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An efficient approach to *H*-pyrazolo[5,1-*a*]isoquinolines via a silver triflate-catalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazide with allenoate

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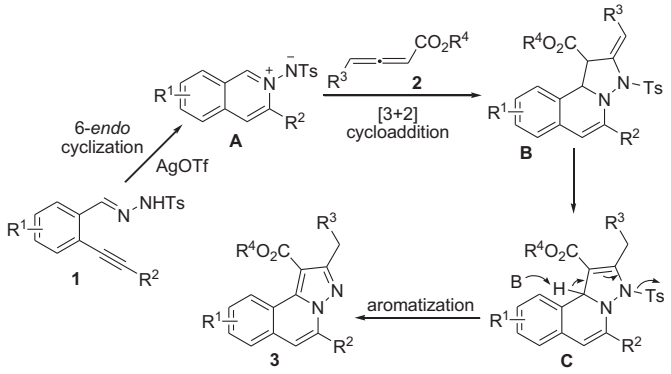
ABSTRACT

A silver triflate-catalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazide with allenoate under mild conditions is described, which provides an efficient approach to diverse *H*-pyrazolo[5,1-*a*]isoquinolines. This reaction proceeds with a wide substrate scope with good functional groups tolerance.

1. Introduction

In the last decade, the chemistry of allenes has been extensively explored, and their potentials in organic chemistry have been demonstrated.[1] The reactivity of allenes, which is different from those of alkenes and alkynes, has been recognized and successfully applied in organic synthesis.[2] For instance, allenoate as a versatile building block has been utilized in different transformations.[3,4] Recently, we are interested in the generation of natural product-like compounds used in different biological assays.[5] A novel structure, *H*-pyrazolo[5,1-*a*]isoquinoline, shows promising activities for inhibition of CDC25B, TC-PTP, and PTP1B.[6f] Additionally, a hit has been discovered based on control of diamondback moth at 50 ppm in level 3 insecticide screen. The discovery of lead compounds but their moderate activity prompted us to develop efficient synthesis protocol and test the resulting compounds in order to find better inhibitors. Consequently, we initiated a program for the methodology development and library construction of diverse *H*-pyrazolo[5,1-*a*]isoquinoline molecules.

In our previous reports, the scaffold of *H*-pyrazolo[5,1-*a*]isoquinoline could be prepared via reactions of *N*′-(2-alkynylbenzylidene)hydrazides.[6] During the reaction process, a key intermediate, isoquinolinium-2-yl amide **A**, could be formed through a silver triflate-catalyzed electrophilic 6-*endo*-cyclization[7] of *N*′-(2-alkynylbenzylidene)hydrazide **1**.[6] So far, different reaction partners have been used in the reactions.[6,8] Prompted by the advancement of allene chemistry, we conceived that the functionalized *H*-pyrazolo[5,1-*a*]isoquinolines could be prepared as well for the reaction of *N*′-(2-alkynylbenzylidene)hydrazide and allenoate. The proposed synthetic route is presented in Scheme 1. Theoretically, after the formation of isoquinolinium-2-yl amide **A**, allenoate **2** would involve in the conversion via a [3+2] cycloaddition to afford intermediate **B**. The subsequent double bond migration and aromatization would occur to



Scheme 1. Generation of *H*-pyrazolo[5,1-*a*]isoquinolines via a silver triflate-catalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazide with allenoate.

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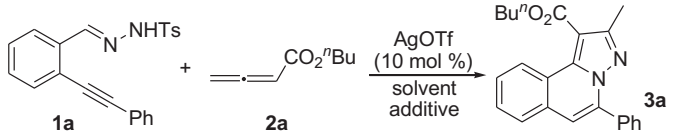
furnish the expected *H*-pyrazolo[5,1-*a*]isoquinoline **3**. To test this hypothesis, we started to examine the feasibility of this transformation.

