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An efficient route to diverse *H*-pyrazolo[5,1-*a*]isoquinolines via sequential multi-component/cross-coupling reactions

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ABSTRACT

Multi-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, electrophile (bromine or iodine), and ketone or aldehyde under mild conditions proceeds smoothly to afford the functionalized *H*-pyrazolo[5,1-*a*]isoquinolines in good yields. This one-pot process involves intermolecular condensation, electrophilic cyclization, nucleophilic addition, intramolecular condensation, and aromatization. The resulting halo-containing *H*-pyrazolo[5,1-*a*]isoquinolines could be further elaborated via palladium-catalyzed cross-coupling reactions.

1. Introduction

1,2-Dihydroisoquinolines are of interest because of their frequent occurrence in nature and their wide range of biological and physiological effects.[1,2] 1,2-Dihydroisoquinoline derivatives currently in pharmaceutical use or development include inhibitor of human topoisomerase I (Lamellarin D)[3] and selective inhibitor against HIV-1 integrase.[4] Recently, we also discovered that 1,2-dihydroisoquinoline compounds displayed promising activity as PTP1B (protein tyrosine phosphatase) inhibitor. The search for better hits encouraged us to construct structural novel 1,2-dihydroisoquinoline library for the subsequent biological assays.

It is well recognized that a focused library can be generated via parallel diversity-oriented synthesis.[5] Recently, we have demonstrated that *H*-pyrazolo[5,1-*a*]isoquinolines could be accessed via AgOTf-catalyzed tandem reactions[6] of *N*′-(2-alkynylbenzylidene) hydrazides with silyl enolates.[7a] For generation of the diverse *H*-pyrazolo[5,1-*a*]isoquinoline library (Fig. 1), we decided to explore efficient strategies that would allow us considerable flexibility to introduce a diversity of functionalities in a high-throughput manner. The strategy for library production is outlined in Scheme 1. In our previous report for the reaction of *N*′-(2-alkynylbenzylidene) hydrazide with enolate,[7] the key isoquinolinium intermediate would be formed during the reaction process via 6-*endo* cyclization of *N*′-(2-alkynylbenzylidene)hydrazide[8] in the presence of silver triflate, which then underwent nucleophilic addition of enolate for further transformation. Prompted by this result, we envisioned that the reaction could be traced back to 2-alkynylbenzaldehyde[9] **1** and sulfonohydrazide (Scheme 1). After intermolecular condensation, *N*′-(2-alkynylbenzylidene)hydrazide **A** would be obtained. Subsequently, in the presence of electrophiles, such as iodine or bromine, *N*′-(2-alkynylbenzylidene)hydrazide **A** would undergo electrophilic cyclization leading to halo-containing isoquinolinium-2-yl amide **B**. Meanwhile, the in situ formed enolate (derived from ketone or aldehyde **2** in the presence of base) would attack the halo-containing isoquinolinium-2-yl amide **B** to produce intermediate **C**. After intramolecular condensation and aromatization, the halo-containing *H*-pyrazolo[5,1-*a*]isoquinoline **3** would be generated. The further elaboration via palladium-catalyzed cross-coupling reactions would afford the diverse *H*-pyrazolo[5,1-*a*]isoquinoline compounds **4**. Thus, based on these considerations, we embark on exploring the possibility of this multi-component reaction[10] of 2-alkynylbenzaldehyde, sulfonohydrazide, electrophile (bromine or iodine), and ketone or aldehyde.

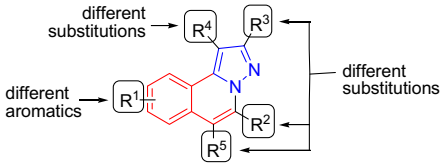

Fig. 1. *H*-Pyrazolo[5,1-*a*]isoquinoline scaffold.

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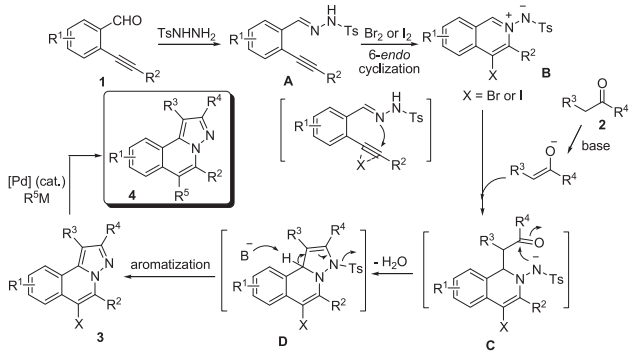
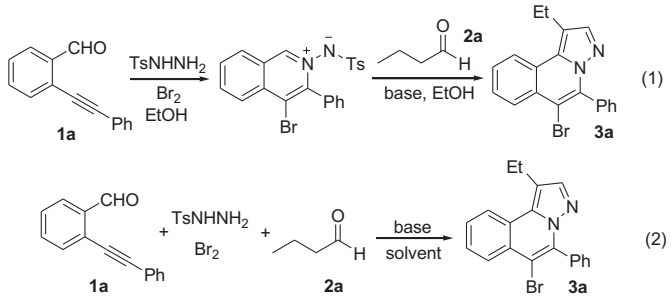


Scheme 1. Proposed synthetic route for the one-pot reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, electrophile, and ketone or aldehyde.

