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Synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines via a silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with alcohol

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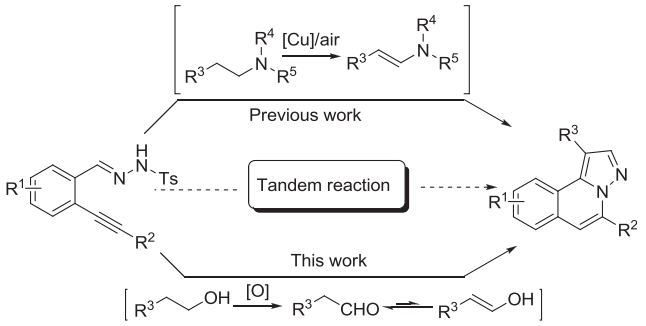
ABSTRACT

A silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with alcohol is reported, which generates *H*-pyrazolo[5,1-*a*]isoquinoline derivatives in good yields under mild conditions.

1. Introduction

It is well-known that isoquinoline skeleton is found in many bioactive natural products and pharmaceuticals.[1,2] Among groups of isoquinolines, *H*-pyrazolo[5,1-*a*]isoquinolines have been recognized as the subjects of in-depth investigation in organic synthesis due to their promising biological activities, such as the inhibitor of PTP1B and CDC25B, TC-PTP.[3] So far, continuous efforts are dedicated for the constructions of these polycyclic compounds.[4] For instance, Wu and co-workers reported the synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines via copper(II)-catalyzed oxidative reactions of tertiary amines with *N*′-(2-alkynylbenzylidene) hydrazides in air.[4] In the process, copper-catalyzed oxidation of tertiary amines to enamines is shown to be an essential step (Scheme 1).

On the other hand, alcohol is an important synthetic intermediate, and many related reactions are extensively studied, such as nucleophilic addition, substitution, and oxidation.[5] Among these well-established reactions, selective oxidation of alcohols to aldehydes is a type of classical transformation with long history. To the best of our knowledge, this type of reaction could perform under mild condition. Inspired by these results and considering the advantages of tandem reactions,[6,7] we hence anticipated that *H*-pyrazolo[5,1-*a*]isoquinolines could be delivered from a one-pot reaction of *N*′-(2-alkynylbenzylidene)hydrazide with alcohol under oxidative conditions (Scheme 1). In the reactions, we hypothesized that the reactions might undergo a silver triflate-catalyzed 6-*endo*-cyclization of *N*′-(2-alkynylbenzylidene)hydrazide to generate a 1,3-dipoles species. In the meantime, the in situ selective oxidation of alcohol would furnish aldehyde, which would go through [3+2] cycloaddition with 1,3-dipole species, and subsequent aromatization to afford *H*-pyrazolo[5,1-*a*]isoquinolines.



Scheme 1. Projected route for the synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines via a reaction of *N*′-(2-alkynylbenzylidene)hydrazide with alcohol.

2. Results and discussion

The starting *N*′-(2-alkynylbenzylidene)hydrazides were prepared via the Sonogashira coupling of 2-bromobenzaldehydes

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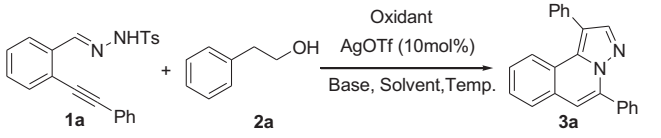
with terminal alkynes, followed by the condensation with sulfonyl hydrazide according to the literature procedure.[8] To test the feasibility of the projected transformation, the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** and 2-phenylethanol **2a** was initially carried out in the presence of silver triflate and an oxidant, and the experimental results are summarized in Table 1. As shown in Table 1, the reactions failed when the reaction occurred by $PhI(OAc)_2$/air, PCC, DMP in DCE using K_3PO_4 as a base (Table 1, entries 1–3). To our delight, by altering the solvent to dichloromethane (DCM), the desired *H*-pyrazolo[5,1-*a*]isoquinolines **3a** was obtained in 47% yield in the presence of DMP as an oxidant (Table 1, entry 4). It is well-known that DCM is the classic solvent in the DMP-mediated oxidative process.[9] As a result, an array of co-solvents was investigated (Table 1, entries 5–10). From the results, it was found that the co-solvent of dichloromethane and dichloroethane (1:1 v/v) was the best choice, leading to the final product in 85% yield. Subsequently, we examined the effect of bases in the reaction (Table 1, entries 11–17), however, no better result was detected. Changing the temperature afforded inferior yields.

