioned that *H*-pyrazolo[5,1-*a*]isoquinoline derivatives could be produced via a reaction of *N*′-(2-alkynylbenzylidene)hydrazide with amine under a cooperative catalysis. The proposed synthetic route is present in Scheme 2.



Scheme 1. A tautomerization from iminium ion toward enamine via two-electron oxidation.

The oxidation reaction of amine could be carried out in the presence of a catalytic system combining metal (such as a palladium catalyst) and oxygen.[3] We envisioned that the Ag(I)/Pd(II) cooperative catalysis[8,9] would be essential for the successful transformation. We reasoned that *N*′-(2-alkynylbenzylidene)hydrazide **1** would be transferred into isoquinolinium-2-yl amide **A** via a silver-catalyzed cyclization. In the meantime, the enamine intermediate **B** could be formed through the tautomerization of iminium generated by the oxidation of amine **2** in the presence of palladium(II) and dioxygen. Subsequently, the intermolecular nucleophilic attack would occur to afford the intermediate **C**, which

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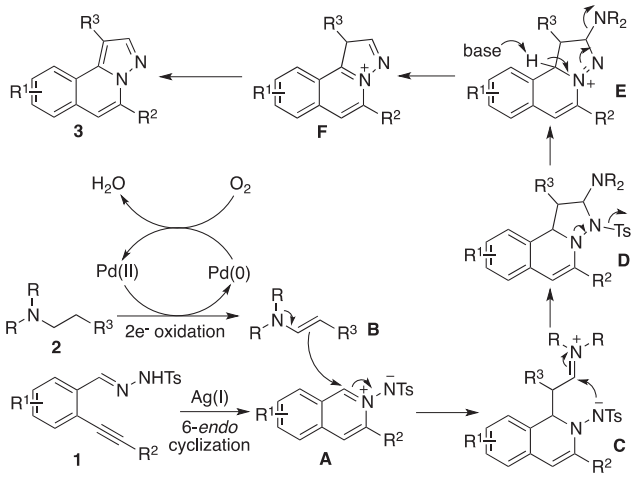


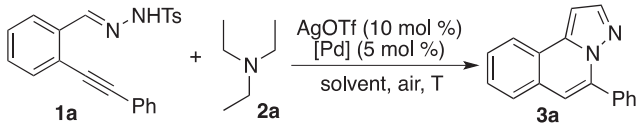
Scheme 2. A proposed synthetic route to *H*-pyrazolo[5,1-*a*]-isoquinolines.

would then release the tosyl group and amino group to furnish intermediate **F**. Followed by aromatization would produce the *H*-pyrazolo[5,1-*a*]-isoquinoline **3**.

2. Results/discussion

To verify the feasibility of the hypothesis presented in Scheme 2, we started to explore the possibility of this protocol. *N*′-(2-Alkynylbenzylidene)hydrazide **1a** and triethylamine **2a** were chosen as the substrates to commence our studies. Initially, the reaction was co-catalyzed by AgOTf (10 mol %) and $Pd(OAc)_2$ (5 mol %) in air. As expected, a moderate yield of product **3a** was obtained (55%, Table 1, entry 1). Therefore, a series of control experiments were performed to optimize the reaction conditions (Table 1). Screening of solvents revealed that DMF was the best choice, affording the corresponding product **3a** in 70% yield (Table 1, entries 2–7). Only a trace amount of product was generated without the addition of palladium catalyst (Table 1, entry 8). From this result, it seemed that Pd(II) could promote the reaction well. The yield was increased to 80% when $PdBr_2$ was used as the catalyst (Table 1, entry 10). The yield was lower when the reaction was performed at room temperature (Table 1, entry 11). No improvement was observed when the reaction occurred at 80 °C (Table 1, entry 12). The efficiency was affected when 2 mol % of $PdBr_2$ was employed (Table 1, entry 13). No better result was obtained when 10 mol % of $PdBr_2$ was used (Table 1, entry 14).