2. Results and discussion

Initially, the studies were performed for the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** and *n*-butyl allenoate **2a** (Table 1). No product was detected when the reaction was treated with 10 mol % of silver triflate in dichloroethane (DCE) at room temperature (Table 1, entry 1). The corresponding *H*-pyrazolo[5,1-*a*]isoquinoline **3a** was formed with 33% yield when the temperature was elevated to 55 °C (Table 1, entry 2). However, only a trace amount of product was observed when the solvent was changed to toluene (Table 1, entry 3). Since dichloroethane has been demonstrated as the best choice for the formation of isoquinolinium-2-yl amide **A**, a mixed solvent was then screened (Table 1, entries 4–8). From the results, it seemed that the combination of DCE and DMF in the reaction gave rise to a better yield (Table 1, entry 8). Recently, the concept of cooperative catalysts has attracted much attention in organic synthesis.[9] Thus, several metal catalysts (10 mol %) were added in the reaction system (Table 1, entries 9–12). The yield could be improved when $PdCl_2$, CuI, or $Yb(OTf)_3$ was employed as an additive. Lewis base was also considered, since allenoates is typically facilitated by phosphine.[3] Indeed, treatment of *N*′-(2-alkynylbenzylidene)hydrazide **1a** and *n*-butyl allenoate **2a** with PPh_3 (20 mol %) provided the expected product **3a** in 60% yield (Table 1, entry 13). Switching the additive to other Lewis bases, however, led to production with lower yields (Table 1, entries 14–16). The yield could be increased to 65% when 2 equiv of *n*-butyl allenoate **2a** was employed in the reaction (Table 1, entry 17).

Table 1
Initial studies for the silver triflate-catalyzed reaction of *N*′-(2-alkynylbenzylidene) hydrazide **1a** with *n*-butyl buta-2,3-dienoate **2a**

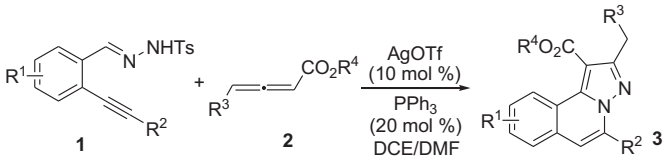


Entry	Solvent	Additive	*T* (°C)	Yield[a] (%)
1	DCE	—	25	NR
2	DCE	—	55	33
3	Toluene	—	55	Trace
4	DCE/MeCN	—	55	29
5	DCE/THF	—	55	28
6	DCE/MeOH	—	55	37
7	DCE/1,4-dioxane	—	55	33
8	DCE/DMF	—	55	41
9	DCE/DMF	$PdCl_2$	55	50
10	DCE/DMF	CuI	55	45
11	DCE/DMF	$Yb(OTf)_3$	55	53
12	DCE/DMF	$In(OTf)_3$	55	42
13	DCE/DMF	PPh_3	55	60
14	DCE/DMF	P^nBu_3	55	41
15	DCE/DMF	DABCO	55	37
16	DCE/DMF	Et_3N	55	42
17[b]	DCE/DMF	PPh_3	55	65

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1a**.
[b] In the presence of 2 equiv of *n*-butyl buta-2,3-dienoate.

With conditions highlighted above (10 mol % of AgOTf, 20 mol % of triphenylphosphine, DCE/DMF, 55–60 °C), the scope of the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1** with allenoate **2** was studied. Table 2 shows the summary of results for the evaluation of various substituted *N*′-(2-alkynylbenzylidene)hydrazides **1** and allenoate **2**. Besides *n*-butyl buta-2,3-dienoate **2a**, ethyl 4-phenylbuta-2,3-dienoate **2b**, and ethyl 4-methylbuta-2,3-dienoate

Table 2
Scope investigation for the silver triflate-catalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1** with allenoate **2**



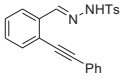
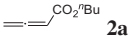
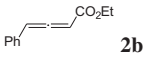
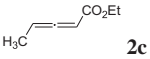
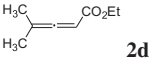
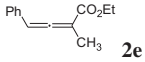
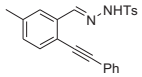
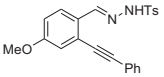
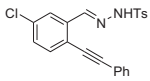
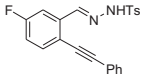
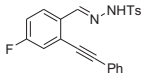
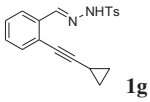
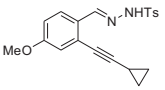
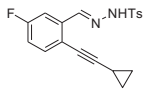
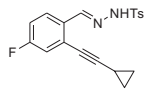
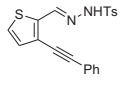
Entry	Substrate **1**	Allene **2**	Yield[a] (%)
1	 **1a**	 **2a**	65 (**3a**)
2	**1a**	 **2b**	80 (**3b**)
3	**1a**	 **2c**	61 (**3c**)
4	**1a**	 **2d**	Trace
5	**1a**	 **2e**	Trace
6	 **1b**	**2a**	63 (**3d**)
7	**1b**	**2b**	62 (**3e**)
8	**1b**	**2c**	65 (**3f**)
9	 **1c**	**2c**	73 (**3g**)
10	 **1d**	**2b**	60 (**3h**)
11	 **1e**	**2a**	52 (**3i**)
12	**1e**	**2b**	75 (**3j**)
13	**1e**	**2c**	62 (**3k**)
14	 **1f**	**2a**	40 (**3l**)
15	**1f**	**2b**	63 (**3m**)
16	 **1g**	**2a**	60 (**3n**)
17	**1g**	**2b**	60 (**3o**)
18	**1g**	**2c**	70 (**3p**)
19	 **1h**	**2a**	60 (**3q**)
20	**1h**	**2b**	72 (**3r**)
21	**1h**	**2c**	75 (**3s**)
22	 **1i**	**2a**	60 (**3t**)