2. Results and discussion

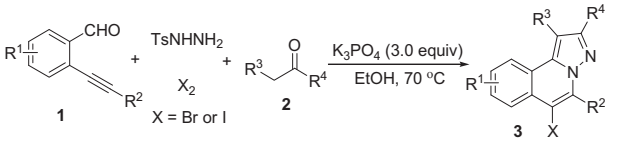
In order to simplify the reaction optimization process, initial attempts were performed for the sequential reaction of 2-alkynylbenzaldehyde **1a** (Scheme 2, Eq. 1). At the outset, 2-alkynylbenzaldehyde **1a** reacted with sulfonohydrazide and bromine, which afforded the isolated 4-bromo-isoquinolinium-2-yl amide. Subsequently, butyraldehyde **2a** was added in ethanol in the presence of different bases (inorganic and organic bases). Gratifyingly, the expected *H*-pyrazolo[5,1-*a*]isoquinoline **3a** was obtained in 87% yield when K_2CO_3 was employed in the reaction. A similar yield was observed when K_3PO_4 was utilized as a replacement. Inferior results were displayed when other bases were used. With this promising result in hands, we started to investigate the one-pot multi-component reaction of 2-alkynylbenzaldehyde **1a**, sulfonohydrazide, bromine, and butyraldehyde **2a** (Scheme 2, Eq. 2). After screening different solvents, bases, and temperatures, we finally identified that the reaction proceeded efficiently in ethanol at 70 °C in the presence of 3.0 equiv of K_3PO_4 as base with a 45% isolated yield.



Scheme 2. Initial studies for multi-component reaction of 2-alkynylbenzaldehyde **1a**, sulfonohydrazide, bromine, and butyraldehyde **2a**.

Under the optimized conditions [K_3PO_4 (3.0 equiv), EtOH, 70 °C], we then examined the reaction scope of this multi-component reaction (Table 1). We found that the condition was demonstrated to be useful for various 2-alkynylbenzaldehydes. Both electron-rich and electron-poor 2-alkynylbenzaldehydes are workable in this process. Besides bromine, iodine was a suitable partner as well in this multi-component reaction. For instance, 2-alkynylbenzaldehyde **1a** reacted with sulfonohydrazide, iodine, and butyraldehyde **2a** leading to the desired 1-ethyl-6-iodo-5-phenyl*H*-pyrazolo[5,1-*a*]isoquinoline **3b** in 75% yield (Table 1, entry 2). We also tested other ketones with α hydrogen. Reaction of 2-alkynylbenzaldehyde **1a**, sulfonohydrazide, bromine, and acetophenone **2b** gave rise to the 6-bromo-2,5-diphenyl*H*-pyrazolo[5,1-*a*]isoquinoline **3c** in 50% yield (Table 1, entry 3). A similar result was obtained when cyclohexanone **2c** was utilized in the reaction (Table 1, entry 4). When iodine was used in the reaction of 2-alkynylbenzaldehyde **1a**, sulfonohydrazide, and cyclohexanone **2c**, the desired product **3e** was isolated with 62% yield (Table 1, entry 5). Pentan-3-one **2d** was found to be a good substrate as well and the expected 6-bromo-2-ethyl-1-methyl-5-phenyl*H*-pyrazolo[5,1-*a*]isoquinoline **3f** was generated in 54% yield (Table 1, entry 6). When 2-alkynylbenzaldehyde with cyclopropyl or *n*-butyl group attached to the C≡C triple bond was employed in the multi-component reactions of sulfonohydrazide, bromine or iodine, and butyraldehyde **2a**, the corresponding products were furnished in good yields (Table 1, entries 7–10). Meanwhile, chloro- or fluoro-substituted 2-alkynylbenzaldehydes **1d**–**g** were explored (Table 1, entries 11–16), and all reactions proceeded efficiently to generate the desired products in good yields.