Table 1
Initial studies for the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** with triethylamine **2a**

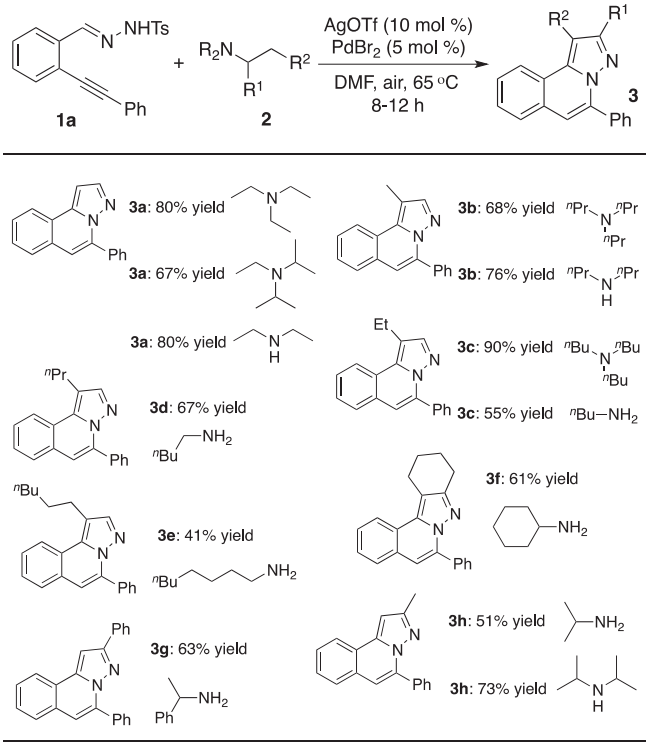


Entry	[Pd] (cat.)	Solvent	*T* (°C)	Yield[a] (%)
1	$Pd(OAc)_2$	DCE	65	55
2	$Pd(OAc)_2$	MeCN	65	49
3	$Pd(OAc)_2$	DMF	65	70
4	$Pd(OAc)_2$	DMA	65	30
5	$Pd(OAc)_2$	DMSO	65	25
6	$Pd(OAc)_2$	1,4-Dioxane	65	27
7	$Pd(OAc)_2$	Toluene	65	24
8	—	DMF	65	Trace
9	$PdCl_2$	DMF	65	45
10	$PdBr_2$	DMF	65	80
11	$PdBr_2$	DMF	rt	36
12	$PdBr_2$	DMF	80	62
13[b]	$PdBr_2$	DMF	65	45
14[c]	$PdBr_2$	DMF	65	77

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1a**.
[b] In the presence of 2 mol % of $PdBr_2$.
[c] In the presence of 10 mol % of $PdBr_2$.

Under the optimized reaction conditions as highlighted in Table 1, we next set out to explore the substrate scope of this reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** with various amine **2**. The results are summarized in Table 2. All reactions proceeded smoothly to afford the expected products **3** in moderate to good yields. Interestingly, not only tertiary amines but also primary and secondary amines could be tolerated under the standard conditions. Additionally, it seemed that no difference was observed for the reaction regardless of the amine containing one or two α-H atoms.

Table 2
Synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines through a reaction of *N*′-(2-alkynylbenzylidene)hydrazide with amine in the presence of a cooperative catalysis[a]



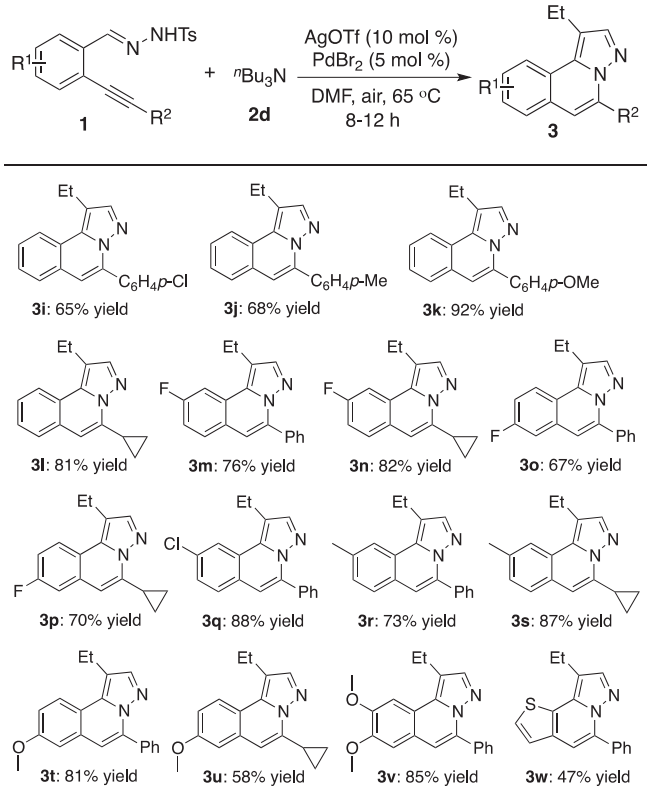
[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1**.

