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PAPER

Silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)-hydrazide with pyridyne†

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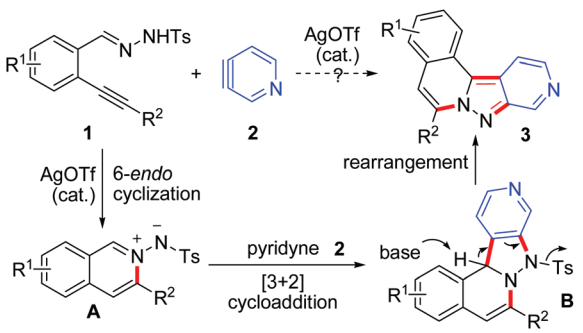
A silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with pyridyne is presented. Different outcomes are obtained, depending on the pyridynes utilized in the transformation.

1. Introduction

For the process of drug development, libraries of natural product-like compounds are in great demand.[1] Therefore, it is highly important to develop efficient and facile approaches for the generation of small molecules with privileged scaffolds.[2] During the transformations, diversity and complexity should be easily incorporated. Concerning efficiency, tandem reaction is the choice for parallel synthesis in combinatorial chemistry.[3] Recently, we developed several routes for the preparation of *H*-pyrazolo[5,1-*a*]isoquinoline derivatives using tandem reactions.[4] Several hits exhibited promising biological activities for anti-bacterial and inhibition of CDC25B, TC-PTP, and PTP1B during the preliminary biological evaluations.[4h] The discovery of more active compounds prompted us to consider their library construction. Although there are reported procedures for the construction of the scaffold of *H*-pyrazolo[5,1-*a*]isoquinoline,[4,5] efficient methods for the concise synthesis of diverse *H*-pyrazolo-[5,1-*a*]isoquinolines with complexity are highly desirable.

It is well known that pyridynes are analogues of arynes containing a nitrogen in the ring. Their reactivity has been demonstrated in cycloaddition and nucleophilic substitution reactions for the construction of complex molecules.[6–8] The pyridine skeleton, which is important in pharmaceutical chemistry, could be incorporated when pyridynes were used as the substrates in organic reactions. Recently, we recognized that *N*′-(2-alkynylbenzylidene)hydrazide was a useful building block for the formation of *N*-heterocycles.[4] Inspired by the advancement of pyridine chemistry, we envisioned that diverse *H*-pyrazolo[5,1-*a*]-isoquinolines would be generated by the reaction of *N*′-(2-alkynylbenzylidene)hydrazides with pyridynes under proper conditions (Scheme 1). The transformation would proceed through 6-*endo* cyclization, [3 + 2] cycloaddition, and intramolecular rearrangement. In connection of our recent efforts for the *N*′-(2-alkynylbenzylidene)hydrazide chemistry and to expand the utility of pyridines, we started to explore the feasibility of the proposed synthetic route as described in Scheme 1.



Scheme 1 A possible route for the generation of diverse *H*-pyrazolo-[5,1-*a*]isoquinolines **3**.

2. Results and discussion

The reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** with pyridyne precursor **2a** was initially studied in the presence of 10 mol% of silver triflate and a fluoro anion at room temperature (Table 1). Interestingly, the corresponding products **3a** and **3a′** were obtained in 31% total yield when the reaction occurred in DCE in the presence of cesium fluoride (Table 1, entry 1). These two products could be separated and isolated. Treatment of the reaction with Et_3NBnCl (0.25 equiv) as the additive provided products **3a** (26%) and **3a′** (16%) in 42% total yield (Table 1, entry 2). A lower yield was obtained by switching the solvent to toluene (Table 1, entry 3). Only a trace amount of product was detected when the reaction took place in ethanol (Table 1, entry 4).