Table 2 (*continued*)

Entry	Substrate **1**	Allene **2**	Yield[a] (%)
23	 **1j**	**2c**	61 (**3u**)
24	 **1k**	**2a**	61 (**3v**)
25	**1k**	**2b**	70 (**3w**)
26	**1k**	**2c**	68 (**3x**)

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

2c were demonstrated as good partner as well. For instance, *N*′-(2-alkynylbenzylidene)hydrazide **1a** reacted with ethyl 4-phenylbuta-2,3-dienoate **2b** leading to the desired *H*-pyrazolo[5,1-*a*]isoquinoline **3b** in 80% yield (Table 2, entry 2). The structural elucidation was confirmed by X-ray diffraction analysis (Fig. 1). However, only a trace amount of product was detected when allenoate **2d** or **2e** was employed in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** (Table 2, entries 4 and 5). It might be due to the steric hinder during the reaction.

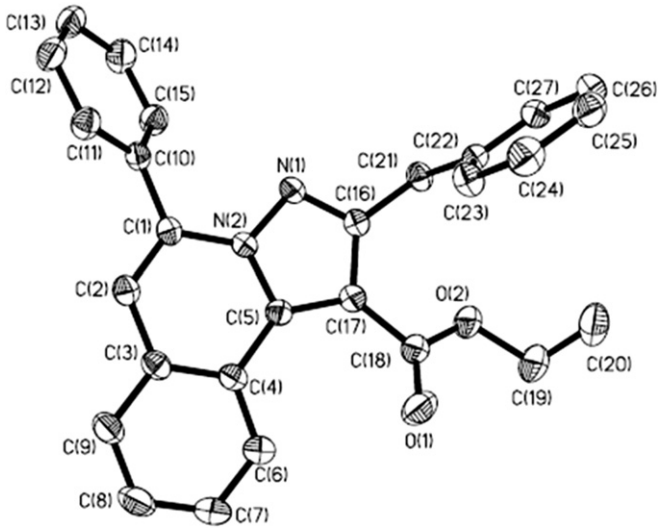


Fig. 1. X-ray ORTEP illustration of *H*-pyrazolo[5,1-*a*]isoquinoline **3b** (30% probability ellipsoids).

Noticeably, reactions of *N*′-(2-alkynylbenzylidene)hydrazides **1** bearing either electron-rich or electron-poor substituents on the aromatic ring (R^1 position) were converted to the desired products with good reactivity. The methyl, methoxy, chloro, and fluoro groups were tolerated under the reaction conditions. Additionally, the reactions were workable for the substrates **1** with a cyclopropyl group attached on the R^2 position, affording the corresponding products in good yields (Table 2, entries 16–23). Moreover, reactions of thiophenyl-incorporated hydrazide **1k** were examined in the meantime. As expected, this substrate was proven to be a good partner for the transformation, and no influence was observed for the final output (Table 2, entries 24–26).

3. Conclusions

In summary, a novel and efficient reaction of *N*′-(2-alkynylbenzylidene)hydrazide with allenoate catalyzed by silver triflate under mild conditions has been successfully developed. Diverse *H*-pyrazolo[5,1-*a*]isoquinolines are generated in good yields. This reaction proceeds with a wide substrate scope with good functional groups tolerance. Library construction and subsequent biological assays are in progress in our laboratory.

4. Experimental section

4.1. General

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. 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 precoated 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 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, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hertz. High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF II instrument.