Based on the above results, we then shifted our focus to *N*′-(2-alkynylbenzylidene)hydrazides, with an expectation for the generation of diverse *H*-pyrazolo[5,1-*a*]isoquinolines **3**. The reaction of *N*′-(2-alkynylbenzylidene)hydrazides **1** with tributylamine **2d** was explored, and the desired products **3i**–**v** was produced in good yields. It was found that all *N*′-(2-alkynylbenzylidene)hydrazides **1** participated successfully in the transformation, including the substrates substituted by electron-donating and electron-withdrawing groups. Different functional groups including fluoro, chloro, methyl, and methoxy groups were compatible under the standard conditions. Additionally, the reaction worked well when 4-methyl-*N*′-((3-(phenylethynyl)thiophen-2-yl)methylene)benzenesulfonohydrazide **1p** was employed, leading to the corresponding product **3w** in 47% yield (Table 3).

3. Conclusions

In conclusion, we have described an efficient approach to *H*-pyrazolo[5,1-*a*]isoquinolines through a reaction of *N*′-(2-alkynylbenzylidene)hydrazide with amine in the presence of

Table 3
Synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines through a reaction of *N*′-(2-alkynylbenzylidene)hydrazide with amine in the presence of a cooperative catalysis[a]



[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1**.

a cooperative catalysis under mild conditions. The silver triflate-palladium(II) bromide cooperative catalysis is essential for the successful transformation. The palladium-catalyzed oxidation of amine in air leading to the formation of enamine is the key step during the reaction process. The reaction scope has been demonstrated. Such excellent applicability and mild reaction conditions would enable the protocol to be attractive for further library construction.

4. Experimental section

4.1. General experimental procedure for the reaction of *N*′-(2-alkynylbenzylidene)benzenesulfonohydrazide 1 and amine 2

AgOTf (0.03 mmol, 7.7 mg) was added to a solution of *N*′-(2-alkynylbenzylidene)hydrazide **1** (0.3 mmol) in DMF (1.0 mL), and the solution was stirred at 65 °C in air for 1 h. Subsequently $PdBr_2$ (0.015 mmol, 4.0 mg) and amine **2** (3.0 mmol) were added and the mixture was stirred at 65 °C in air. After completion of the reaction as indicated by TLC, the reaction was quenched by the addition of saturated aqueous NH_4Cl (5.0 mL), and the mixture was extracted with EtOAc (3×4.0 mL). The combined organic layer was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluted with PE/EA=50:1) to provide the product **3**.

*4.1.1. 5-Phenylpyrazolo[5,1-a]isoquinoline (**3a**).*[3k] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 7.07 (d, J=2.0 Hz, 1H), 7.49–7.55 (m, 5H), 7.70–7.73 (m, 1H), 7.87–7.89 (m, 2H), 8.00 (d, J=1.4 Hz, 1H), 8.09–8.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.8, 112.5, 123.5, 124.0, 127.1, 127.3, 127.9, 128.3, 129.1, 129.2, 129.4, 133.8, 138.5, 139.3, 140.8.

*4.1.2. 1-Methyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3b**).*[3k] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H), 6.94 (s, 1H), 7.44–7.56 (m, 5H), 7.69 (d, J=7.6 Hz, 1H), 7.80 (s, 1H), 7.83–7.85 (m, 2H), 8.26 (d, J=7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 110.0, 112.3, 123.1, 125.6, 127.1, 128.3, 129.1, 129.4, 134.0, 135.1, 138.6, 142.0.