Table 1
Multi-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, electrophile, and ketone or aldehyde

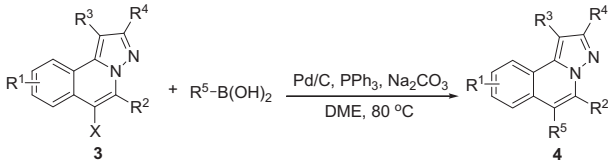


Entry	R^1, R^2	X_2	R^3, R^4	Yield[a] (%)
1	H, Ph (**1a**)	Br_2	Et, H (**2a**)	45 (**3a**)
2	H, Ph (**1a**)	I_2	Et, H (**2a**)	75 (**3b**)
3	H, Ph (**1a**)	Br_2	H, Ph (**2b**)	50 (**3c**)
4	H, Ph (**1a**)	Br_2	$-(CH_2)_4-$ (**2c**)	50 (**3d**)
5	H, Ph (**1a**)	I_2	$-(CH_2)_4-$ (**2c**)	62 (**3e**)
6	H, Ph (**1a**)	Br_2	Me, Et (**2d**)	54 (**3f**)
7	H, cyclopropyl (**1b**)	Br_2	Et, H (**2a**)	71 (**3g**)
8	H, cyclopropyl (**1b**)	I_2	Et, H (**2a**)	86 (**3h**)
9	H, *n*-Bu (**1c**)	Br_2	Et, H (**2a**)	46 (**3i**)
10	H, *n*-Bu (**1c**)	I_2	Et, H (**2a**)	80 (**3j**)
11	5-Cl, Ph (**1d**)	Br_2	Et, H (**2a**)	50 (**3k**)
12	4-F, Ph (**1e**)	Br_2	Et, H (**2a**)	60 (**3l**)
13	4-F, cyclopropyl (**1f**)	Br_2	Et, H (**2a**)	60 (**3m**)
14	4-F, cyclopropyl (**1f**)	I_2	Et, H (**2a**)	76 (**3n**)
15	4-F, *n*-Bu (**1g**)	Br_2	Et, H (**2a**)	55 (**3o**)
16	4-F, *n*-Bu (**1g**)	I_2	Et, H (**2a**)	78 (**3p**)

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.

After successful generation of 6-halo-*H*-pyrazolo[5,1-*a*]-isoquinoline **3**, we considered to introduce more diversities in the *H*-pyrazolo[5,1-*a*]isoquinoline scaffold via palladium-catalyzed cross-coupling reaction. Thus, Suzuki–Miyaura coupling reaction[11] using arylboronic acid derivatives was investigated. After optimization of the reaction conditions, we found that the reactions worked efficiently in the presence of Pd/C (5 mol %), PPh_3 (10 mol %), and Na_2CO_3 in DME at 80 °C (Table 2). As expected, all the reactions proceeded well to afford the desired product **4** in good to excellent yields. For example, reaction of 6-bromo-1-ethyl-5-phenyl *H*-pyrazolo[5,1-*a*]isoquinoline **3a** with 4-methoxyphenylboronic acid gave rise to the corresponding product **4a** in 88% yield (Table 2, entry 1). When 4-acetylphenylboronic acid was used as a partner, compound **4b** was isolated with 76% yield (Table 2, entry 2). Compound **3e** was a suitable substrate as well in the reaction of 4-methoxyphenylboronic acid, which furnished the desired product **4c** in 80% yield (Table 2, entry 3). Excellent yields were obtained when fluoro-substituted *H*-pyrazolo[5,1-*a*]isoquinoline **3l** or **3p** was employed in the coupling reaction (Table 2, entries 6 and 7).

Table 2
Palladium-catalyzed cross-coupling reactions of 6-halo-*H*-pyrazolo[5,1-*a*]isoquinoline **3** with arylboronic acids



Entry	Substrate **3**	R^5	Product **4**	Yield[a] (%)
1	**3a**	4-$MeOC_6H_4$	**4a**	88
2	**3a**	4-AcC_6H_4	**4b**	76
3	**3e**	4-$MeOC_6H_4$	**4c**	80
4	**3g**	4-$MeOC_6H_4$	**4d**	91
5	**3j**	4-AcC_6H_4	**4e**	77
6	**3l**	4-AcC_6H_4	**4f**	99
7	**3p**	4-$MeOC_6H_4$	**4g**	93

[a] Isolated yield based on 6-halo-*H*-pyrazolo[5,1-*a*]isoquinoline **3**.

3. Conclusions

In summary, we have described a multi-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, electrophile (bromine or iodine), and ketone or aldehyde under mild conditions, which generates the halo-containing *H*-pyrazolo[5,1-*a*]isoquinolines in good yields. In the reaction process, intermolecular condensation, electrophilic cyclization, nucleophilic addition, intramolecular condensation, and aromatization may be involved. The resulting halo-containing *H*-pyrazolo[5,1-*a*]isoquinolines could be further decorated via palladium-catalyzed Suzuki–Miyaura cross-coupling reactions to afford the functionalized *H*-pyrazolo[5,1-*a*]isoquinoline derivatives. We believe that this method provides an excellent complement for the *H*-pyrazolo[5,1-*a*]isoquinoline synthesis. Further efforts for the focused library construction and screening for biological activity of these small molecules are ongoing in our laboratory, and the result will be reported in due course.

