Tandem Reactions of *N*′-(2-Alkynylbenzylidene)hydrazides with Silyl Enolates: A Facile Route to *H*-Pyrazolo[5,1-*a*]isoquinolines

Xingxin Yu,[†] Zhiyuan Chen,[†] Xiaodi Yang,[§] and Jie Wu*[,†,‡]

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China, State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China, and Laboratory of Advanced Materials, Fudan University, 220 Handan Road, Shanghai 200433, China

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A silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with silyl enolate is described, which generates the unexpected *H*-pyrazolo[5,1-*a*]isoquinolines in good to excellent yields. Intramolecular cyclization, nucleophilic addition, condensation, and aromatization may be involved in the reaction process.

Introduction

High-throughput screening has created a critical demand to develop practical routes for rapid chemical synthesis of natural-product-like molecules.[1] Among the approaches utilized, tandem reactions have been recognized as a powerful method for combinatorial synthesis of small molecule libraries.[2] 1,2-Dihydroisoquinoline and related compounds are found abundantly in nature and many alkaloids exist this kind of scaffold.[3] For instance, the lamellarin alkaloids, a family of novel marine natural products, contain a highly substituted fused 1,2-dihydroisoquinoline core.[4] Among this family, lamellarin D is a potent inhibitor of human topoisomerase I[5] and lamellarin α-20-sulfate shows selective inhibition against HIV-1 integrase in vitro.[6,7] We are interested in development of a methodology for the construction of 1,2-dihydroisoquinoline library.[8–10] Subsequent biological assay revealed that this kind of compound displayed promising activity as PTP1B inhibitor. This result prompted us to undertake preparation of structural novel 1,2-dihydroisoquinolines, with an expectation for finding better hits in the assays.

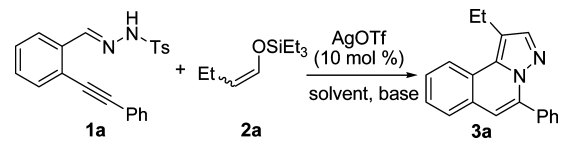
Although several efficient methods have been appeared for the formation of 1,2-dihydroisoquinoline derivatives recently,[8–13] development of novel and efficient routes for the generation of functionalized 1,2-dihydroisoquinolines under mild conditions is still of high interest. Recently, we identified that *N*′-(2-alkynylbenzylidene)hydrazide was a versatile building block leading to biologically active isoquinoline-related compounds.[9] Herein, we would like to disclose another application, which reacts with silyl enolate under mild conditions giving rise to the unexpected *H*-pyrazolo[5,1-*a*]isoquinoline in good to excellent yields.

Result and Discussion

N′-(2-Alkynylbenzylidene)hydrazide could be easily accessed via condensation of 2-alkynylbenzaldehyde with hydrazine. Since the treatment of *N*′-(2-alkynylbenzylidene-)hydrazide in the presence of suitable Lewis acid would lead to isoquinolinium intermediate,[9] we anticipated that the presence of a nucleophile, such as silyl enolate, could provide access to functionalized 1,2-dihydroisoquinolines after subsequent reaction processes. To identify suitable conditions for this proposed transformation, we first evaluated the tandem cyclization-nucleophilic addition of *N*′-(2-alkynylbenzylidene)hydrazide **1a** with silyl enoalte **2a** (Scheme 1). As described previously, silver triflate was the most effective catalyst for the isoquinolinium intermediate generation.[9] Thus, the AgOTf-catalyzed reaction was carried out in the presence of Na_2CO_3 as base in dichloroethane. However, only isoquinolinium intermediate was isolated, and no further transformation was observed. Similar results were obtained when the solvent was changed to THF, CH_3CN, toluene, or 1,4-dioxane. Further screening of solvents led to the identification of CH_3CN/DMF (v/v 1:3) as the most effective condition for the transformation, with an isolated unexpected product in high yield (97%). Structural identification revealed that the compound obtained was the *H*-pyrazolo[5,1-*a*]isoquinoline **3a**. Subsequent reaction optimization recognized that 3.0 equiv of Na_2CO_3 was the best choice after base screening.