*4.1.3. 1-Ethyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3c**).*[3k] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J=8.0 Hz, 3H), 3.09 (q, J=8.0 Hz, 2H), 6.94 (s, 1H), 7.46–7.56 (m, 5H), 7.69 (d, J=8.0 Hz, 1H), 7.83–7.85 (m, 3H), 8.23 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.4, 112.3, 117.0, 123.1, 125.4, 127.0, 127.1, 127.2, 128.3, 129.1, 129.3, 129.4, 134.0, 134.4, 138.5, 140.2.

*4.1.4. 5-Phenyl-1-propylpyrazolo[5,1-a]isoquinoline (**3d**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, J=7.2 Hz, 3H), 1.82–1.91 (m, 2H), 3.05 (t, J=7.6 Hz, 2H), 6.97 (s, 1H), 7.46–7.59 (m, 5H), 7.72 (d, J=7.6 Hz, 1H), 7.83–7.85 (m, 3H), 8.24 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 28.2, 112.3, 115.5, 123.2, 125.4, 127.1, 127.1, 127.2, 128.3, 129.1, 129.4, 129.5, 134.1, 134.6, 138.6, 141.1; HRMS (ESI) calcd for $C_{20}H_{18}N_2$: 287.1543 $(M+H)^+$, found: 287.1546.

*4.1.5. 1-Hexyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3e**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J=6.8 Hz, 3H), 1.32–1.40 (m, 4H), 1.48–1.53 (m, 2H), 1.79–1.87 (m, 2H), 3.07 (t, J=7.6 Hz, 2H), 6.98 (s, 1H), 7.48–7.61 (m, 5H), 7.74 (d, J=7.6 Hz, 1H), 7.83–7.86 (m, 3H), 8.26 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 26.2, 29.3, 29.5, 31.7, 112.4, 115.7, 123.2, 125.5, 127.1, 127.1, 127.2, 128.3, 129.2, 129.4, 129.6, 134.1, 134.6, 138.7, 141.1; HRMS (ESI) calcd for $C_{23}H_{24}N_2$: 329.2012 $(M+H)^+$, found: 329.2010.

*4.1.6. 6-Phenyl-9,10,11,12-tetrahydroindazolo[3,2-a]isoquinoline (**3f**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92–1.97 (m, 4H), 2.91 (t, J=6.0 Hz, 2H), 3.13 (t, J=6.0 Hz, 2H), 6.89 (s, 1H), 7.44–7.54 (m, 5H), 7.69 (d, J=8.0 Hz, 1H), 7.88–7.90 (m, 2H), 8.16 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 23.0, 23.5, 24.2, 109.8, 111.4, 123.2, 125.3, 126.7, 126.9, 128.3, 129.1, 129.4, 129.5, 134.2, 134.8, 138.4, 151.0; HRMS (ESI) calcd for $C_{21}H_{18}N_2$: 299.1543 $(M+H)^+$, found: 299.1539.

*4.1.7. 2,5-Diphenylpyrazolo[5,1-a]isoquinoline (**3g**).* Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 7.33 (t, J=7.2 Hz, 1H), 7.37 (s, 1H), 7.33 (t, J=7.6 Hz, 2H), 7.47–7.54 (m, 5H), 7.71 (d, J=7.2 Hz, 1H), 7.98–8.03 (m, 4H), 8.12 (d, J=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.8, 112.5, 123.5, 124.0, 126.4, 127.2, 127.3, 128.0, 128.2, 128.6, 129.2, 129.3, 129.7, 133.4, 133.8, 138.4, 140.8, 152.3; HRMS (ESI) calcd for $C_{23}H_{16}N_2$: 321.1386 $(M+H)^+$, found: 321.1388.

*4.1.8. 2-Methyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3h**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H), 6.88 (s, 1H), 6.96 (s, 1H), 7.46–7.54 (m, 5H), 7.70–7.72 (m, 1H), 7.92–7.94 (m, 2H), 8.05–8.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 97.6, 111.6, 123.4, 127.0, 127.1, 127.7, 128.3, 129.2, 129.5, 134.0, 138.3, 140.2, 150.5; HRMS (ESI) calcd for $C_{18}H_{14}N_2$: 259.1230 $(M+H)^+$, found: 259.1223.