4.2. General experimental procedure for the silver triflate-catalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazide 1 with allenoate 2

Silver triflate (10 mol %) was added to a solution of *N*′-(2-alkynylbenzylidene)hydrazide **1** (0.2 mmol) in DCE (0.5 mL). The solution was stirred at 55 °C in air for 1 h. After consumption of *N*′-(2-alkynylbenzylidene)hydrazide **1**, PPh_3 (20 mol %), allenoate **2** (2.0 equiv), and DMF (1.5 mL) was then added. The mixture was stirred at 60 °C in air for 3–10 h. After completion of reaction as indicated by TLC, the reaction was quenched by addition of saturated aqueous NH_4Cl (5.0 mL), and the mixture was extracted with EtOAc (4.0 mL×3). The combined organic layer was dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to provide the desired product **3**.

*4.2.1. Butyl 2-methyl-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, *J*=7.4, 3H), 1.47–1.56 (m, 2H), 1.77–1.84 (m, 2H), 2.63 (s, 3H), 4.40 (t, *J*=6.9 Hz, 2H), 7.08 (s, 1H), 7.47–7.50 (m, 3H), 7.54–7.58 (m, 2H), 7.68 (d, *J*=7.3 Hz, 1H), 7.81 (d, *J*=6.4 Hz, 2H), 9.56 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 15.9, 19.4, 30.8, 64.3, 106.3, 114.5, 123.4, 126.9, 127.0, 127.1 128.1, 128.9, 129.2, 129.6, 130.8, 133.5, 137.7, 140.2, 153.3, 165.2; HRMS (ESI) calcd for $C_{23}H_{22}N_2O_2$: 359.1760 ($M+H^+$), found: 359.1760.

*4.2.2. Ethyl 2-benzyl-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J*=6.9 Hz, 3H), 4.28 (m, 2H), 4.45 (s, 2H), 7.16 (s, 2H), 7.23–7.26 (m, 4H), 7.49 (d, *J*=8.0 Hz, 3H), 7.57–7.80 (m, 2H), 7.72–7.73 (m, 1H), 7.87 (d, *J*=8.0 Hz, 2H), 9.44 (d, *J*=4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 34.9, 60.4, 106.2, 114.8, 123.5, 125.8, 126.9, 127.1, 127.3, 128.1, 128.2, 128.4, 129.0, 129.3, 129.7, 130.8, 133.5, 137.9, 139.8, 140.3, 154.8, 164.9; HRMS (ESI) calcd for $C_{27}H_{20}N_2O_2$: 407.1760 ($M+H^+$), found: 407.1773.

*4.2.3. Ethyl 2-ethyl-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J*=7.4 Hz, 3H), 1.48 (t, *J*=7.1 Hz, 3H), 3.05–3.11 (m, 2H), 4.46–4.51 (m, 2H),

7.14 (s, 1H), 7.32 (d, J=6.9 Hz, 3H), 7.55–7.65 (m, 2H), 7.66–7.81 (m, 1H), 7.88 (d, J=7.0 Hz, 2H), 9.46 (d, J=4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.3, 22.7, 60.5, 105.5, 114.5, 123.5, 126.8, 127.0, 127.2, 128.2, 128.9, 129.2, 129.7, 130.8, 133.6, 137.9, 140.1, 158.3, 165.4; HRMS (ESI) calcd for $C_{22}H_{20}N_2O_2$: 345.1603 ($M+H^+$), found: 345.1603.

*4.2.4. Butyl 2,9-dimethyl-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J=8.0 Hz, 3H), 1.51–1.56 (m, 2H), 1.80–1.85 (m, 2H), 2.59 (s, 3H), 2.63 (s, 3H), 4.41–4.44 (m, 2H), 7.10 (s, 1H), 7.43–7.63 (m, 5H), 7.82–7.84 (m, 2H), 9.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 15.9, 19.4, 22.1, 30.9, 64.4, 107.8, 114.5, 123.5, 126.6, 126.9, 128.2, 128.7, 129.2, 129.7, 130.7, 133.7, 136.7, 137.3, 140.1; HRMS (ESI) calcd for $C_{24}H_{24}N_2O_2$: 373.1916 ($M+H^+$), found: 373.1923.