Using AgOTf-catalzyed conditions (3.0 equiv of Na_2CO_3, CH_3CN/DMF), silyl enolates **2** reacted with various *N*′-(2-

Scheme 1. Initial Studies for the Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide **1a** and Silyl Enolate **2a**



* To whom correspondence should be addressed. E-mail: jie_wu@fudan.edu.cn.
[†] Department of Chemistry, Fudan University.
[‡] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry.
[§] Laboratory of Advanced Materials, Fudan University.

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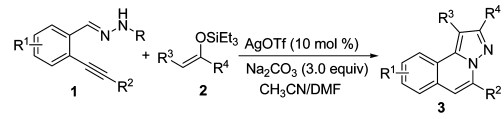
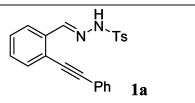
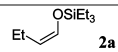
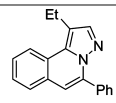
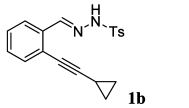
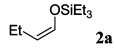
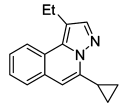
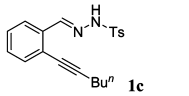
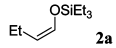
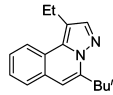
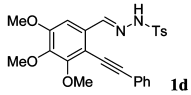
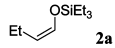
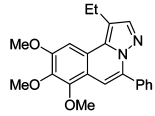
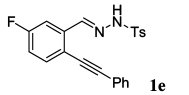
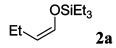
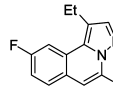
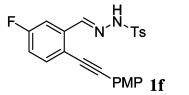
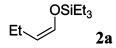
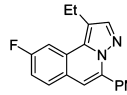
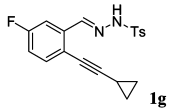
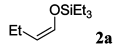
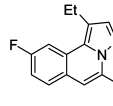
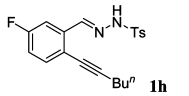
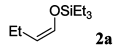
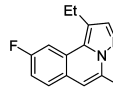
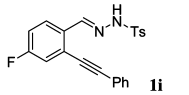
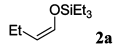
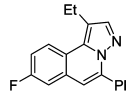
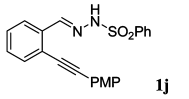
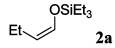
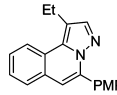
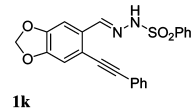
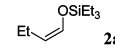
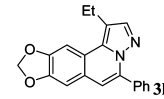
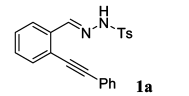
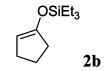
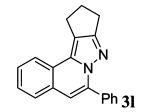
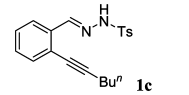
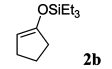
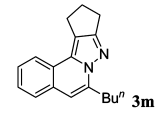
Table 1. Silver Triflate-Catalyzed Reactions of *N*′-(2-Alkynylbenzylidene)hydrazides **1** with Silyl Enolate **2**



Entry	Substrate **1**	Substrate **2**	Product	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	97
2	 **1b**	 **2a**	 **3b**	91
3	 **1c**	 **2a**	 **3c**	84
4	 **1d**	 **2a**	 **3d**	80
5	 **1e**	 **2a**	 **3e**	96
6	 **1f**	 **2a**	 **3f**	97
7	 **1g**	 **2a**	 **3g**	94
8	 **1h**	 **2a**	 **3h**	82
9	 **1i**	 **2a**	 **3i**	92
10	 **1j**	 **2a**	 **3j**	98
11	 **1k**	 **2a**	 **3k**	93
12	 **1a**	 **2b**	 **3l**	95
13	 **1c**	 **2b**	 **3m**	60
14	**1e**	**2b**	**3n**	81
15	**1f**	**2b**	**3o**	60
16	**1g**	**2b**	**3p**	61
17	**1h**	**2b**	**3q**	67
18	**1i**	**2b**	**3r**	78
19	**1f**	**2c**	**3s**	87