*4.1.9. 5-(4-Chlorophenyl)-1-ethylpyrazolo[5,1-a]isoquinoline (**3i**).*[3k] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, J=7.5 Hz, 3H), 3.10 (q, J=7.5 Hz, 2H), 6.94 (s, 1H), 7.47–7.53 (m, 3H), 7. 56–7.60 (m, 1H), 7.71 (d, J=7.7 Hz, 1H), 7.78–7.80 (m, 2H), 7.84 (s, 1H), 8.24 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.4, 112.5, 117.2, 123.2, 125.5, 127.2, 127.2, 127.4, 128.6, 129.3, 130.7, 132.4, 134.5, 135.1, 137.4, 140.3.

*4.1.10. 1-Ethyl-5-p-tolylpyrazolo[5,1-a]isoquinoline (**3j**).*[3k] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, J=7.5 Hz, 3H), 2.43 (s, 3H), 3.10 (q, J=7.5 Hz, 2H), 6.94 (s, 1H), 7.32 (d, J=8.0 Hz, 2H), 7.48–7.57 (m, 2H), 7.70–7.74 (m, 3H), 7.84 (s, 1H), 8.24 (d, J=8.0 Hz, 1H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 14.1, 19.5, 21.4, 112.0, 117.0, 123.2, 125.4, 127.0, 127.0, 127.1, 129.0, 129.3, 129.6, 131.2, 134.4, 138.7, 139.1, 140.2.

*4.1.11. 1-Ethyl-5-(4-methoxyphenyl)pyrazolo[5,1-a]isoquinoline (**3k**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, J=7.5 Hz, 3H), 3.10 (q, J=7.5 Hz, 2H), 3.87 (s, 3H), 6.94 (s, 1H), 7.04 (d, J=8.7 Hz, 2H), 7.48–7.57 (m, 2H), 7.71 (d, J=7.6 Hz, 1H), 7.79–7.81 (m, 2H), 7.84 (s, 1H), 8.24 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.5, 55.4, 111.8, 113.8, 117.1, 123.2, 125.3, 126.5, 126.9, 127.0, 129.6, 130.8, 134.5, 138.4, 140.2, 160.2; HRMS (ESI) calcd for $C_{20}H_{18}N_2O$: 303.1492 $(M+H)^+$, found: 303.1510.

*4.1.12. 5-Cyclopropyl-1-ethylpyrazolo[5,1-a]isoquinoline (**3l**).*[3k] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87–0.91 (m, 2H), 1.15–1.20 (m, 2H), 1.44 (t, J=7.5 Hz, 3H), 2.62–2.69 (m, 1H), 3.08 (q, J=7.5 Hz, 2H), 6.60 (s, 1H), 7.43–7.51 (m, 2H), 7.61 (d, J=7.6 Hz, 1H), 7.91 (s, 1H), 8.19 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8, 11.4, 14.1, 19.4, 106.7, 117.1, 123.1, 124.7, 126.4, 126.5, 126.8, 129.4, 134.0, 140.0, 140.8.

*4.1.13. 1-Ethyl-9-fluoro-5-phenylpyrazolo[5,1-a]isoquinoline (**3m**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, J=7.5 Hz, 3H), 3.09 (q, J=7.5 Hz, 2H), 6.96 (s, 1H), 7.24–7.28 (m, 1H), 7.47–7.54 (m, 3H), 7.71 (dd, J_1=5.8 Hz, J_2=8.6 Hz, 1H), 7.82–7.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.3, 108.8 (d, $^2J_{CF}$=23.7 Hz), 111.7, 115.6 (d, $^2J_{CF}$=23.4 Hz), 117.6, 126.0, 126.5, 128.4, 129.2, 129.2, 129.4, 133.9, 138.0, 140.3, 161.6 (d, $^1J_{CF}$=244.7 Hz); HRMS (ESI) calcd for $C_{19}H_{15}FN_2$: 291.1292 $(M+H)^+$, found: 291.1300.