*4.2.5. Ethyl 2-benzyl-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3e**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J=8.0 Hz, 3H), 2.59 (s, 3H), 4.28–4.33 (m, 2H), 4.44 (s, 2H), 7.14–7.16 (m, 2H), 7.23–7.26 (m, 4H), 7.42–7.50 (m, 4H), 7.64 (d, J=6.4 Hz, 1H), 7.86 (d, J=4.0 Hz, 2H), 9.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.1, 34.9, 60.4, 106.0, 114.7, 123.6, 125.8, 126.4, 127.0, 128.1, 128.2, 128.4, 128.7, 129.2, 129.7, 130.7, 133.6, 137.1, 137.4, 139.9, 140.1, 154.8, 165.0; HRMS (ESI) calcd for $C_{28}H_{24}N_2O_2$: 421.1916 ($M+H^+$), found: 421.1931.

*4.2.6. Ethyl 2-ethyl-9-methyl-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3f**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=16.0 Hz, 3H), 1.48 (t, J=16.0 Hz, 3H), 2.58 (s, 3H), 3.04–3.09 (m, 2H), 4.46–4.51 (m, 2H), 7.10 (s, 1H), 7.41–7.51 (m, 4H), 7.62–7.64 (m, 1H), 7.86–7.87 (m, 2H), 9.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.3, 22.1, 22.6, 60.4, 105.3, 114.4, 123.6, 126.4, 126.9, 128.1, 128.7, 129.1, 129.7, 130.5, 133.8, 137.1, 137.2, 139.9, 158.2, 165.4; HRMS (ESI) calcd for $C_{23}H_{22}N_2O_2$: 359.1760 ($M+H^+$), found: 359.1782.

*4.2.7. Ethyl 2-ethyl-8-methoxy-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3g**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=8.0 Hz, 3H), 1.46 (t, J=8.0 Hz, 3H), 3.03–3.09 (m, 2H), 3.92 (s, 1H), 4.43–4.49 (m, 2H), 7.06–7.10 (m, 2H), 7.20–7.21 (m, 1H), 7.48–7.50 (m, 2H), 7.85–7.87 (m, 2H), 9.48 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.3, 22.8, 55.3, 60.3, 104.3, 107.6, 114.2, 116.9, 117.8, 128.1, 128.9, 129.2, 129.7, 132.9, 133.6, 138.2, 140.5, 158.4, 159.8, 165.3; HRMS (ESI) calcd for $C_{23}H_{22}N_2O_3$: 375.1709 ($M+H^+$), found: 375.1698.

*4.2.8. Ethyl 2-benzyl-9-chloro-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3h**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J=8.0 Hz, 3H), 4.31–4.34 (m, 2H), 4.45 (s, 2H), 7.14–7.25 (m, 6H), 7.50–7.67 (m, 5H), 7.85–7.86 (m, 2H), 9.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 34.9, 60.7, 106.6, 114.0, 124.5, 125.9, 126.4, 128.1, 128.2, 128.4, 129.1, 129.5, 129.6, 129.7, 133.1, 133.2, 138.2, 139.2, 139.6, 155.3, 164.6; HRMS (ESI) calcd for $C_{27}H_{21}ClN_2O_2$: 441.1370 ($M+H^+$), found: 441.1372.

*4.2.9. Butyl 9-fluoro-2-methyl-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3i**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J=8.0 Hz, 3H), 1.49–1.55 (m, 2H), 1.80–1.83 (m, 2H), 2.62(s, 3H), 4.38–4.41 (m, 2H), 7.05 (s, 1H), 7.24–7.36 (m, 2H), 7.50 (s, 3H), 7.81–7.82 (m, 2H), 9.68–9.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 16.0, 19.4, 30.8, 64.4, 105.6, 111.4 ($^2J_{CF}$=22 Hz), 113.8, 115.8 ($^2J_{CF}$=23 Hz), 120.2, 128.3, 129.5, 129.7, 130.2, 133.2, 133.3, 138.8, 140.6, 153.7, 162.3 ($^1J_{CF}$=249 Hz), 165.3; HRMS (ESI) calcd for $C_{23}H_{21}FN_2O_2$: 377.1665 ($M+H^+$), found: 377.1672.

*4.2.10. Ethyl 2-benzyl-9-fluoro-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3j**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J=8.0 Hz, 3H), 4.27–4.31 (m, 2H), 4.45 (s, 2H), 7.12–7.86 (m, 11H), 7.86–7.88 (m, 2H), 9.58–9.61(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 35.0, 60.5, 105.9, 111.5 ($^2J_{CF}$=22 Hz), 114.0, 115.9 ($^2J_{CF}$=20 Hz) 120.3, 127.0 ($^1J_{CF}$=230 Hz), 128.2, 128.3, 129.6, 129.8 ($^2J_{CF}$=20 Hz), 130.0, 132.9, 133.0, 133.1, 138.9, 139.7, 140.3, 155.1, 162.5 ($^1J_{CF}$=249 Hz), 164.8; HRMS (ESI) calcd for $C_{27}H_{21}FN_2O_2$: 425.1665 ($M+H^+$), found: 425.1688.