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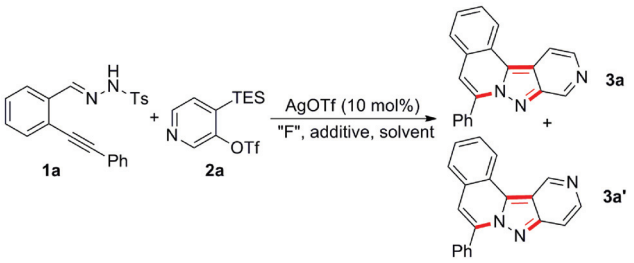
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra of compounds **3** and **4**, CIF of compound **4a**. CCDC reference number 892699. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26379c

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



Entry	"F"	Additive	Solvent	Yield[a] (%)
1	CsF	—	DCE	31 (**3a**/**3a′**: 20/11)
2	CsF	Et_3NBnCl	DCE	42 (**3a**/**3a′**: 26/16)
3	CsF	Et_3NBnCl	Toluene	18 (**3a**/**3a′**: 10/8)
4	CsF	Et_3NBnCl	EtOH	Trace
5	CsF	Et_3NBnCl	MeCN	60 (**3a**/**3a′**: 36/24)
6	CsF	Et_3NBnCl	THF	62 (**3a**/**3a′**: 40/22)
7	CsF	Et_3NBnCl	1,4-Dioxane	61 (**3a**/**3a′**: 38/23)
8	CsF	Et_3NBnCl	THF/MeCN	60 (**3a**/**3a′**: 35/25)
9	CsF	Et_3NBnCl	1,4-Dioxane/MeCN	73 (**3a**/**3a′**: 46/27)
10	CsF	Et_3NBnCl	1,4-Dioxane/DCM	40 (**3a**/**3a′**: 26/14)
11	CsF	Et_3NBnCl	1,4-Dioxane/DMF	54 (**3a**/**3a′**: 34/20)
12	KF	Et_3NBnCl	1,4-Dioxane/DMF	48 (**3a**/**3a′**: 28/20)
13	TBAF	Et_3NBnCl	1,4-Dioxane/DMF	65 (**3a**/**3a′**: 41/24)
14[b]	CsF	Et_3NBnCl	1,4-Dioxane/MeCN	62 (**3a**/**3a′**: 40/22)

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

The result could be dramatically improved when the solvent was changed to MeCN, THF, or 1,4-dioxane (Table 1, entries 5–7). A mixed solvent of 1,4-dioxane/MeCN gave rise to the desired products **3a** (46%) and **3a′** (27%) in 73% total yield (Table 1, entry 9). No better results were observed when other combinations of solvents were examined.

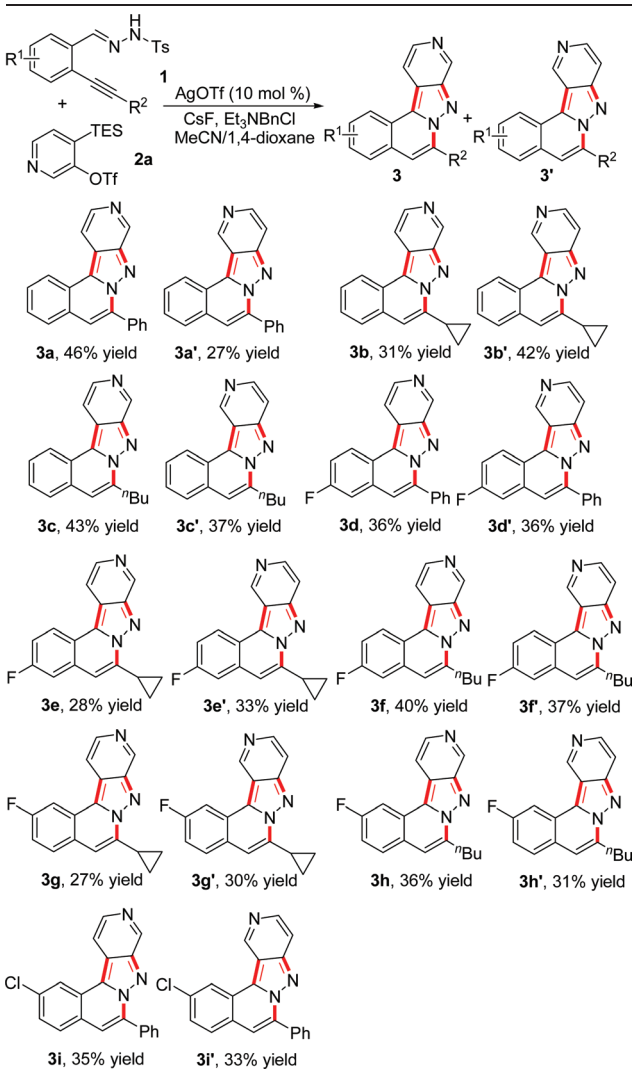
We next explored the scope of this silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1** with pyridyne precursor **2a** under the optimized conditions (10 mol% of AgOTf, CsF, Et_3NBnCl, 1,4-dioxane/MeCN, rt). The results are summarized in Table 2. Various *N*′-(2-alkynylbenzylidene) hydrazides **1** with substitutions on the aromatic ring were evaluated. All the reactions produced the expected pyridinyl-fused *H*-pyrazolo[5,1-*a*]isoquinolines in good yields. Additionally, reactions of *N*′-(2-alkynylbenzylidene)hydrazides **1** bearing either aryl or alkyl substituents on the triple bond (R^2 position) worked well. Although the transformation was not regioselective and two regioisomers were isolated, the total yield demonstrated the efficiency of the conversion.