Table 1
Initial studies for the silver triflate-catalyzed reaction of *N*′-(2-alkynylbenzylidene) hydrazide **1a** with 2-phenylethanol **2a**[a]

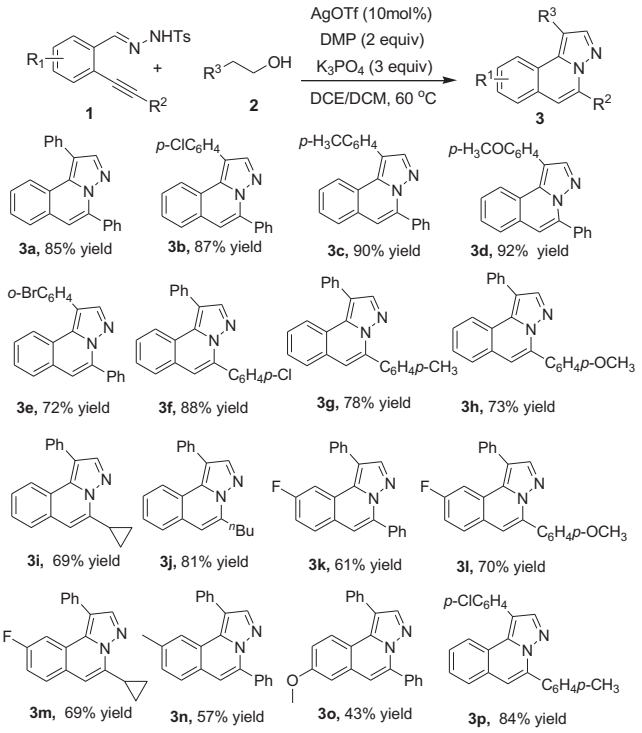


Entry	Oxidant	Base	Solvent[b]	*T* (°C)	Yield (%)[c]
1	$PhI(OAc)_2$/air	K_3PO_4	DCE	60	NR
2	PCC	K_3PO_4	DCE	60	Complex
3	DMP	K_3PO_4	DCE	60	NR
4	DMP	K_3PO_4	DCM	Reflux	47
5	DMP	K_3PO_4	DCE/DCM	60	85
6	DMP	K_3PO_4	THF/DCM	60	55
7	DMP	K_3PO_4	Toluene/DCM	60	44
8	DMP	K_3PO_4	CH_3CN/DCM	60	46
9	DMP	K_3PO_4	DMF/DCM	60	51
10	DMP	K_3PO_4	EtOH/DCM	60	61
11	DMP	Et_3N	DCE/DCM	60	21
12	DMP	DABCO	DCE/DCM	60	11
13	DMP	$CsCO_3$	DCE/DCM	60	45
14	DMP	Na_2CO_3	DCE/DCM	60	37
15	DMP	DBU	DCE/DCM	60	NR
16	DMP	K_3PO_4	DCE/DCM	25	9
17	DMP	K_3PO_4	DCE/DCM	85	40

[a] Reaction was performed with **1a** (0.3 mmol), **2a** (0.6 mmol), base (0.9 mmol), oxidant (0.6 mmol) in solvent (4 mL).
[b] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide.
[c] DMP: Dess–Martin reagent.