*4.2.11. Ethyl 2-ethyl-9-fluoro-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3k**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J=8.0 Hz, 3H), 1.45 (t, J=8.0 Hz, 3H), 3.02–3.06 (m, 2H), 4.43–4.46 (m, 2H), 7.07–7.85 (m, 9H), 9.57–9.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.3, 22.8, 60.5, 105.6, 111.49 ($^2J_{CF}$=22 Hz), 113.7, 115.7, 115.9, 128.2, 129.5, 129.7, 129.9, 130.0, 132.9, 133.3, 138.9, 140.1, 158.6, 165.3; HRMS (ESI) calcd for $C_{22}H_{19}FN_2O_2$: 363.1509 ($M+H^+$), found: 363.1543.

*4.2.12. Butyl 8-fluoro-2-methyl-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3l**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J=7.3 Hz, 3H), 1.48–1.56 (m, 2H), 1.79–1.86 (m, 2H), 2.63 (s, 3H), 4.40 (t, J=12.0 Hz, 2H), 7.07 (s, 1H), 7.25–7.37 (m, 2H), 7.52–7.52 (m, 3H), 7.82–7.83 (m, 2H), 9.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1($^1J_{CF}$=227 Hz), 19.59, 30.99, 64.60, 76.82, 77.14, 77.45, 106.21, 111.5 ($^2J_{CF}$=22 Hz), 113.88, 116.0 ($^2J_{CF}$=22 Hz) 128.40, 129.7 ($^3J_{CF}$=13 Hz), 130.36, 133.32, 138.94, 140.17, 140.5 ($^2J_{CF}$=21 Hz), 153.80, 163.79, 165.38; HRMS (ESI) calcd for $C_{23}H_{21}FN_2O_2$: 377.1665 ($M+H^+$), found: 377.1660.

*4.2.13. Ethyl 2-benzyl-8-fluoro-5-phenylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3m**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J=16.0 Hz, 3H), 4.26–4.31 (m, 2H), 4.44 (s, 2H), 7.10 (s, 1H), 7.15–7.37 (m, 7H), 7.49–7.50 (m, 3H), 7.85 (d, J=4.0 Hz, 2H), 9.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 35.0, 60.5, 111.4, 111.6, 113.9, 114.0, 114.9 ($^2J_{CF}$=23 Hz), 120.3, 125.9, 128.2($^3J_{CF}$=9.0 Hz), 128.3, 129.6, 129.9 ($^2J_{CF}$=23 Hz), 130.0 ($^3J_{CF}$=9.0 Hz), 133.0, 133.1, 138.9, 139.7, 155.1, 161.2, 163.7, 164.8; HRMS (ESI) calcd for $C_{27}H_{21}FN_2O_2$: 425.1665 ($M+H^+$), found: 425.1693.

*4.2.14. Butyl 5-cyclopropyl-2-methylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3n**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.90 (m, 2H), 1.01 (t, J=7.3 Hz, 3H), 1.17–1.22 (m, 2H), 1.50–1.56 (m, 2H), 1.79–1.84 (m, 2H), 2.72–2.76 (m, 4H), 4.41 (t, J=6.4 Hz, 2H), 6.72 (s, 1H), 7.53–7.63 (m, 3H), 9.54 (d, J=4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.5, 11.4, 13.8, 15.9, 19.4, 30.9, 64.3, 108.4, 122.7, 126.3, 126.4, 127.0, 128.8, 130.9, 139.9, 140.4, 153.4, 165.4; HRMS (ESI) calcd for $C_{20}H_{22}N_2O_2$: 323.1760 ($M+H^+$), found: 323.1777.

*4.2.15. Ethyl 2-benzyl-5-cyclopropylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3o**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.93 (m, 2H), 1.19–1.21 (m, 2H), 1.26 (t, J=7.3 Hz, 3H), 2.77–2.80 (m, 1H), 4.27–4.32 (m, 2H), 4.53 (s, 2H), 6.75 (s, 1H), 7.16–7.26 (m, 5H), 7.53–7.62 (m, 3H), 9.41 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6, 11.4, 14.2, 35.1, 60.4, 106.1, 108.5, 122.8, 125.8, 126.4, 126.4, 126.8, 128.1, 128.4, 128.8, 130.9, 139.8, 139.9, 140.6, 154.7, 165.0; HRMS (ESI) calcd for $C_{24}H_{22}N_2O_2$: 371.1760 ($M+H^+$), found: 371.1741.