*4.1.14. 5-Cyclopropyl-1-ethyl-9-fluoropyrazolo[5,1-a]isoquinoline (**3n**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.89 (m, 2H), 1.15–1.20 (m, 2H), 1.44 (t, J=7.5 Hz, 3H), 2.59–2.66 (m, 1H), 3.03 (q, J=7.5 Hz, 2H), 6.56 (s, 1H), 7.16–7.21 (m, 1H), 7.57 (dd, J_1=5.7 Hz, J_2=8.7 Hz, 1H), 7.13 (dd, J_1=2.4 Hz, J_2=10.3 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.7, 11.3, 14.0, 19.2, 106.1, 108.5 (d, $^2J_{CF}$=23.6 Hz), 115.3 (d, $^2J_{CF}$=23.3 Hz), 117.5, 125.6 (d, $^3J_{CF}$=9.3 Hz), 125.9, 128.4 (d, $^3J_{CF}$=9.8 Hz), 133.3 (d, $^4J_{CF}$=3.7 Hz), 140.0, 140.1, 161.1 (d, $^1J_{CF}$=243.9 Hz); HRMS (ESI) calcd for $C_{16}H_{15}FN_2$: 255.1292 $(M+H)^+$, found: 255.1308.

*4.1.15. 1-Ethyl-8-fluoro-5-phenylpyrazolo[5,1-a]isoquinoline (**3o**).*[3k] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J=7.5 Hz, 3H), 3.06 (q, J=7.5 Hz, 2H), 6.89 (s, 1H), 7.26–7.31 (m, 1H), 7.36 (dd, J_1=2.5 Hz, J_2=9.3 Hz, 1H), 7.46–7.54 (m, 3H), 7.82–7.85 (m, 3H), 7.36 (dd, J_1=5.3 Hz, J_2=8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.4, 111.5, 112.0 (d, $^2J_{CF}$=21.5 Hz), 115.5 (d, $^2J_{CF}$=23.3 Hz), 116.6, 122.0, 125.3 (d, $^3J_{CF}$=8.7 Hz), 128.4, 129.3, 129.4, 131.3 (d, $^3J_{CF}$=9.0 Hz), 133.7, 134.2, 139.7, 140.6, 161.4 (d, $^1J_{CF}$=245.9 Hz).

*4.1.16. 5-Cyclopropyl-1-ethyl-8-fluoropyrazolo[5,1-a]isoquinoline (**3p**).*[3k] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.92 (m, 2H), 1.17–1.22 (m, 2H), 1.44 (t, J=7.5 Hz, 3H), 2.64–2.71 (m, 1H), 3.05 (q, J=7.5 Hz, 2H), 6.53 (s, 1H), 7.21–7.29 (m, 2H), 7.91 (s, 1H), 8.14–8.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.0, 11.4, 14.0, 19.4, 105.8, 111.4 (d, $^2J_{CF}$=21.5 Hz), 114.8 (d, $^2J_{CF}$=23.2 Hz), 116.6, 121.3, 125.2 (d, $^3J_{CF}$=8.7 Hz), 131.3 (d, $^3J_{CF}$=8.8 Hz), 133.8, 140.3, 142.1, 161.3 (d, $^1J_{CF}$=245.6 Hz).

*4.1.17. 9-Chloro-1-ethyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3q**).*[3k] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (t, J=7.2 Hz, 3H), 3.06 (q, J=7.2 Hz, 2H), 6.92 (s, 1H), 7.44–7.52 (m, 4H), 7.64 (d, J=8.3 Hz, 1H), 7.82–7.87 (m, 3H), 8.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.3, 111.6, 117.6, 122.6, 126.4, 126.9, 127.5, 127.8, 128.4, 128.5, 129.3, 132.8, 133.4, 133.7, 138.9, 140.4.

*4.1.18. 1-Ethyl-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3r**).*[3k] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (t, J=7.4 Hz, 3H), 2.58 (s, 3H), 3.14 (q, J=7.4 Hz, 2H), 6.95 (s, 1H), 7.35 (d, J=8.0 Hz, 1H), 7.47–7.55 (m, 3H), 7.63 (d, J=8.0 Hz, 1H), 7.86–7.87 (m, 3H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.5, 22.0, 112.3, 116.9, 123.0, 125.5, 127.0, 127.2, 128.3, 128.6, 129.0, 129.4, 134.2, 134.3, 137.0, 137.8, 140.0.