We then started to investigate the tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with aromatic alcohol **2**, catalyzed by silver triflate under the optimized reaction conditions (DMP as the oxidant, K_3PO_4, 1,2-dichloroethane/1,2-dichloroethane, 60 °C). The results are shown in Table 2. From Table 2, it was noticed that a variety of *H*-pyrazolo[5,1-*a*]isoquinolines were furnished in good to excellent yields. For example, reaction of *N*′-(2-alkynyl benzylidene)hydrazide with 2-(4-methoxyphenyl)ethanol gave rise to the desired product **3d** in 92% yield under the standard conditions. The product **3e** was obtained in 72% yield when 2-(2-bromophenyl) ethanol was utilized as a reaction partner. The reactions were compatible with the substituent R^2 including butyl and cyclopropyl groups. Meanwhile, the reaction also worked well when R^2 was replaced by not only electron-rich but also electron-deficient aryl groups. However, the yield drastically decreased when *N*′-(2-

Table 2
Synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines through a reaction of *N*′-(2-alkynylbenzylidene)hydrazide with alcohol[a]

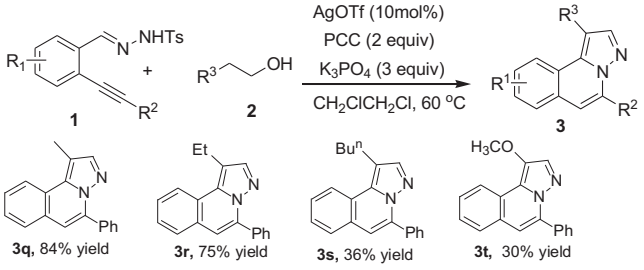


[a] Reaction was performed with **1** (0.3 mmol), **2** (0.6 mmol) in DCE/DCM (4 mL, v/v=1:1). Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1**.

alkynylbenzylidene)hydrazides with the substituted groups (electron-withdrawing groups or electron-donating groups) attached on the aromatic ring were employed. As shown in the Table, the desired product **3o** was achieved in 43% when the reaction was performed between *N*′-(4-methoxy-2-(phenylethynyl)benzylidene)-4-methylbenzenesulfonohydrazide and 2-phenylethanol.

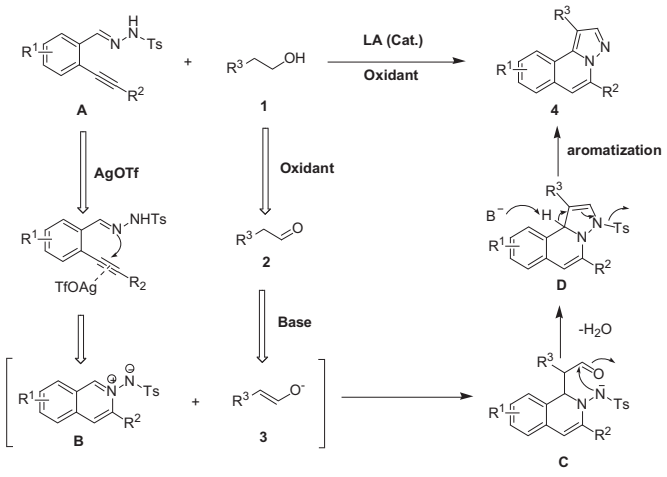
In order to further expand the scope of the substrates, we examined the reaction of *N*′-(2-alkynylbenzylidene)hydrazides with aliphatic alcohols. To our surprise, the corresponding products were not obtained in the present of DMP. After screening the oxidants, it was found that the reaction of *N*′-(2-alkynylbenzylidene) hydrazide with propanol could proceed smoothly in 84% yield when PCC was used as the oxidant. The experimental results were presented in Table 3. Inferior results were obtained when *N*′-(2-alkynylbenzylidene)hydrazides **1** reacted with various aliphatic alcohols, such as butanol, 2-methoxylethanol.

Table 3
Synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines through a reaction of *N*′-(2-alkynylbenzylidene)hydrazides with aliphatic alcohols[a]



[a] Reaction was performed with **1** (0.3 mmol), **2** (0.6 mmol) in DCE (2 mL). Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1**.