*4.2.16. Ethyl 5-cyclopropyl-2-ethylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3p**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.90 (m, 2H), 1.17–1.24 (m, 2H), 1.36 (t, J=8.0 Hz, 3H), 1.44 (t, J=8.0 Hz, 3H), 2.74–2.79 (m, 1H), 3.11–3.16 (m, 2H), 4.44–4.49 (m, 2H), 6.70 (s, 1H), 7.52–7.53 (m, 2H), 7.54–7.61 (m, 1H), 9.42 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6, 11.3, 14.1, 14.3, 22.8, 29.7, 60.4, 105.4, 108.2, 122.8, 126.3, 126.8, 128.7, 130.8, 139.7, 140.6, 158.3, 165.3; HRMS (ESI) calcd for $C_{19}H_{20}N_2O_2$: 309.1603 ($M+H^+$), found: 309.1585.

*4.2.17. Butyl 5-cyclopropyl-8-methoxy-2-methylH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3q**).* ^{1}H NMR (400 MHz, $CDCl_3$)

δ 0.87–0.89 (m, 2H), 0.99 (t, *J*=8.0 Hz, 1H), 1.17–1.19 (m, 2H), 1.49–1.50 (m, 2H), 1.71–1.82 (m, 2H), 2.69–2.72 (m, 4H), 3.90 (s, 3H), 4.38 (t, *J*=8.0 Hz, 2H), 6.64 (s, 1H), 6.9–7.25 (m, 2H), 9.52 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6, 11.4, 13.8, 16.1, 19.5, 30.9, 55.3, 64.2, 106.8, 108.0, 116.2, 117.1, 129.1, 133.0, 140.8, 153.5, 159.7, 165.4; HRMS (ESI) calcd for $C_{21}H_{24}N_2O_3$: 353.1865 ($M+H^+$), found: 353.1876.

*4.2.18. Ethyl 2-benzyl-5-cyclopropyl-8-methoxyH-pyrazolo[5,1-a] isoquinoline-1-carboxylate (**3r**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J*=8.0 Hz, 3H), 1.19–1.28 (m, 2H), 3.91 (s, 1H), 4.24–4.28 (m, 2H), 4.51 (s, 1H), 6.68 (s, 1H), 7.02–7.25 (m, 7H), 9.42 (d, *J*=12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 11.4, 14.2, 35.2, 55.3, 60.2, 107.0, 108.2, 116.3, 117.2, 125.8, 128.1, 128.4, 128.9, 133.0, 138.0, 139.9, 140.3, 141.1, 154.8, 159.8, 165.0; HRMS (ESI) calcd for $C_{25}H_{24}N_2O_3$: 401.1865 ($M+H^+$), found: 401.1869.

*4.2.19. Ethyl 5-cyclopropyl-2-ethyl-8-methoxyH-pyrazolo[5,1-a] isoquinoline-1-carboxylate (**3s**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–0.89 (m, 2H), 1.15–1.24 (m, 2H), 1.37 (t, *J*=8.0 Hz, 3H), 1.45 (t, *J*=8.0 Hz, 3H), 3.09–3.31 (m, 2H), 3.88 (s, 3H), 4.41–4.46 (m, 2H), 6.61 (s, 1H), 6.97 (d, *J*=4.0 Hz, 1H), 7.11–7.14 (m, 1H), 9.43 (d, *J*=12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 11.3, 14.1, 14.3, 22.9, 55.2, 60.2, 104.2, 106.8, 107.7, 116.1, 117.1, 128.8, 133.0, 140.1, 141.0, 158.4, 159.6, 165.3; HRMS (ESI) calcd for $C_{20}H_{22}N_2O_3$: 339.1709 ($M+H^+$), found: 339.1718.