4. Experimental section

4.1. General

All reactions were performed in test tubes under nitrogen atmosphere. 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 (house vacuum) at 25–35 °C. Commercial reagents and solvents were used as received.

General procedure for multi-component reactions of 2-alkynylbenzaldehyde, sulfonohydrazide, electrophile, and ketone or aldehyde: A solution of 2-alkynylbenzaldehyde **1** (0.3 mmol), sulfonohydrazide (0.3 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 10 min in a tube. Then Br_2 or I_2 (0.33 mmol, 1.1 equiv) were added. The reaction mixture was stirred at room temperature for 10 min with Br_2 or 24 h with I_2. After workup with $Na_2S_2O_3$, ketone or aldehyde **3** (0.6 mmol, 2.0 equiv) and K_3PO_4 (0.9 mmol, 3.0 equiv) were added to the solution. The reaction mixture was stirred at 70 °C vigorously until completion of the reaction. Then the mixture was diluted with ethyl acetate (5.0 mL) and quenched with water (5.0 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with PE/EA=50/1 to 20/1) to provide the desired product **3**.

*4.1.1. 6-Bromo-1-ethyl-5-phenylH-pyrazolo[5,1-a]isoquinoline (**3a**).* Light yellow solid, mp: 141.1–141.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.43 (t, *J*=7.3 Hz, 3H), 3.04–3.10 (m, 2H), 7.49–7.64 (m, 7H), 7.78 (s, 1H), 8.23–8.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.6, 109.0, 117.4, 123.4, 125.5, 127.8, 128.3, 128.5, 128.8, 129.5, 130.1, 133.5, 134.6, 138.0, 141.1; HRMS calcd for $C_{19}H_{16}BrN_2$ (M^++H): 351.0497, found: 351.0498.

*4.1.2. 1-Ethyl-6-iodo-5-phenylH-pyrazolo[5,1-a]isoquinoline (**3b**).* Light yellow solid, mp: 144.5–145.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.41 (t, *J*=7.3 Hz, 3H), 3.02–3.08 (m, 2H), 7.41–7.43 (m, 2H), 7.51–7.61 (m, 7H), 7.74 (s, 1H), 8.16 (d, *J*=7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.6, 87.2, 117.1, 123.4, 125.3, 128.1, 128.2, 128.9, 129.5, 130.0, 130.3, 133.1, 133.9, 138.4, 141.2, 141.6; HRMS calcd for $C_{19}H_{16}IN_2$ (M^++H): 399.0358, found: 399.0366.

*4.1.3. 6-Bromo-2,5-diphenylH-pyrazolo[5,1-a]isoquinoline (**3c**).* Light yellow solid, mp: 147.6–148.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.26–7.42 (m, 4H), 7.50–7.60 (m, 6H), 7.83–7.85 (m, 2H), 7.97–8.02 (m, 1H), 8.08–8.10 (m, 1H), 8.17–8.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.1, 108.9, 123.7, 123.9, 126.5, 127.9, 128.3, 128.4, 128.5, 128.7, 128.8, 129.4, 129.7, 130.7, 133.0, 134.1, 137.9, 139.7, 152.6; HRMS calcd for $C_{23}H_{16}BrN_2$ (M^++H): 399.0497, found: 399.0501.

*4.1.4. 5-Bromo-6-phenyl-9,10,11,12-tetrahydroindazolo[3,2-a]isoquinoline (**3d**).* Light yellow solid, mp: 225.4–226.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.83–1.96 (m, 4H), 2.79–2.81 (m, 2H), 3.04–3.06 (m, 2H), 7.48–7.58 (m, 7H), 8.11–8.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 23.1, 23.5, 24.4, 107.7, 110.2, 123.4, 125.4, 127.5, 127.6, 127.8, 128.5, 128.6, 129.3, 130.3, 133.8, 134.8, 137.9, 151.8; HRMS calcd for $C_{21}H_{18}BrN_2$ (M^++H): 377.0653, found: 377.0664.

*4.1.5. 5-Iodo-6-phenyl-9,10,11,12-tetrahydroindazolo[3,2-a]isoquinoline (**3e**).* Light yellow solid, mp: 207.0–207.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.83–1.91 (m, 4H), 2.77–2.80 (m, 2H), 3.03–3.06 (m, 2H), 7.40–7.42 (m, 2H), 7.49–7.56 (m, 5H), 8.04–8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 23.1, 23.5, 24.3, 85.7, 110.0, 123.4, 125.2, 127.8, 127.9, 128.8, 129.4, 130.2, 130.3, 132.7, 134.1, 138.5, 141.5, 151.8; HRMS calcd for $C_{21}H_{18}IN_2$ (M^++H): 425.0515, found: 425.0522.