Based on the above results, we proposed a plausible mechanism for this one-pot tandem reaction (Scheme 2). *N*′-(2-Alkynylbenzylidene)hydrazide **A** through a 6-*endo*-cyclization reaction would occur to generate the isoquinolinium-2-yl amide **B** in the presence of suitable Lewis acid. In this step, the formation of a *p*-complex via coordination of the alkynyl moiety of **A** to the Lewis acid would be involved, thus activating the triple bond for further cyclization. Meanwhile, the in situ formed enolate **3** (derived from aldehyde **2**, which was produced by the oxidation of alcohols **1** in the presence of base) would attack the isoquinolinium-2-yl amide **B** to produce intermediate **C**. Subsequent intramolecular condensation and aromatization would give rise to the desired *H*-pyrazolo[5,1-*a*]isoquinolines **4**.



Scheme 2. Proposed mechanistic pathway.

3. Conclusions

In conclusion, we have described an efficient route for the synthesis of *H*-pyrazolo[5,1-*a*]isoquinoline derivatives via a silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene) hydrazides with alcohols. The reaction proceeds smoothly under mild conditions, leading to the diverse products in good yields. The efficiency of this method combined with the operational simplicity of the present process makes it potential attractive for structure construction.

4. Experimental section

4.1. General

Unless otherwise stated, all commercial reagents and solvents were used as received. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 Spectrometer operating at 400 MHz and 100 MHz. High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF II Instrument.

4.2. General experimental procedure for tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with aromatic alcohol

Silver trifluoromethanesulfonate (0.03 mmol), *N*′-(2-alkynylbenzylidene)hydrazide **1** (0.30 mmol, 1.0 equiv), and anhydrous dichloroethane (2.0 mL) were added into a tube equipped with a magnetic stirring bar under sealing plug. The mixture was stirred at 60 °C for 3 h. When *N*′-(2-alkynylbenzylidene)hydrazide **1** disappeared as indicated by TLC, the solution was cooled to rt, then DMP (0.6 mmol, 2.0 equiv), aromatic alcohol **2** (0.6 mmol, 2.0 equiv), K_3PO_4 (0.9 mmol, 3.0 equiv), and anhydrous dichloromethane (2.0 mL) were added into the solution. The mixture was stirred at 60 °C. After completion of the reaction as indicated by TLC, the reaction was quenched with water (10 mL), extracted with EtOAc (3×10 mL), dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **3**.

*4.2.1. 1,5-Diphenyl-pyrazolo[5,1-a]isoquinoline (**3a**).* Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.05 (d, *J*=8.0 Hz, 1H), 7.94 (s, 1H), 7.89 (d, *J*=7.2 Hz, 2H), 7.71 (d, *J*=8.0 Hz, 1H), 7.42–7.59 (m, 8H), 7.31 (t, *J*=7.6 Hz, 2H), 7.05 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.65, 138.55, 134.62, 134.27, 133.99, 130.10, 129.75, 129.51, 129.33, 128.76, 128.44, 127.83, 127.47, 127.27, 126.93, 124.64, 123.25, 117.13, 113.02. HRMS calcd for $C_{23}H_{17}N_2^+$ ($M+H^+$): 321.1386, Found: 321.1418.

*4.2.2. 1-(4-Chlorophenyl)-5-phenyl-pyrazolo[5,1-a]isoquinoline (**3b**).* Yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.00 (d, *J*=8.0 Hz, 1H), 7.92 (s, 1H), 7.88 (d *J*=6.8 Hz, 2H), 7.75 (d, *J*=7.6 Hz, 1H), 7.47–7.58 (m, 8H), 7.36 (t, *J*=7.6 Hz, 1H), 7.08 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.46, 138.53, 134.65, 133.81, 133.43, 132.72, 131.37, 129.78, 129.47, 129.40, 128.98, 128.46, 128.01, 127.39, 127.04, 124.39, 123.08, 115.80, 113.16. HRMS calcd for $C_{23}H_{16}ClN_2^+$ ($M+H^+$): 355.0997, Found: 355.0979.