To our surprise, an unexpected result was generated for the silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1** with 2-chloropyridyne precursor **2b**. 6,11-Dihydro-5*H*-11,6-(azenometheno)benzo[*e*]pyrido[4,3-*b*]azepines **4** were isolated and obtained (Table 3). The structure of compound **4a** was confirmed by X-ray diffraction analysis (Fig. 1, see the ESI†). Again, different functional groups were compatible under the standard conditions. According to the previous report,[4g] we proposed a possible mechanism which was presented in Scheme 2. After the silver(I)-mediated 6-*endo* cyclization of *N*′-(2-alkynylbenzylidene)hydrazide **1**, isoquinolinium-2-yl amide **A** would be formed. Then 2-chloropyridyne would be involved and the following [3 + 2] cycloaddition would occur to produce an intermediate **C**. We reasoned that the presence of a chloro group in the intermediate **C** would promote the cleavage of N–N bond to generate a radical **D**, which would undergo an intramolecular addition to provide compound **4**.

3. Conclusion

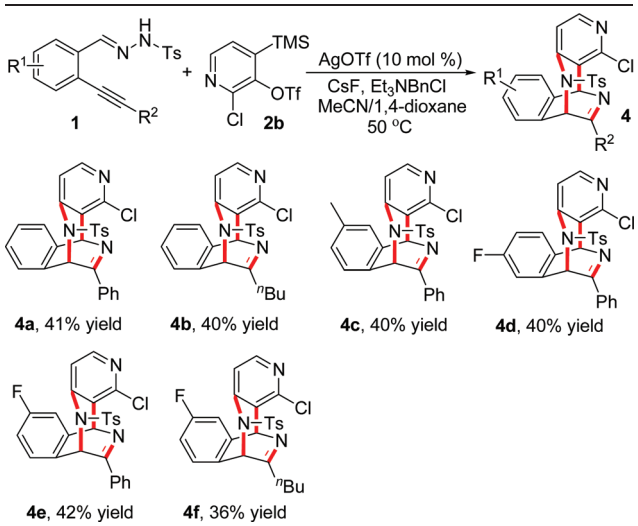
In summary, we have developed an efficient silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with pyridyne. Different outcomes are obtained, depending on the pyridynes utilized in the transformation. The scaffold diversity and complexity are easily introduced under mild conditions. The transformation provides a facile route to pyridinyl-fused *H*-pyrazolo[5,1-*a*]isoquinolines. Additionally, 6,11-dihydro-5*H*-

Table 2 Silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazides **1** with pyridyne **2a**[a]



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

Table 3 Silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1** with 2-chloropyridyne **2b**[a]