*4.1.6. 6-Bromo-2-ethyl-1-methyl-5-phenylH-pyrazolo[5,1-a]isoquinoline (**3f**).* Light yellow solid, mp: 138.5–139.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.19 (t, *J*=7.3 Hz, 3H), 2.53 (s, 3H), 2.71–2.77 (m, 2H), 7.49–7.57 (m, 7H), 8.17–8.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 14.2, 20.1, 107.5, 107.6, 123.1, 125.6, 127.5, 127.6, 127.8, 128.4, 128.7, 129.2, 130.5, 134.7, 137.9, 155.5; HRMS calcd for $C_{20}H_{18}BrN_2$ (M^++H): 365.0653, found: 365.0661.

*4.1.7. 6-Bromo-5-cyclopropyl-1-ethylH-pyrazolo[5,1-a]isoquinoline (**3g**).* Light yellow solid, mp: 87.3–88.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.24–1.28 (m, 2H), 1.31–1.35 (m, 2H), 1.40 (t, *J*=7.8 Hz, 3H), 2.26–2.33 (m, 1H), 2.97–3.03 (m, 2H), 7.48–7.53 (m, 2H), 7.83 (s, 1H), 8.09–8.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 14.0, 14.1, 19.6, 110.8, 116.9, 123.0, 124.8, 127.1, 127.4, 128.5, 133.2, 137.8, 140.1; HRMS calcd for $C_{16}H_{16}BrN_2$ (M^++H): 315.0497, found: 315.0486.

*4.1.8. 5-Cyclopropyl-1-ethyl-6-iodoH-pyrazolo[5,1-a]isoquinoline (**3h**).* Light yellow solid, mp: 82.8–84.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.14–1.18 (m, 2H), 1.40 (t, *J*=7.3 Hz, 3H), 1.41–1.46 (m, 2H), 2.24–2.28 (m, 1H), 2.97–3.02 (m, 2H), 7.46–7.49 (m, 2H), 7.81 (s, 1H), 8.03–8.05 (m, 1H), 8.09–8.13 (m, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 12.4, 14.0, 18.3, 19.6, 89.2, 116.8, 123.0, 124.5, 127.5, 127.8, 130.4, 132.3, 133.6, 140.0, 140.7; HRMS calcd for $C_{16}H_{16}IN_2$ (M^++H): 363.0358, found: 363.0357.

*4.1.9. 6-Bromo-5-butyl-1-ethylH-pyrazolo[5,1-a]isoquinoline (**3i**).* Light yellow solid, mp: 98.9–100.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 0.99 (t, J=7.3 Hz, 3H), 1.43 (t, J=7.3 Hz, 3H), 1.52–1.58 (m, 2H), 1.75–1.81 (m, 2H), 3.03–3.09 (m, 2H), 3.49–3.53 (m, 2H), 7.56–7.58 (m, 2H), 7.85 (s, 1H), 8.15–8.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 19.6, 22.9, 28.9, 31.6, 107.9, 117.3, 123.2, 124.8, 127.2, 127.3, 127.6, 128.4, 133.0, 139.5, 140.3; HRMS calcd for $C_{17}H_{20}BrN_2$ (M^++H): 331.0810, found: 331.0789.

*4.1.10. 5-Butyl-1-ethyl-6-iodoH-pyrazolo[5,1-a]isoquinoline (**3j**).* Light yellow solid, mp: 95.7–96.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.00 (t, J=7.3 Hz, 3H), 1.41 (t, J=7.3 Hz, 3H), 1.52–1.59 (m, 2H), 1.72–1.80 (m, 2H), 2.97–3.03 (m, 2H), 3.55–3.59 (m, 2H), 7.45–7.50 (m, 2H), 7.79 (s, 1H), 8.04–8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 19.6, 23.0, 29.0, 36.5, 85.7, 117.0, 123.2, 124.6, 127.3, 127.8, 130.1, 132.3, 133.3, 140.3, 142.4; HRMS calcd for $C_{17}H_{20}IN_2$ (M^++H): 379.0671, found: 379.0639.

*4.1.11. 6-Bromo-9-chloro-1-ethyl-5-phenylH-pyrazolo[5,1-a]isoquinoline (**3k**).* Light yellow solid, mp: 127.9–129.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.44 (t, J=7.3 Hz, 3H), 3.02–3.08 (m, 2H), 7.47–7.60 (m, 6H), 7.79 (s, 1H), 8.15–8.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.4, 108.2, 117.9, 122.7, 126.3, 127.0, 128.1, 128.8, 129.4, 129.6, 130.0, 132.4, 134.2, 138.3, 141.2; HRMS calcd for $C_{19}H_{15}BrClN_2$ (M^++H): 385.0107, found: 385.0113.