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

alkynylbenzylidene)hydrazides **1** to generate a number of *H*-pyrazolo[5,1-*a*]isoquinolines **3** (Table 1). This silver-catalyzed *H*-pyrazolo[5,1-*a*]isoquinoline formation was found to be workable with *N*′-(2-alkynylbenzylidene)hydrazides **1a**−**1k** with electron-withdrawing and -donating substituents on the aromatic backbone (Table 1, entries 1−11). In addition to the aromatic groups attached to the C≡C triple bond, cyclopropyl and *n*-butyl groups were found suitable as well to cleanly generate the desired products in good yields. Furthermore, reactions of *N*′-(2- alkynylbenzylidene)hydrazides **1** with silyl enolates **2b** or **2c** provided the corresponding *H*-pyrazolo[5,1-*a*]isoquinolines with good yields (Table 1, entries 12−19). The structure of **3i** was verified by X-ray diffraction analysis meanwhile (Figure 1).

For the reaction process, we reasoned that *N*′-(2-alkynylbenzylidene)hydrazide **1** would be cyclized to isoquinolinium intermediate **A** in the presence of silver triflate. The subsequent nucleophilic addition of silyl enolate **2** to isoquinolinium intermediate **A** would afford intermediate **B**, which then underwent intramolecular condensation and subsequent aromatization to generate the *H*-pyrazolo[5,1-*a*]isoquinoline **3** (Scheme 2).

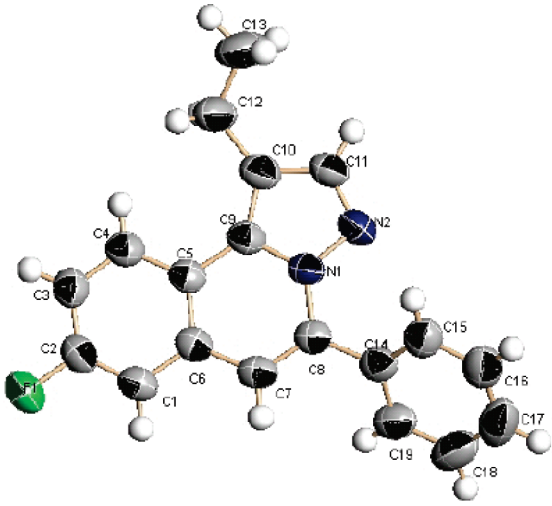
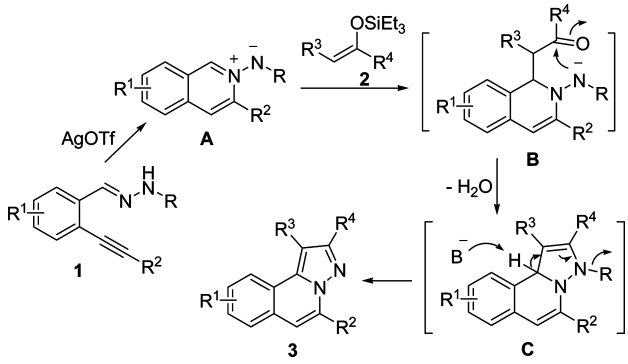


Figure 1. ORTEP illustration of compound **3i** (30% probability ellipsoids).