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

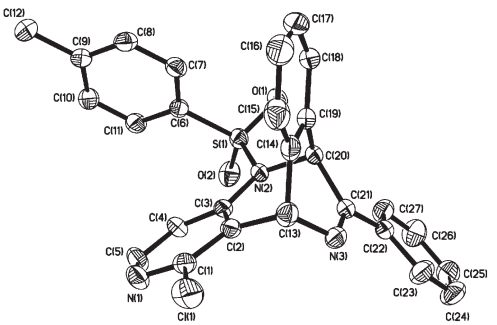
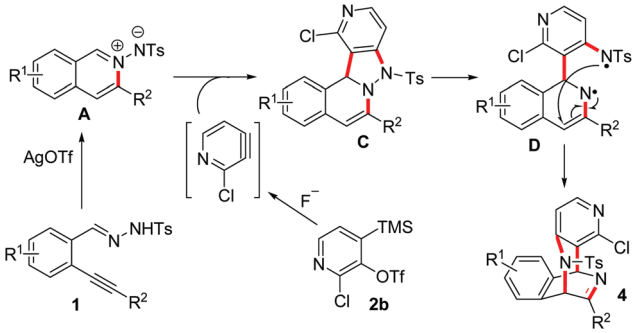


Fig. 1 X-ray ORTEP illustration of 6,11-dihydro-5*H*-11,6-(azenometheno)benzo[*e*]pyrido[4,3-*b*]azepines **4a** (30% probability ellipsoids).

11,6-(azenometheno)benzo[*e*]pyrido[4,3-*b*]azepines are generated as a different outcome when 2-chloropyridyne is used as the substrate. Employing pyridynes for the construction of other *N*-heterocycles is ongoing in our laboratory.

Experimental section

General experimental procedure for the silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with pyridyne. A mixture of *N*′-(2-alkynylbenzylidene)hydrazide **1** (0.3 mmol) and AgOTf (10 mol%) in 1,4-dioxane (2.0 mL) was heated at 70 °C with vigorous stirring for 1 hour. Then, pyridyne precursor **2** (0.45 mmol, 1.5 equiv), CsF (0.9 mmol, 3.0 equiv), TEBAC (0.075 mmol, 0.25 equiv), and MeCN (2.0 mL) were added. The reaction mixture was stirred at room temperature or 50 °C until completion of the reaction. The reaction 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 to provide the desired product.



Scheme 2 A possible mechanism for the silver triflate-catalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazide with 2-chloropyridyne.

6-Phenylpyrido[3′,4′:3,4]pyrazolo[5,1-*a*]isoquinoline 3a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.61 (m, 4H), 7.66 (t, J = 7.6 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 6.4 Hz, 2H), 8.26 (d, J = 6.0 Hz, 1H), 8.43 (d, J = 6.0 Hz, 1H), 8.64 (d, J = 7.8 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.5, 118.9, 119.0, 122.7, 125.8, 127.9, 128.0, 128.6, 128.8, 129.8, 129.9, 131.4, 133.3, 137.8, 138.7, 144.3, 144.8; HRMS calcd for $C_{20}H_{14}N_3$ (M^+ + H): 296.1188, found: 296.1180.

6-Phenylpyrido[4′,3′:3,4]pyrazolo[5,1-*a*]isoquinoline 3a′

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.64 (m, 4H), 7.73–7.77 (m, 2H), 7.85 (t, J = 7.6 Hz, 1H), 7.95–8.00 (m, 3H), 8.47 (d, J = 6.4 Hz, 1H), 8.76 (d, J = 8.2 Hz, 1H), 9.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.3, 114.9, 118.7, 123.6, 124.6, 128.0, 128.7, 129.1, 129.2, 129.6, 129.8, 130.0, 133.2, 138.7, 142.1, 146.1, 150.1; HRMS calcd for $C_{20}H_{14}N_3$ (M^+ + H): 296.1188, found: 296.1181.