*4.1.12. 6-Bromo-1-ethyl-8-fluoro-5-phenylH-pyrazolo[5,1-a]isoquinoline (**3l**).* Light yellow solid, mp: 145.9–146.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.41 (t, J=7.3 Hz, 3H), 2.98–3.04 (m, 2H), 7.31–7.35 (m, 1H), 7.46–7.59 (m, 5H), 7.77 (s, 1H), 7.88–7.91 (m, 1H), 8.17–8.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.5, 107.7, 113.6 (d, $^2J_{CF}$=24 Hz), 116.6 (d, $^2J_{CF}$=23 Hz), 116.9, 122.1, 125.7 (d, $^3J_{CF}$=9 Hz), 128.8, 129.7, 130.0, 130.9 (d, $^3J_{CF}$=9 Hz), 133.2, 134.3, 139.1, 141.4, 162.0 (d, $^1J_{CF}$=247 Hz); HRMS calcd for $C_{19}H_{15}BrFN_2$ (M^++H): 369.0403, found: 369.0411.

*4.1.13. 6-Bromo-5-cyclopropyl-1-ethyl-8-fluoroH-pyrazolo[5,1-a]isoquinoline (**3m**).* Light yellow solid, mp: 159.1–160.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.28–1.34 (m, 4H), 1.40 (t, J=7.3 Hz, 3H), 2.27–2.34 (m, 1H), 2.92–2.97 (m, 2H), 7.19–7.23 (m, 1H), 7.79–7.82 (m, 2H), 8.02–8.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 13.8, 14.2, 19.5, 109.4, 112.8 (d, $^2J_{CF}$=24 Hz), 115.8 (d, $^2J_{CF}$=23 Hz), 116.4, 121.3, 125.3 (d, $^3J_{CF}$=9 Hz), 130.8 (d, $^3J_{CF}$=9 Hz), 132.8, 139.0, 140.3, 161.7 (d, $^1J_{CF}$=246 Hz); HRMS calcd for $C_{16}H_{15}BrFN_2$ (M^++H): 333.0403, found: 333.0392.

*4.1.14. 5-Cyclopropyl-1-ethyl-8-fluoro-6-iodoH-pyrazolo[5,1-a]isoquinoline (**3n**).* Light yellow solid, mp: 103.1–103.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.17–1.22 (m, 2H), 1.41 (t, J=7.3 Hz, 3H), 1.42–1.46 (m, 2H), 2.25–2.30 (m, 1H), 2.97–3.01 (m, 2H), 7.20–7.24 (m, 1H), 7.82 (s, 1H), 7.85–7.88 (m, 1H), 8.05–8.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 13.9, 18.5, 19.6, 87.4, 115.8 (d, $^2J_{CF}$=24 Hz), 116.3, 118.0 (d, $^2J_{CF}$=25 Hz), 121.1, 125.4 (d, $^3J_{CF}$=9 Hz), 132.9 (d, $^3J_{CF}$=9 Hz), 133.3, 140.2, 141.9, 161.9 (d, $^1J_{CF}$=245 Hz); HRMS calcd for $C_{16}H_{15}FIN_2$ (M^++H): 381.0264, found: 381.0264.

*4.1.15. 6-Bromo-5-butyl-1-ethyl-8-fluoroH-pyrazolo[5,1-a]isoquinoline (**3o**).* Light yellow solid, mp: 87.6–88.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 0.99 (t, J=7.3 Hz, 3H), 1.41 (t, J=7.3 Hz, 3H), 1.51–1.57 (m, 2H), 1.73–1.78 (m, 2H), 2.96–3.01 (m, 2H), 3.44–3.48 (m, 2H), 7.22–7.25 (m, 1H), 7.78–7.84 (m, 2H), 8.07–8.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.0, 19.5, 22.9, 28.8, 31.7, 106.5, 112.8 (d, $^2J_{CF}$=24 Hz), 115.7 (d, $^2J_{CF}$=23 Hz), 116.7, 121.3, 125.5 (d, $^3J_{CF}$=9 Hz), 130.6 (d, $^3J_{CF}$=9 Hz), 132.6, 140.5, 140.7, 161.9 (d, $^1J_{CF}$=246 Hz); HRMS calcd for $C_{17}H_{19}BrFN_2$ (M^++H): 349.0716, found: 349.0701.