*4.2.3. 5-Phenyl-1-(p-tolyl)-pyrazolo[5,1-a]isoquinoline (**3c**).* Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07 (d, *J*=8.0 Hz, 1H), 7.91 (s, 1H), 7.87 (d, *J*=8.0 Hz, 2H), 7.68 (d, *J*=8.0 Hz, 1H), 7.43–7.55 (m, 6H), 7.28–7.31 (m, 3H), 7.01 (s, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.76, 138.59, 137.22, 134.61, 134.07, 131.23, 129.98, 129.75, 129.54, 129.34, 128.74, 128.46, 127.78, 127.26, 126.91, 124.78, 123.30, 117.10, 112.97, 21.39. HRMS calcd for $C_{24}H_{19}N_2^+$ ($M+H^+$): 335.1543, Found: 355.1571.

*4.2.4. 1-(4-Methoxyphenyl)-5-phenyl-pyrazolo[5,1-a]isoquinoline (**3d**).* Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.03 (d, *J*=8.0 Hz, 1H), 7.91 (s, 1H), 7.88 (d, *J*=6.8 Hz, 2H), 7.70 (d, *J*=6.8 Hz, 1H), 7.45–7.56 (m, 6H), 7.32 (t, *J*=7.4 Hz, 1H), 7.06 (s, 1H), 7.03 (d, *J*=2.4 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.12, 141.74, 138.56, 134.65, 134.04, 131.23, 129.70, 129.51, 129.32, 128.45, 127.74, 127.25, 126.92, 126.39, 124.78, 123.20, 116.73, 114.23, 112.91, 55.41. HRMS calcd for $C_{24}H_{19}N_2O^+$ ($M+H^+$) 351.1492, Found: 351.1492.

*4.2.5. 1-(2-Bromophenyl)-5-phenyl-pyrazolo[5,1-a]isoquinoline (**3e**).* Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.93–7.94 (m, 2H), 7.92 (s, 1H), 7.79 (d, *J*=7.6 Hz, 1H), 7.73 (d, *J*=7.6 Hz, 1H), 7.43–7.61 (m, 7H), 7.24–7.36 (m, 2H), 7.09 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.96, 138.03, 134.71, 134.66, 133.37, 132.63, 132.26, 129.24, 129.09, 129.01, 128.87, 127.94, 127.44, 127.15, 126.70, 126.65, 125.35, 123.97, 122.92, 114.89, 112.61. HRMS calcd for $C_{23}H_{16}BrN_2^+$ ($M+H^+$): 399.0491, Found: 399.0497.

*4.2.6. 5-(4-Chlorophenyl)-1-phenyl-pyrazolo[5,1-a]isoquinoline (**3f**).* Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.05 (d, *J*=8.4 Hz, 1H), 7.94 (s, 1H), 7.86 (d, *J*=8.0 Hz, 2H), 7.74 (d, *J*=8.0 Hz, 1H), 7.59 (d, *J*=7.2 Hz, 2H), 7.44–7.54 (m, 6H), 7.34 (t, *J*=7.6 Hz, 1H), 7.06 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=140.59, 136.25, 134.23, 133.52, 133.02, 131.26, 129.79, 128.99, 128.47, 127.72, 127.61, 126.85, 126.47, 126.25, 126.09, 123.63, 122.19, 116.19, 111.99. HRMS calcd for $C_{23}H_{16}ClN_2^+$ ($M+H^+$): 355.0997, Found: 355.0995.

*4.2.7. 1-Phenyl-5-(p-tolyl)-pyrazolo[5,1-a]isoquinoline (**3g**).* Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (d, J=8.0 Hz, 1H), 7.93 (s, 1H), 7.77 (d, J=8.0 Hz, 2H), 7.71 (d, J=7.6 Hz, 1H), 7.59 (d, J=7.6 Hz, 2H), 7.44–7.52 (m, 4H), 7.36 (d, J=7.6 Hz, 2H), 7.30 (t, J=7.6 Hz, 1H), 7.03 (s, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.61, 139.36, 138.66, 134.59, 134.34, 131.10, 130.11, 129.83, 129.41, 129.16, 128.76, 127.80, 127.45, 127.21, 126.79, 124.57, 123.25, 117.08, 112.64, 21.50. HRMS calcd for $C_{24}H_{19}N_2^+$ ($M+H^+$): 335.1543, Found: 335.1553.