Scheme 2. Possible Mechanism for Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide **1** with Silyl Enolate **2**



Conclusion

In conclusion, we have described silver triflate catalyzed tandem reactions of *N*′-(2-alkynylbenzylidene)hydrazides with silyl enolates. A number of *H*-pyrazolo[5,1-*a*]isoquinolines are generated in good to excellent yields using this approach. In the reaction process, intramolecular cyclization, nucleophilic addition, condensation, and aromatization may be involved. Small library construction and further studies by adaptation of the method described herein for the synthesis of 1,2-dihydroisoquinoline alkaloids are currently in progress and the results will be reported in due course.

Experimental Section

General Experimental Procedure for Silver Triflate-Catalyzed Reactions of *N*′-(2-Alkynylbenzylidene)hydrazides 1 with Silyl Enolate 2. A mixture of *N*′-(2-Alkynylbenzylidene)hydrazides **1** (0.2 mmol) and AgOTf (5.2 mg, 10 mol %) in CH_3CN (1.0 mL) was stirred at 70 °C for 1 h. Then, silyl enolate **2** (0.6 mmol, 3.0 equiv) and Na_2CO_3 (0.6 mmol, 3.0 equiv) in DMF (3.0 mL) were added subsequently. The reaction mixture was stirred at room temperature vigorously. After completion of the reaction as indicated by TLC, 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 obtained was purified by flash chromatography column on silica gel (eluting with PE/EA = 60/1 to 20/1) to provide the desired product **3**.

1-Ethyl-5-phenyl-*H*-pyrazolo[5,1-*a*]isoquinoline 3a. Yield: 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (t, J = 7.3 Hz, 3H), 3.07−3.13 (m, 2H), 6.95 (s, 1H), 7.46−7.57 (m, 5H), 7.70 (d, J = 7.3 Hz, 1H), 7.83−7.85 (m, 3H), 8.24 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.6, 112.5, 117.2, 123.3, 125.5, 127.2, 127.3, 127.4, 128.4, 129.3, 129.5, 129.6, 134.2, 134.6, 138.7, 140.4. HRMS calcd for $C_{19}H_{17}N_2$ (M^+ + H): 273.1392, found 273.1380.

5-Cyclopropyl-1-ethyl-*H*-pyrazolo[5,1-*a*]isoquinoline 3b. Yield: 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87−0.91 (m, 2H), 1.16−1.18 (m, 2H), 1.43 (t, J = 7.8 Hz, 3H), 2.63−2.67 (m, 1H), 3.07−3.09 (m, 2H), 6.60 (s, 1H), 7.45−7.50 (m, 2H), 7.61 (d, J = 7.4 Hz, 1H), 7.90 (s, 1H), 8.19 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 6.9, 11.5, 14.2, 19.5, 106.8, 117.2, 123.2, 124.8, 126.5, 126.6, 129.5, 134.1, 140.1, 140.9. HRMS calcd for $C_{16}H_{17}N_2$ (M^+ + H): 237.1392, found 237.1372.

5-Butyl-1-ethyl-*H*-pyrazolo[5,1-*a*]isoquinoline 3c. Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.3 Hz, 3H), 1.43 (t, J = 7.3 Hz, 3H), 1.48−1.55 (m, 2H), 1.82−1.88 (m, 2H), 3.05−3.09 (m, 2H), 3.10−3.16 (m, 2H), 6.76 (s, 1H), 7.46−7.52 (m, 2H), 7.65 (d, J = 7.3 Hz, 1H), 7.86 (s, 1H), 8.20 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.2, 19.5, 22.7, 29.0, 30.8, 109.3, 117.0, 123.2, 124.9, 126.4, 126.6, 126.9, 129.5, 134.1, 139.6, 139.9. HRMS calcd for $C_{17}H_{21}N_2$ (M^+ + H): 253.1705, found 253.1694.