*4.1.16. 5-Butyl-1-ethyl-8-fluoro-6-iodoH-pyrazolo[5,1-a]isoquinoline (**3p**).* Light yellow solid, mp: 93.2–94.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.00 (t, J=7.3 Hz, 3H), 1.40 (t, J=7.3 Hz, 3H), 1.51–1.59 (m, 2H), 1.70–1.75 (m, 2H), 2.93–2.98 (m, 2H), 3.50–3.56 (m, 2H), 7.16–7.20 (m, 1H), 7.74–7.78 (m, 2H), 8.00–8.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.0, 19.5, 23.0, 28.9, 36.6, 83.8, 115.5 (d, $^2J_{CF}$=24 Hz), 116.5, 117.9 (d, $^2J_{CF}$=24 Hz), 121.1, 125.5 (d, $^3J_{CF}$=9 Hz), 132.5 (d, $^3J_{CF}$=9 Hz), 132.8, 140.5, 143.5, 162.0 (d, $^1J_{CF}$=246 Hz); HRMS calcd for $C_{17}H_{19}FIN_2$ (M^++H): 397.0577, found: 397.0566.

4.2. General procedure for palladium-catalyzed cross-coupling reactions of 6-halo-*H*-pyrazolo[5,1-*a*]isoquinoline 3 with arylboronic acids

To a solution of 6-halo-*H*-pyrazolo[5,1-*a*]isoquinoline **3** (0.2 mmol), boronic acid (0.3 mmol), and PPh_3 (0.036 mmol) in DME (2.0 mL) was added Na_2CO_3 (2.0 M, 1.0 mL) and 5% Pd/C (water content 54%) (0.01 mmol). The reaction mixture was stirred at 80 °C for 9 h. After filtration, the water layer was extracted twice with EtOAc (10 mL). The combined organic layers were washed with 10% NaOH (aq) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA=20/1 to 5/1) to give the product **4**.

*4.2.1. 1-Ethyl-6-(4-methoxyphenyl)-5-phenylH-pyrazolo[5,1-a]isoquinoline (**4a**).* Light yellow solid, mp: 219.7–220.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.47 (t, J=7.3 Hz, 3H), 3.11–3.16 (m, 2H), 3.76 (s, 3H), 6.79 (d, J=8.7 Hz, 2H), 7.09 (d, J=8.7 Hz, 2H), 7.23–7.30 (m, 5H), 7.38–7.45 (m, 2H), 7.57 (t, J=7.3 Hz, 1H), 7.82 (s, 1H), 8.32 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.7, 55.2, 113.5, 116.9, 123.3, 123.4, 125.6, 126.8, 126.9, 127.2, 128.1, 128.2, 128.6, 130.7, 130.8, 132.7, 133.7, 133.8, 136.8, 140.6, 158.5; HRMS calcd for $C_{26}H_{23}N_2O$ (M^++H): 379.1810, found: 379.1819.

*4.2.2. 1-(3-(1-Ethyl-5-phenylH-pyrazolo[5,1-a]isoquinolin-6-yl)phenyl)ethanone (**4b**).* Light yellow solid, mp: 203.5–204.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.48 (t, J=7.3 Hz, 3H), 2.47 (s, 3H), 3.12–3.17 (m, 2H), 7.24–7.29 (m, 5H), 7.35–7.44 (m, 4H), 7.60 (t, J=7.3 Hz, 1H), 7.78 (s, 1H), 7.82–7.85 (m, 2H), 8.33–8.36 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 19.7, 26.7, 117.1, 122.6, 123.5, 125.7, 126.4, 127.1, 127.2, 127.5, 128.2, 128.5, 128.6, 129.9, 130.8, 131.8, 133.2, 133.9, 136.4, 136.9, 137.0, 140.9, 197.9; HRMS calcd for $C_{27}H_{23}N_2O$ (M^++H): 391.1810, found: 391.1809.

*4.2.3. 5-(4-Methoxyphenyl)-6-phenyl-9,10,11,12-tetrahydroindazolo[3,2-a]isoquinoline (**4c**).* Light yellow solid, mp: 214.7–215.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.88–1.98 (m, 4H), 2.83–2.86 (m, 2H), 3.14–3.17 (m, 2H), 3.77 (s, 3H), 6.78 (d, J=8.7 Hz, 2H), 7.06 (d, J=8.2 Hz, 2H), 7.23–7.31 (m, 5H), 7.38–7.42 (m, 2H), 7.51–7.55 (m, 1H), 8.23 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 23.2, 23.6, 24.3, 55.2, 109.6, 113.4, 114.6, 116.1, 123.3, 125.4, 126.5, 126.7, 126.8, 127.9, 128.1, 128.8, 130.7, 131.0, 132.8, 133.7, 134.1, 151.2, 158.4; HRMS calcd for $C_{28}H_{25}N_2O$ (M^++H): 405.1967, found: 405.1961.