*4.2.8. 5-(4-Methoxyphenyl)-1-phenyl-pyrazolo[5,1-a]isoquinoline (**3h**).* Yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (d, J=8.0 Hz, 1H), 7.94 (s, 1H), 7.85 (d, J=8.4 Hz, 2H), 7.71 (d, J=8.4 Hz, 1H), 7.59 (d, J=6.8 Hz, 2H), 7.44–7.53 (m, 4H), 7.30 (t, J=7.6 Hz, 1H), 7.08 (d, J=8.4 Hz, 2H), 7.02 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.37, 141.56, 138.34, 134.63, 134.33, 130.90, 130.11, 129.88, 128.76, 127.81, 127.45, 127.15, 126.70, 126.32, 124.45, 123.24, 117.09, 113.90, 112.43, 55.45. HRMS calcd for $C_{24}H_{19}N_2O^+$ ($M+H^+$): 351.1492, Found: 351.1509.

*4.2.9. 5-Cyclopropyl-1-phenyl-pyrazolo[5,1-a]isoquinoline (**3i**).* Yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.01 (d, J=5.2 Hz, 1H), 8.01 (s, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.58 (d, J=7.2 Hz, 2H), 7.42–7.52 (m, 4H), 7.24–7.28 (m, 1H), 6.71 (s, 1H), 2.70–2.74 (m, 1H), 1.21–1.25 (m, 2H), 0.93–0.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.41, 140.76, 134.36, 134.19, 130.09, 129.71, 128.73, 127.64, 127.40, 126.68, 126.22, 123.95, 123.17, 117.14, 107.44, 11.61, 6.96. HRMS calcd for $C_{20}H_{17}N_2^+$ ($M+H^+$): 285.1386, Found: 285.1386.

*4.2.10. 5-Butyl-1-phenyl-pyrazolo[5,1-a]isoquinoline (**3j**).* Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.93 (d, J=8.4 Hz, 1H), 7.87 (s, 1H), 7.56 (d, J=7.6 Hz, 1H), 7.48 (d, J=6.8 Hz, 2H), 7.31–7.42 (m, 3H), 7.17 (t, J=8.0 Hz, 2H), 6.77 (s, 1H), 3.12 (t, J=7.8 Hz, 2H), 1.81–1.85 (m, 2H), 1.43–1.49 (m, 2H), 0.93 (t, J=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.24, 139.49, 134.44, 134.16, 130.10, 129.74, 128.73, 127.62, 127.38, 126.62, 126.15, 124.08, 123.16, 116.98, 109.98, 30.91, 29.08, 22.69, 14.07. HRMS calcd for $C_{21}H_{21}N_2^+$ ($M+H^+$): 301.1699, Found: 301.1671.

*4.2.11. 9-Fluoro-1,5-diphenyl-pyrazolo[5,1-a]isoquinoline (**3k**).* Yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.94 (s, 1H), 7.87 (d, J=7.2 Hz, 2H), 7.67–7.72 (m, 2H), 7.46–7.58 (m, 8H), 7.20–7.25 (m, 1H), 7.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.11 (d, $^1J_{CF}$=246 Hz), 141.60, 137.91, 133.90, 133.86, 133.73, 133.57, 129.97, 129.45, 129.35 (d, $^3J_{CF}$=9 Hz), 128.91, 128.46, 127.78, 126.29, 125.80 (d, $^3J_{CF}$=9 Hz), 117.65, 116.50 (d, $^2J_{CF}$=24 Hz), 112.29, 108.74 (d, $^2J_{CF}$=24 Hz). HRMS calcd for $C_{23}H_{16}FN_2^+$ ($M+H^+$): 339.1292, Found: 339.1280.