6-Cyclopropylpyrido[3′,4′:3,4]pyrazolo[5,1-*a*]isoquinoline 3b

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99–1.03 (m, 2H), 1.32–1.36 (m, 2H), 2.87–2.95 (m, 1H), 7.17 (s, 1H), 7.61 (t, J = 7.3 Hz, 1H), 7.71 (t, J = 7.3 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 8.22 (d, J = 6.0 Hz, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.55 (d, J = 7.8 Hz, 1H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6, 11.9, 113.1, 114.6, 119.2, 122.6, 124.9, 127.2, 127.8, 128.0, 128.5, 130.9, 137.6, 141.2, 143.9, 144.9; HRMS calcd for $C_{17}H_{13}N_3$ (M^+ + H): 260.1188, found: 260.1181.

6-Cyclopropylpyrido[4′,3′:3,4]pyrazolo[5,1-*a*]isoquinoline 3b′

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99–1.04 (m, 2H), 1.32–1.36 (m, 2H), 2.90–2.97 (m, 1H), 7.18 (s, 1H), 7.67 (t, J = 7.3 Hz, 1H), 7.75 (t, J = 7.3 Hz, 1H), 7.81–7.85 (m, 2H), 8.51 (d, J = 6.0 Hz, 1H), 8.66 (d, J = 7.8 Hz, 1H), 9.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 12.0, 110.8, 112.6, 115.1, 123.4, 123.9, 127.3, 128.2, 128.6, 129.4, 132.5, 141.2, 143.1, 146.6, 150.1; HRMS calcd for $C_{17}H_{13}N_3$ (M^+ + H): 260.1188, found: 260.1170.

6-Butylpyrido[3′,4′:3,4]pyrazolo[5,1-*a*]isoquinoline 3c

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3H), 1.56–1.60 (m, 2H), 1.91–1.99 (m, 2H), 3.32–3.36 (m, 2H), 7.32 (s, 1H), 7.61 (t, J = 7.3 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 8.40 (d, J = 5.5 Hz, 1H), 8.51 (d, J = 7.8 Hz, 1H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 28.8, 31.0, 114.6, 115.7, 119.0, 122.5, 125.1, 127.2, 127.7, 127.9, 128.4, 130.8, 137.6, 139.8, 143.9, 144.8; HRMS calcd for $C_{18}H_{18}N_3$ (M^+ + H): 276.1501, found: 276.1485.

6-Butylpyrido[4′,3′:3,4]pyrazolo[5,1-*a*]isoquinoline 3c′

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, J = 6.8 Hz, 3H), 1.53–1.58 (m, 2H), 1.91–1.95 (m, 2H), 3.30–3.34 (m, 2H), 7.31 (s, 1H), 7.64–7.76 (m, 3H), 7.83 (d, J = 7.8 Hz, 1H), 8.49 (d, J = 6.0 Hz, 1H), 8.57 (d, J = 7.8 Hz, 1H), 9.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 28.8, 31.1, 110.8, 114.9, 115.3, 123.3, 123.9, 127.2, 128.1, 128.6, 129.3, 132.4, 139.8, 142.8, 146.4, 149.9; HRMS calcd for $C_{18}H_{18}N_3$ (M^+ + H): 276.1501, found: 276.1483.

3-Fluoro-6-phenylpyrido[3′,4′:3,4]pyrazolo[5,1-*a*]isoquinoline 3d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.60 (m, 6H), 7.95–7.97 (m, 2H), 8.19 (d, J = 5.5 Hz, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.60–8.64 (m, 1H), 9.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.6 (d, $^2J_{CF}$ = 22 Hz), 114.2, 117.8 (d, $^2J_{CF}$ = 24 Hz), 117.9, 118.5, 122.5, 125.1 (d, $^3J_{CF}$ = 9 Hz), 128.7, 129.7, 130.2, 130.3, 131.2, 132.9, 137.9, 139.8, 144.4, 144.9, 161.8 (d, $^1J_{CF}$ = 248 Hz); HRMS calcd for $C_{20}H_{13}FN_3$ (M^+ + H): 314.1094, found: 314.1071.