1-Ethyl-7,8,9-trimethoxy-5-phenyl-*H*-pyrazolo[5,1-*a*]isoquinoline 3d. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (t, J = 7.3 Hz, 3H), 3.07−3.12 (m, 2H), 3.99 (s, 3H), 4.03 (s, 3H), 4.04 (s, 3H), 7.26 (s, 1H), 7.46−7.53 (m, 4H), 7.81 (s, 1H), 7.84−7.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 19.6, 56.1, 61.2, 61.7, 100.6, 106.5, 116.1, 119.0, 122.1, 128.4, 129.0, 129.5, 134.3, 134.5, 136.9, 140.2, 141.5, 148.8, 153.6. HRMS calcd for $C_{22}H_{23}N_2O_3$ (M^+ + H): 363.1709, found 363.1704.

1-Ethyl-9-fluoro-5-phenyl-*H*-pyrazolo[5,1-*a*]isoquinoline 3e. Yield: 96%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (t, J = 7.4 Hz, 3H), 3.03−3.09 (m, 2H), 6.93 (s, 1H), 7.21−7.25 (m, 1H), 7.47−7.52 (m, 3H), 7.65−7.69 (m, 1H), 7.79−7.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.3, 108.8 (d, $^2J_{CF}$ = 24 Hz), 111.8, 115.6 (d, $^2J_{CF}$ = 24 Hz), 117.7, 126.1, 126.6 (d, $^3J_{CF}$ = 9 Hz), 128.4, 129.2, 129.3, 129.4, 133.9, 138.0, 140.3, 161.7 (d, $^1J_{CF}$ = 245 Hz). HRMS calcd for $C_{19}H_{16}FN_2$ (M^+ + H): 291.1298, found 291.1284.

1-Ethyl-9-fluoro-5-(4-methoxyphenyl)-*H*-pyrazolo[5,1-*a*]isoquinoline 3f. Yield: 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (t, J = 7.3 Hz, 3H), 3.02−3.07 (m, 2H), 3.86 (s, 3H), 6.84 (s, 1H), 7.03 (d, J = 8.7 Hz, 2H), 7.23−7.34 (m, 2H), 7.78 (d, J = 8.2 Hz, 2H), 7.84 (s, 1H), 8.16−8.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.5, 55.4, 110.9, 111.0, 111.9 (d, $^2J_{CF}$ = 22 Hz), 113.9, 115.3 (d, $^2J_{CF}$ = 23 Hz), 116.6, 121.9, 125.4 (d, $^3J_{CF}$ = 9 Hz), 126.1, 130.8, 131.5 (d, $^3J_{CF}$ = 10 Hz), 134.3, 139.5, 140.5, 161.6 (d, $^1J_{CF}$ = 218 Hz). HRMS calcd for $C_{20}H_{18}FN_2O$ (M^+ + H): 321.1403, found 321.1389.

5-Cyclopropyl-1-ethyl-9-fluoro-*H*-pyrazolo[5,1-*a*]isoquinoline 3g. Yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85−0.89 (m, 2H), 1.15−1.20 (m, 2H), 1.44 (t, J = 7.3 Hz, 3H), 2.59−2.66 (m, 1H), 3.02−3.08 (m, 2H), 6.57 (s, 1H), 7.17−7.21 (m, 1H), 7.56−7.60 (m, 1H), 7.79−7.83 (m, 1H), 7.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 6.8, 11.4, 14.0, 19.3, 106.3, 108.6 (d, $^2J_{CF}$ = 24 Hz), 115.4 (d, $^2J_{CF}$ = 24 Hz), 117.6, 125.8 (d, $^3J_{CF}$ = 9 Hz), 126.0, 128.6 (d, $^3J_{CF}$ = 9 Hz), 133.4, 140.0, 140.1, 161.2 (d, $^1J_{CF}$ = 243 Hz). HRMS calcd for $C_{16}H_{16}FN_2$ (M^+ + H): 255.1298, found 255.1294.