*4.2.12. 9-Fluoro-5-(4-methoxyphenyl)-1-phenyl-pyrazolo[5,1-a]isoquinoline (**3l**).* Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.94 (s, 1H), 7.83 (d, J=8.8 Hz, 2H), 7.66–7.70 (m, 2H), 7.45–7.57 (m, 5H), 7.20–7.23 (m, 1H), 7.07 (d, J=8.8 Hz, 2H), 6.99 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.99 (d, $^1J_{CF}$=245 Hz), 141.53, 137.73, 133.94, 133.90, 133.67, 130.86, 130.00, 129.20 (d, $^3J_{CF}$=9 Hz), 128.93, 127.77, 126.44, 126.08, 125.60 (d, $^3J_{CF}$=10 Hz), 117.62, 116.46 (d, $^2J_{CF}$=24 Hz), 113.91, 111.70, 108.71 (d, $^2J_{CF}$=24 Hz), 55.44. HRMS calcd for $C_{24}H_{18}FN_2O^+$ ($M+H^+$): 369.1398, Found: 369.1394.

*4.2.13. 5-Cyclopropyl-9-fluoro-1-phenyl-pyrazolo[5,1-a]isoquinoline (**3m**).* Yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.02 (s, 1H), 7.60–7.67 (m, 2H) 7.50–7.57 (m, 4H), 7.46–7.47 (m, 1H), 7.17–7.22 (m, 1H), 6.70 (s, 1H), 2.65–2.70 (m, 1H), 1.21–1.25 (m, 2H), 0.92–0.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.59 (d, $^1J_{CF}$=244 Hz), 140.33, 139.01, 135.44, 132.64, 128.90, 127.81, 127.63 (d, $^3J_{CF}$=9 Hz), 126.64, 125.16, 123.96 (d, $^3J_{CF}$=10 Hz), 116.58, 115.20 (d, $^2J_{CF}$=24 Hz), 107.49 (d, $^2J_{CF}$=24 Hz), 105.80, 10.46, 5.83. HRMS calcd for $C_{20}H_{16}FN_2^+$ ($M+H^+$): 303.1292, Found: 303.1261.

*4.2.14. 9-Methyl-1,5-diphenyl-pyrazolo[5,1-a]isoquinoline (**3n**).* Yield: 57%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.92 (s, 1H), 7.86–7.89 (m, 3H), 7.59–7.63 (m, 3H), 7.49–7.58 (m, 5H), 7.44–7.46 (m, 1H), 7.30–7.32 (m, 1H), 7.02 (s, 1H), 2.32 (s. 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.46, 137.70, 136.88, 134.35, 134.13, 130.07, 129.48, 129.39, 129.17, 128.63, 128.40, 127.48, 127.42, 127.14, 124.66, 123.10, 116.95, 112.93, 21.82. HRMS calcd for $C_{24}H_{19}N_2^+$ ($M+H^+$): 335.1543, Found: 335.1522.

*4.2.15. 8-Methoxy-1,5-diphenyl-pyrazolo[5,1-a]isoquinoline (**3o**).* Yield: 43%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.99 (d, J=8.0 Hz, 1H), 7.92 (s, 1H), 7.88–7.92 (m, 2H), 7.50–7.61 (m, 7H), 7.42–7.47 (m, 1H), 7.13 (d, J=4.0 Hz, 1H), 7.00 (s, 1H), 6.95–6.98 (m, 1H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.09. 141.74, 138.93, 134.40, 134.01, 131.49, 130.07, 129.48, 129.31, 128.74, 128.42, 127.32, 124.86, 118.72, 116.44, 115.82, 112.69, 108.36, 55.40. HRMS calcd for $C_{24}H_{19}N_2O^+$ ($M+H^+$): 351.1492, Found: 351.1481.

*4.2.16. 1-(4-Chlorophenyl)-5-(p-tolyl)-pyrazolo[5,1-a]isoquinoline (**3p**).* Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.99 (d, J=8.0 Hz, 1H), 7.90 (s, 1H), 7.73–7.78 (m, 3H), 7.47–7.54 (m, 5H), 7.33–7.38 (m, 3H), 7.06 (s, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.44, 139.45, 138.65, 134.64, 133.40, 132.82, 131.39, 130.95, 129.88, 129.39, 129.17, 128.99, 127.98, 127.34, 126.91, 124.34, 123.08, 115.76, 112.78, 21.50. HRMS calcd for $C_{24}H_{18}ClN_2^+$ ($M+H^+$): 369.1153, Found: 369.1134.