*4.1.19. 5-Cyclopropyl-1-ethyl-9-methylpyrazolo[5,1-a]isoquinoline (**3s**).*[3k] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–0.90 (m, 2H), 1.14–1.19 (m, 2H), 1.45 (t, J=7.5 Hz, 3H), 2.53 (s, 3H), 2.60–2.66 (m, 1H), 3.09 (q, J=7.5 Hz, 2H), 6.58 (s, 1H), 7.29 (d, J=8.0 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.90 (s, 1H), 7.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.7, 11.4, 14.1, 19.5, 21.9, 106.7, 116.9, 122.9, 124.8, 126.4, 127.2, 128.4, 133.9, 136.2, 139.8.

*4.1.20. 1-Ethyl-8-methoxy-5-phenylpyrazolo[5,1-a]isoquinoline (**3t**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J=7.4 Hz, 3H), 3.07 (q, J=7.4 Hz, 2H), 3.92 (s, 3H), 6.91 (s, 1H), 7.13 (d, J=2.0 Hz, 1H), 7.19 (dd, J_1=2.0 Hz, J_2=8.8 Hz, 1H), 7.46–7.54 (m, 3H), 7.83–7.86 (m, 3H), 8.16 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.4, 55.4, 108.5, 112.1, 115.7, 116.6, 119.6, 124.8, 128.3, 129.2, 129.4, 131.2, 134.2, 134.7, 139.0, 140.4, 158.6; HRMS (ESI) calcd for $C_{20}H_{18}N_2O$: 309.1368 $(M+Na)^+$, found: 309.1371.

*4.1.21. 5-Cyclopropyl-1-ethyl-8-methoxypyrazolo[5,1-a]isoquinoline (**3u**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.92 (m, 2H), 1.16–1.21 (m, 2H), 1.43 (t, J=7.5 Hz, 3H), 2.63–2.70 (m, 1H), 3.06 (q, J=7.5 Hz, 2H), 3.91 (s, 3H), 6.56 (s, 1H), 7.06 (d, J=2.4 Hz, 1H), 7.13 (dd, J_1=2.5 Hz, J_2=8.9 Hz, 1H), 7.88 (s, 1H), 8.13 (d, J=8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9, 11.4, 14.2, 19.3, 55.3, 106.3, 107.9, 115.7, 115.9, 118.9, 124.7, 131.2, 134.3, 140.2, 141.3, 158.4; HRMS (ESI) calcd for $C_{17}H_{18}N_2O$: 267.1492 $(M+H)^+$, found: 267.1509.

*4.1.22. 1-Ethyl-8,9-dimethoxy-5-phenylpyrazolo[5,1-a]isoquinoline (**3v**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (t, J=7.5 Hz, 3H), 3.10 (q, J=7.5 Hz, 2H), 4.00 (s, 3H), 4.05 (s, 3H), 6.89 (s, 1H), 7.11 (s, 1H), 7.44–7.52 (m, 3H), 7.68 (s, 1H), 7.82–7.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 19.5, 55.9, 56.0, 104.4, 107.7, 111.9, 115.0, 119.7, 124.2, 128.3, 129.0, 129.3, 134.3, 137.1, 140.2, 149.4; HRMS (ESI) calcd for $C_{21}H_{20}N_2O_2$: 333.1598 $(M+H)^+$, found: 333.1592.

*4.1.23. 9-Ethyl-5-phenylpyrazolo[1,5-a]thieno[2,3-c]pyridine (**3w**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J=7.5 Hz, 3H), 3.09 (q, J=7.5 Hz, 2H), 7.11 (s, 1H), 7.37 (d, J=5.6 Hz, 1H), 7.46–7.54 (m, 4H), 7.84–7.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 17.9, 108.1, 113.6, 124.1, 126.3, 127.3, 128.4, 129.1, 129.3, 134.0, 134.2, 134.4, 137.8, 140.2; HRMS (ESI) calcd for $C_{17}H_{14}N_2S$: 279.0950 $(M+H)^+$, found: 279.0969.

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Supplementary data

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