5-Butyl-1-ethyl-9-fluoro-*H*-pyrazolo[5,1-*a*]isoquinoline 3h. Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.3 Hz, 3H), 1.44 (t, J = 7.3 Hz, 3H), 1.48−1.53 (m, 2H), 1.81−1.89 (m, 2H), 3.01−3.06 (m, 2H), 3.12 (t, J = 7.3 Hz, 2H), 6.73 (s, 1H), 7.19−7.23 (m, 1H), 7.59−7.65 (m, 1H), 7.81−7.83 (m, 1H), 7.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.1, 19.3, 22.6, 29.0, 30.6, 108.6 (d, $^2J_{CF}$ = 24 Hz), 108.7, 115.4 (d, $^2J_{CF}$ = 23 Hz), 117.5, 125.9 (d, $^3J_{CF}$ = 10 Hz), 126.0, 128.5 (d, $^3J_{CF}$ = 10 Hz), 133.4, 138.9, 139.8, 161.2 (d, $^1J_{CF}$ = 244 Hz). HRMS calcd for $C_{17}H_{20}FN_2$ (M^+ + H): 271.1611, found 271.1607.

1-Ethyl-8-fluoro-5-phenyl-*H*-pyrazolo[5,1-*a*]isoquinoline 3i. Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (t, J = 7.3 Hz, 3H), 3.03−3.09 (m, 2H), 6.89 (s, 1H), 7.26−7.37 (m, 2H), 7.46−7.53 (m, 3H), 7.81−7.85 (m, 3H), 8.18−8.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.5, 111.6, 112.1 (d, $^2J_{CF}$ = 22 Hz), 115.6 (d, $^2J_{CF}$ = 23 Hz), 116.7, 122.1, 125.5 (d, $^3J_{CF}$ = 9 Hz), 128.4, 129.4, 129.5, 131.5 (d, $^3J_{CF}$ = 10 Hz), 133.8, 134.3, 139.7, 140.7, 161.5 (d, $^1J_{CF}$ = 246 Hz). HRMS calcd for $C_{19}H_{16}FN_2$ (M^+ + H): 291.1298, found 291.1298.

1-Ethyl-5-(4-methoxyphenyl)-*H*-pyrazolo[5,1-*a*]isoquinoline 3j. Yield: 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (t, J = 7.8 Hz, 3H), 3.05−3.10 (m, 2H), 3.84 (s, 3H), 6.90 (s, 1H), 7.00−7.03 (m, 2H), 7.44−7.53 (m, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.76−7.79 (m, 2H), 7.84 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.6, 55.4, 111.9, 113.9, 117.1, 123.2, 125.3, 126.5, 127.0, 127.1, 129.7, 130.9, 134.6, 138.5, 140.3, 160.3. HRMS calcd for $C_{20}H_{19}N_2O$ (M^+ + H): 303.1497, found 303.1490.

1-Ethyl-5-phenyl-*H*-pyrazolo[5,1-*a*][1,3]dioxolo[8,9-*g*]isoquinoline 3k. Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, J = 7.3 Hz, 3H), 2.98−3.04 (m, 2H), 6.03 (s, 2H), 6.81 (s, 1H), 7.03 (s, 1H), 7.44−7.50 (m, 3H), 7.59 (s, 1H), 7.79−7.82 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.5, 101.6, 101.9, 105.3, 112.3, 115.4, 120.9, 125.5, 128.4, 129.0, 129.4, 134.2, 134.7, 137.1, 140.2, 147.5, 148.0. HRMS calcd for $C_{20}H_{17}N_2O_2$ (M^+ + H): 317.1290, found 317.1279.