3-Fluoro-6-phenylpyrido[4′,3′:3,4]pyrazolo[5,1-*a*]isoquinoline 3d′

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.63 (m, 6H), 7.74 (d, J = 6.0 Hz, 1H), 7.95–7.97 (m, 2H), 8.48–8.49 (m, 1H), 8.75–8.77 (m, 1H), 9.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.2, 112.6 (d, $^2J_{CF}$ = 21 Hz), 114.6, 117.6, 117.7, 118.4 (d, $^2J_{CF}$ = 24 Hz), 121.5, 126.1 (d, $^3J_{CF}$ = 9 Hz), 128.7, 129.8, 130.2, 131.3 (d, $^3J_{CF}$ = 9 Hz), 133.0, 139.7, 143.0, 146.4, 150.2, 162.3 (d, $^1J_{CF}$ = 251 Hz); HRMS calcd for $C_{20}H_{13}FN_3$ (M^+ + H): 314.1094, found: 314.1097.

6-Cyclopropyl-3-fluoropyrido[3′,4′:3,4]pyrazolo[5,1-*a*]-isoquinoline 3e

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01–1.05 (m, 2H), 1.34–1.39 (m, 2H), 2.91–2.98 (m, 1H), 7.13 (s, 1H), 7.46–7.50 (m, 2H), 8.19 (d, J = 6.0 Hz, 1H), 8.41–8.43 (m, 1H), 8.56–8.59 (m, 1H), 9.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 11.9, 112.0 (d, $^2J_{CF}$ = 22 Hz), 112.2, 114.5, 117.1 (d, $^2J_{CF}$ = 24 Hz), 118.8, 121.7, 125.0 (d, $^3J_{CF}$ = 9 Hz), 126.5, 129.7, 130.3 (d, $^3J_{CF}$ = 9 Hz), 137.4, 142.5, 143.9, 161.7 (d, $^1J_{CF}$ = 248 Hz); HRMS calcd for $C_{17}H_{13}FN_3$ (M^+ + H): 278.1094, found: 278.1088.

6-Cyclopropyl-3-fluoropyrido[4′,3′:3,4]pyrazolo[5,1-*a*]-isoquinoline 3e′

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01–1.05 (m, 2H), 1.34–1.39 (m, 2H), 2.93–3.00 (m, 1H), 7.13 (s, 1H), 7.50–7.52 (m, 2H), 7.82 (d, J = 6.0 Hz, 1H), 8.51–8.53 (m, 1H), 8.66–8.70 (m, 1H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0, 12.0, 110.9, 111.7, 111.9 (d, $^2J_{CF}$ = 22 Hz), 114.8, 117.6 (d, $^2J_{CF}$ = 25 Hz), 120.7, 125.9 (d, $^3J_{CF}$ = 10 Hz), 131.3 (d, $^3J_{CF}$ = 10 Hz), 132.4, 142.5, 143.2, 146.5, 150.2, 162.2 (d, $^1J_{CF}$ = 249 Hz); HRMS calcd for $C_{17}H_{13}FN_3$ (M^+ + H): 278.1094, found: 278.1085.

6-Butyl-3-fluoropyrido[3′,4′:3,4]pyrazolo[5,1-*a*]isoquinoline 3f

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3H), 1.53–1.60 (m, 2H), 1.92–2.00 (m, 2H), 3.35–3.39 (m, 2H), 7.30 (s, 1H), 7.46–7.52 (m, 2H), 8.15 (d, J = 5.5 Hz, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.53–8.56 (m, 1H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 28.7, 31.1, 111.9 (d, $^2J_{CF}$ = 22 Hz), 114.3, 114.9, 117.1 (d, $^2J_{CF}$ = 24 Hz), 118.6, 121.9, 124.9 (d, $^3J_{CF}$ = 9 Hz), 130.2 (d, $^3J_{CF}$ = 10 Hz), 130.6, 137.7, 141.1, 144.1, 144.9, 161.6 (d, $^1J_{CF}$ = 248 Hz); HRMS calcd for $C_{18}H_{17}FN_3$ (M^+ + H): 294.1407, found: 294.1379.