*4.2.20. Butyl 5-cyclopropyl-9-fluoro-2-methylH-pyrazolo[5,1-a] isoquinoline-1-carboxylate (**3t**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.91 (m, 2H), 1.01 (t, *J*=7.3 Hz, 3H), 1.20–1.25 (m, 2H), 1.50–1.56 (m, 2H), 1.78–1.84 (m, 2H), 2.71–2.74 (m, 4H), 4.40 (t, *J*=6.9 Hz, 2H), 6.63 (s, 1H), 7.23–7.27 (m, 2H), 9.63–9.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.74, 11.4, 13.7, 16.1, 19.4, 30.8, 64.4, 105.5, 107.5, 110.7 ($^2J_{CF}$=21 Hz), 115.0 ($^2J_{CF}$=23 Hz), 119.5, 130.0, 131.1, 132.8, 139.5, 141.6, 153.6, 162.3 ($^1J_{CF}$=250 Hz), 165.3; HRMS (ESI) calcd for $C_{20}H_{21}FN_2O_2$: 341.1665 ($M+H^+$), found: 341.1683.

*4.2.21. Ethyl 5-cyclopropyl-2-ethyl-8-fluoroH-pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3u**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J*=4.0 Hz, 2H), 1.18–1.25 (m, 3H), 1.38 (t, *J*=8.0 Hz, 3H), 1.37 (t, *J*=8.0 Hz, 2H), 2.76–2.78 (m, 2H), 3.11–3.16 (m, 2H), 4.43–4.48 (m, 2H), 6.62 (s, 1H), 7.22–7.26 (m, 2H), 9.53–9.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.86, 11.3, 13.9, 14.3, 22.9, 64.4, 105.2, 107.3, 110.7 ($^2J_{CF}$=21 Hz), 114.9 ($^2J_{CF}$=23 Hz), 119.5, 129.8, 129.9, 132.9, 133.0, 139.6, 141.8, 158.5, 162.3 ($^1J_{CF}$=249 Hz), 165.3; HRMS (ESI) calcd for $C_{19}H_{19}FN_2O_2$: 327.1509 ($M+H^+$), found: 327.1500.

*4.2.22. Butyl 8-methyl-5-phenylpyrazolo[1,5-a]thieno[2,3-c]pyridine- 9-carboxylate (**3v**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J*=8.0 Hz, 3H), 1.48–1.54 (m, 2H), 1.80–1.84 (m, 2H), 2.65 (s, 3H), 4.40–4.43 (m, 2H), 7.25 (s, 1H), 7.36 (d, *J*=8.0 Hz, 1H), 7.48–7.50 (m, 3H), 7.66 (d, *J*=8.0 Hz, 1H), 7.82–7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 15.3, 19.4, 31.0, 64.0, 110.1, 123.4, 128.3, 129.3, 129.6, 130.9, 133.6, 137.2, 137.9, 153.6, 164.6; HRMS (ESI) calcd for $C_{21}H_{20}N_2O_2S$: 365.1324 ($M+H^+$), found: 365.1332.

*4.2.23. Ethyl 8-benzyl-5-phenylpyrazolo[1,5-a]thieno[2,3-c]pyridine-9-carboxylate (**3w**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J*=8.0 Hz, 3H), 4.37–4.42 (m, 2H), 4.47 (s, 2H), 7.25–7.40 (m, 7H), 7.50–7.52 (m, 3H), 7.67–7.69 (m, 1H), 7.88–7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 34.4, 60.1, 101.6, 123.5, 125.9, 127.1, 128.1, 128.3, 128.7, 129.3, 129.7, 131.0, 133.5, 137.4, 138.0, 139.6; HRMS (ESI) calcd for $C_{25}H_{20}N_2O_2S$: 413.1343 ($M+H^+$), found: 413.1324.

*4.2.24. Ethyl 8-ethyl-5-phenylpyrazolo[1,5-a]thieno[2,3-c]pyridine-9-carboxylate (**3x**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J*=8.0 Hz, 3H); 1.48 (t, *J*=8.0 Hz, 3H), 3.08–3.12 (m, 2H), 4.47–4.51 (m, 2H), 7.28 (s, 1H), 7.27–7.38 (m, 1H), 7.49–7.51 (m, 3H), 7.66–7.67 (m, 1H), 7.86–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 14.5, 22.3, 60.0, 101.0, 110.2, 123.5, 127.0, 128.2, 129.2, 129.6, 130.8, 133.6, 137.4, 137.9, 139.6; HRMS (ESI) calcd for $C_{20}H_{18}N_2O_2S$: 351.1167 ($M+H^+$), found: 351.1205.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.02.013. These data include MOL file and InChiKeys of the most important compound described in this article.

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