5-Phenyl-*H*-cyclopenta[c]pyrazolo[5,1-*a*]isoquinoline 3l. Yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56−2.63 (m, 2H), 2.92−2.97 (m, 2H), 3.11−3.14 (m, 2H), 6.85 (s, 1H), 7.43−7.52 (m, 5H), 7.65−7.67 (m, 1H), 7.85−7.87 (m, 2H), 7.97−7.99 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 25.4, 30.3, 110.8, 118.3, 123.9, 124.5, 126.7, 126.9, 127.3, 128.4, 129.2, 129.4, 129.5, 133.5, 134.5, 139.5, 163.3. HRMS calcd for $C_{20}H_{17}N_2$ (M^+ + H): 285.1392, found 285.1382.

5-Butyl-*H*-cyclopenta[c]pyrazolo[5,1-*a*]isoquinoline 3m. Yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.3 Hz, 3H), 1.48−1.55 (m, 2H), 1.83−1.91 (m, 2H), 2.60−2.65 (m, 2H), 3.00−3.02 (m, 2H), 3.09−3.15 (m, 4H), 6.68 (s, 1H), 7.43−7.46 (m, 2H), 7.60−7.63 (m, 1H), 7.94−7.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 24.4, 25.1, 29.0, 30.3, 31.0, 107.5, 118.0, 123.8, 123.9, 126.0, 126.1, 127.1, 129.5, 133.0, 140.4, 162.8. HRMS calcd for $C_{18}H_{21}N_2$ (M^+ + H): 265.1705, found 265.1691.

9-Fluoro-5-phenyl-*H*-cyclopenta[*c*]pyrazolo[5,1-*a*]isoquinoline 3n. Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62−2.69 (m, 2H), 2.99−3.02 (m, 2H), 3.14−3.17 (m, 2H), 6.87 (s, 1H), 7.22−7.27 (m, 1H), 7.50−7.57 (m, 3H), 7.62−7.68 (m, 2H), 7.89−7.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 25.3, 30.3, 109.0 (d, $^2J_{CF}$ = 22 Hz), 110.1, 115.9 (d, $^2J_{CF}$ = 24 Hz), 118.8, 125.7 (d, $^3J_{CF}$ = 10 Hz), 126.0, 128.4, 128.9 (d, $^3J_{CF}$ = 9 Hz), 129.2, 129.3, 132.8, 134.2, 138.8, 161.5 (d, $^1J_{CF}$ = 245 Hz), 163.3. HRMS calcd for $C_{20}H_{16}FN_2$ (M^+ + H): 303.1298, found 303.1296.

9-Fluoro-5-methoxyphenyl-*H*-cyclopenta[*c*]pyrazolo[5,1-*a*]isoquinoline 3o. Yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.57−2.64 (m, 2H), 2.93−2.97 (m, 2H), 3.09−3.12 (m, 2H), 3.87 (s, 3H), 6.76 (s, 1H), 7.02−7.04 (m, 2H), 7.20−7.25 (m, 1H), 7.30−7.32 (m, 1H), 7.79−7.82 (m, 2H), 7.93−7.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 25.3, 30.2, 55.4, 109.4, 111.3 (d, $^2J_{CF}$ = 22 Hz), 113.9, 115.2 (d, $^2J_{CF}$ = 24 Hz), 117.8, 121.0, 126.0 (d, $^3J_{CF}$ = 8 Hz), 126.4, 130.7, 131.3 (d, $^3J_{CF}$ = 10 Hz), 133.1, 140.3, 160.4, 161.8 (d, $^1J_{CF}$ = 245 Hz), 163.6. HRMS calcd for $C_{21}H_{18}FN_2O$ (M^+ + H): 333.1403, found 333.1386.