4.3. General experimental procedure for tandem reaction of *N′*-(2-alkynylbenzylidene)hydrazide with aliphatic alcohol

Silver trifluoromethanesulfonate (0.03 mmol), *N′*-(2-alkynylbenzylidene)hydrazide **1** (0.30 mmol, 1.0 equiv), anhydrous dichloroethane (2 mL) were placed into a tube equipped with a magnetic stirring bar under sealing plug. The mixture was stirred at 60 °C for 3 h. When *N′*-(2-)hydrazide **1** disappeared as indicated by TLC, the solution was cooled to 0 °C, then PCC (0.6 mmol, 2.0 equiv), aliphatic alcohol **2** (0.6 mmol, 2.0 equiv), K_3PO_4 (0.9 mmol, 3.0 equiv) were added into the solution for stirring about 2 h, the solution was heated to 60 °C again. After completion of the reaction as indicated by TLC, the reaction was quenched with water (10 mL), extracted with EtOAc (3×10 mL), dried by anhydrate Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **3**.

*4.3.1. 1-Methyl-5-phenyl-pyrazolo[5,1-a]isoquinoline[10] (**3q**).* Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.28 (d, J=7.6 Hz, 1H), 7.85 (d, J=6.8 Hz, 2H), 7.81 (s, 1H), 7.72 (d, J=6.8 Hz, 1H), 7.50–7.57 (m, 5H), 6.97 (s, 1H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=142.04, 138.63, 135.23, 134.06, 129.49, 129.42, 129.25, 128.42, 127.16, 125.69, 123.23, 112.40, 110.13, 11.93.

*4.3.2. 1-Ethyl-5-phenyl-pyrazolo[5,1-a]isoquinoline[11] (**3r**).* Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.25 (d, J=8.0 Hz, 1H), 7.84–7.86 (m, 3H), 7.72 (d, J=7.6 Hz, 1H), 7.48–7.57 (m, 5H), 6.97 (s, 1H), 3.09–3.14 (m, 2H), 1.46 (t, J=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.31, 137.61, 133.48, 133.08, 128.50, 128.37, 128.15, 127.33, 126.18, 126.13, 126.07, 124.43, 122.19, 116.10, 111.39, 18.45, 13.10.

*4.3.3. 1-Butyl-5-phenyl-pyrazolo[5,1-a]isoquinoline (**3s**).* Yield: 36%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.18 (d, J=8.0 Hz, 1H), 7.77 (d,

J=8.0 Hz, 2H), 7.76 (s, 1H), 7.66 (d, J=7.8 Hz, 1H), 7.39–7.53 (m, 5H), 6.90 (s, 1H), 3.00 (t, J=7.6 Hz, 2H), 1.73–1.76 (m, 2H), 1.43–1.48 (m, 2H), 0.94 (t, J=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.07, 137.64, 133.55, 133.09, 128.52, 128.38, 128.16, 127.33, 126.21, 126.12, 126.08, 124.45, 122.18, 114.65, 111.34, 30.70, 28.68, 21.67, 13.11. HRMS calcd for $C_{21}H_{21}N_2^+$ ($M+H^+$): 301.1699, Found: 301.1650.

*4.3.4. 1-Methoxy-5-phenyl-pyrazolo[5,1-a]isoquinoline (**3t**).* Yield: 30%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.52 (d, J=8.0 Hz, 1H), 7.85 (d, J=7.8 Hz, 1H), 7.84 (s, 1H), 7.68–7.73 (m, 2H), 7.47–7.57 (m, 5H), 6.94 (s, 1H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.29, 138.12, 133.44, 130.93, 129.42, 129.31, 128.85, 128.42, 127.32, 127.02, 126.55, 126.34, 124.88, 123.14, 112.65, 59.21. HRMS calcd for $C_{18}H_{15}N_2O^+$ ($M+H^+$): 275.1179, Found: 275.1192.

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