*4.2.4. 5-Cyclopropyl-1-ethyl-6-(4-methoxyphenyl)H-pyrazolo[5,1-a]isoquinoline (**4d**).* Light yellow solid, mp: 113.9–114.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 0.62–0.66 (m, 2H), 0.84–0.89 (m, 2H), 1.46 (t, J=7.3 Hz, 3H), 2.14–2.19 (m, 1H), 3.09–3.14 (m, 2H), 3.90 (s, 3H), 7.03 (d, J=8.2 Hz, 2H), 7.27 (d, J=8.7 Hz, 2H), 7.35–7.41 (m, 2H), 7.48–7.52 (m, 1H), 7.91 (s, 1H), 8.26 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3, 12.1, 14.2, 19.7, 55.4, 113.8, 116.6, 123.1, 125.0,

126.2, 126.5, 126.6, 129.2, 130.5, 132.5, 133.5, 136.5, 139.9, 158.9; HRMS calcd for $C_{23}H_{23}N_2O$ (M^++H): 343.1810, found: 343.1799.

*4.2.5. 1-(3-(5-Butyl-1-ethylH-pyrazolo[5,1-a]isoquinolin-6-yl)phenyl)ethanone (**4e**).* Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 0.77 (t, J=7.3 Hz, 3H), 1.26–1.31 (m, 2H), 1.48 (t, J=7.3 Hz, 3H), 1.69–1.74 (m, 2H), 2.64 (s, 3H), 2.91–2.96 (m, 2H), 3.10–3.16 (m, 2H), 7.11 (d, J=7.8 Hz, 1H), 7.36 (t, J=8.2 Hz, 1H), 7.50–7.56 (m, 2H), 7.64 (t, J=7.3 Hz, 1H), 7.91–7.95 (m, 2H), 8.08 (d, J=7.8 Hz, 1H), 8.28 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.2, 19.7, 22.8, 26.8, 29.2, 30.0, 117.0, 120.9, 123.3, 124.8, 126.0, 126.6, 126.9, 127.7, 129.1, 130.1, 131.0, 133.5, 135.8, 137.6, 137.8, 138.0, 140.2, 197.9; HRMS calcd for $C_{25}H_{27}N_2O$ (M^++H): 371.2123, found: 371.2110.

*4.2.6. 1-(3-(1-Ethyl-8-fluoro-5-phenylH-pyrazolo[5,1-a]isoquinolin-6-yl)phenyl)ethanone (**4f**).* Light yellow solid, mp: 187.0–188.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.47 (t, J=7.3 Hz, 3H), 2.49 (s, 3H), 3.08–3.14 (m, 2H), 6.99–7.02 (m, 1H), 7.25–7.41 (m, 8H), 7.76 (s, 1H), 7.83–7.86 (m, 2H), 8.30–8.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.6, 26.7, 111.8 (d, $^2J_{CF}$=23 Hz), 115.8 (d, $^2J_{CF}$=24 Hz), 116.6, 122.0, 122.3, 125.7 (d, $^3J_{CF}$=9 Hz), 127.4, 128.2, 128.7, 128.8, 130.6, 131.6, 132.0 (d, $^3J_{CF}$=9 Hz), 132.9, 133.5, 136.2, 136.5, 137.1, 138.0, 141.2, 161.4 (d, $^1J_{CF}$=245 Hz), 197.7; HRMS calcd for $C_{27}H_{22}FN_2O$ (M^++H): 409.1716, found: 409.1718.

*4.2.7. 5-Butyl-1-ethyl-8-fluoro-6-(4-methoxyphenyl)H-pyrazolo[5,1-a]isoquinoline (**4g**).* Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 0.80 (t, J=7.3 Hz, 3H), 1.27–1.33 (m, 2H), 1.45 (t, J=7.3 Hz, 3H), 1.67–1.71 (m, 2H), 2.94–2.98 (m, 2H), 3.04–3.08 (m, 2H), 3.90 (s, 3H), 6.85–6.89 (m, 1H), 7.05 (d, J=7.8 Hz, 2H), 7.20–7.23 (m, 3H), 7.89 (s, 1H), 8.19–8.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.1, 19.6, 22.9, 29.2, 30.0, 55.4, 111.6 (d, $^2J_{CF}$=23 Hz), 114.2, 114.7 (d, $^2J_{CF}$=24 Hz), 116.3, 121.4, 125.2 (d, $^3J_{CF}$=9 Hz), 127.8, 128.7, 131.9, 133.0 (d, $^3J_{CF}$=9 Hz), 133.1, 139.2, 140.1, 159.2, 161.3 (d, $^1J_{CF}$=245 Hz); HRMS calcd for $C_{24}H_{26}FN_2O$ (M^++H): 377.2029, found: 377.2021.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.12.005.

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