9-Fluoro-5-cyclopropyl-*H*-cyclopenta[*c*]pyrazolo[5,1-*a*]isoquinoline 3p. Yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86−0.90 (m, 2H), 1.16−1.19 (m, 2H), 2.60−2.66 (m, 3H), 3.01−3.05 (m, 2H), 3.09−3.12 (m, 2H), 6.48 (s, 1H), 7.15−7.21 (m, 1H), 7.55−7.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.00, 11.6, 24.3, 25.2, 30.3, 104.3, 108.9 (d, $^2J_{CF}$ = 23 Hz), 115.8 (d, $^2J_{CF}$ = 24 Hz), 118.7, 124.9 (d, $^3J_{CF}$ = 10 Hz), 125.9, 128.3 (d, $^1J_{CF}$ = 9 Hz), 132.4, 140.9, 161.0 (d, $^1J_{CF}$ = 244 Hz), 163.1. HRMS calcd for $C_{17}H_{16}FN_2$ (M^+ + H): 267.1298, found 267.1290.

9-Fluoro-5-butyl-*H*-cyclopenta[*c*]pyrazolo[5,1-*a*]isoquinoline 3q. Yield: 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.3 Hz, 3H), 1.46−1.55 (m, 2H), 1.82−1.90 (m, 2H), 2.59−2.66 (m, 2H), 2.95−3.01 (m, 2H), 3.04−3.13 (m, 4H), 6.65 (s, 1H), 7.16−7.21 (m, 1H), 7.55−7.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 24.3, 25.4, 28.9, 30.3, 30.9, 106.9, 108.8 (d, $^2J_{CF}$ = 23 Hz), 115.8 (d, $^2J_{CF}$ = 23 Hz), 125.0 (d, $^3J_{CF}$ = 9 Hz), 126.0, 128.2 (d, $^3J_{CF}$ = 9 Hz), 132.3, 132.4, 139.7, 161.0 (d, $^1J_{CF}$ = 244 Hz), 162.8. HRMS calcd for $C_{18}H_{20}FN_2$ (M^+ + H): 283.1611, found 283.1610.

8-Fluoro-5-phenyl-*H*-cyclopenta[*c*]pyrazolo[5,1-*a*]isoquinoline 3r. Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56−2.63 (m, 2H), 2.93−2.96 (m, 2H), 3.07−3.11 (m, 2H), 6.77 (s, 1H), 7.22−7.25 (m, 1H), 7.28−7.31 (m, 1H), 7.45−7.53 (m, 3H), 7.83−8.00 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 25.3, 30.2, 110.0, 111.5 (d, $^2J_{CF}$ = 22 Hz), 115.5 (d, $^2J_{CF}$ = 24 Hz), 117.9, 121.1, 126.0 (d, $^3J_{CF}$ = 9 Hz), 128.4, 129.3, 129.4, 131.2 (d, $^3J_{CF}$ = 9 Hz), 133.1, 134.1, 140.5, 161.8 (d, $^1J_{CF}$ = 246 Hz), 163.7. HRMS calcd for $C_{20}H_{16}FN_2$ (M^+ + H): 303.1298, found 303.1286.

9-Fluoro-5-methoxyphenyl-*H*-cyclohexa[*c*]pyrazolo[5,1-*a*]isoquinoline 3s. Yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88−1.97 (m, 4H), 2.88−2.91 (m, 2H), 3.07−3.09 (m, 2H), 3.87 (s, 3H), 6.79 (s, 1H), 7.01−7.04 (m, 2H), 7.20−7.25 (m, 1H), 7.30−7.33 (m, 1H), 7.81−7.85 (m, 2H), 8.09−8.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 23.0, 23.5, 24.2, 55.4, 109.4, 111.5 (d, $^2J_{CF}$ = 21 Hz), 113.8, 115.0 (d, $^2J_{CF}$ = 23 Hz), 121.8, 125.4 (d, $^3J_{CF}$ = 9 Hz), 126.3, 130.7, 130.8, 131.5 (d, $^3J_{CF}$ = 10 Hz), 134.5, 139.3, 151.3, 160.4, 161.4 (d, $^1J_{CF}$ = 247 Hz). HRMS calcd for $C_{22}H_{20}FN_2O$ (M^+ + H): 347.1560, found 347.1540.

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Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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