6-Butyl-3-fluoropyrido[4′,3′:3,4]pyrazolo[5,1-*a*]isoquinoline 3f′

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3H), 1.54–1.59 (m, 2H), 1.92–1.96 (m, 2H), 3.33–3.37 (m, 2H), 7.29 (s, 1H), 7.48–7.52 (m, 2H), 7.76 (d, J = 4.2 Hz, 1H), 8.51 (s, 1H), 8.61–8.64 (m, 1H), 9.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 28.8, 31.2, 110.7, 111.9 (d, $^2J_{CF}$ = 22 Hz), 114.4, 117.5 (d, $^2J_{CF}$ = 23 Hz), 120.8, 125.8 (d, $^3J_{CF}$ = 9 Hz), 131.1 (d, $^3J_{CF}$ = 9 Hz), 132.1, 141.0, 143.4, 146.5, 150.0, 162.1 (d, $^1J_{CF}$ = 249 Hz); HRMS calcd for $C_{18}H_{17}FN_3$ (M^+ + H): 294.1407, found: 294.1428.

6-Cyclopropyl-2-fluoropyrido[3′,4′:3,4]pyrazolo[5,1-*a*]-isoquinoline 3g

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01–1.05 (m, 2H), 1.34–1.39 (m, 2H), 2.94–2.96 (m, 1H), 7.13 (s, 1H), 7.46–7.50 (m, 2H), 8.19 (d, J = 6.0 Hz, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.56–8.60 (m, 1H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 11.9, 112.0 (d, $^2J_{CF}$ = 22 Hz), 112.2, 114.4, 117.1 (d, $^2J_{CF}$ = 24 Hz), 118.8, 121.7, 125.0 (d, $^3J_{CF}$ = 9 Hz), 130.3 (d, $^3J_{CF}$ = 9 Hz), 130.7, 137.6, 142.6, 144.1, 144.9, 161.7 (d, $^1J_{CF}$ = 248 Hz); HRMS calcd for $C_{17}H_{13}FN_3$ (M^+ + H): 278.1094, found: 278.1107.

6-Cyclopropyl-2-fluoropyrido[4′,3′:3,4]pyrazolo[5,1-*a*]-isoquinoline 3g′

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01–1.05 (m, 2H), 1.33–1.39 (m, 2H), 2.94–2.99 (m, 1H), 7.14 (s, 1H), 7.45–7.54 (m, 2H), 7.81 (d, J = 6.0 Hz, 1H), 8.52 (d, J = 6.0 Hz, 1H), 8.67–8.71 (m, 1H), 9.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.1, 12.0, 110.9, 111.6, 111.9 (d, $^2J_{CF}$ = 22 Hz), 114.7, 117.6 (d, $^2J_{CF}$ = 24 Hz), 120.7, 125.9 (d, $^3J_{CF}$ = 10 Hz), 131.3 (d, $^3J_{CF}$ = 10 Hz),

132.4, 142.5, 143.2, 146.5, 150.2, 162.2 (d, $^{1}J_{CF}$ = 249 Hz); HRMS calcd for $C_{17}H_{13}FN_3$ (M^+ + H): 278.1094, found: 278.1102.

6-Butyl-2-fluoropyrido[3′,4′:3,4]pyrazolo[5,1-*a*]isoquinoline 3h

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3H), 1.54–1.60 (m, 2H), 1.90–1.98 (m, 2H), 3.31–3.34 (m, 2H), 7.30–7.37 (m, 2H), 7.80–7.84 (m, 1H), 8.09–8.10 (m, 2H), 8.42–8.43 (m, 1H), 9.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 28.7, 30.9, 107.7 (d, $^{2}J_{CF}$ = 24 Hz), 114.1, 115.1, 116.7 (d, $^{2}J_{CF}$ = 24 Hz), 119.2, 124.9, 126.1 (d, $^{3}J_{CF}$ = 10 Hz), 129.5 (d, $^{3}J_{CF}$ = 9 Hz), 129.9, 138.0, 139.2, 143.9, 144.7, 161.9 (d, $^{1}J_{CF}$ = 247 Hz); HRMS calcd for $C_{18}H_{17}FN_3$ (M^+ + H): 294.1407, found: 294.1410.

6-Butyl-2-fluoropyrido[4′,3′:3,4]pyrazolo[5,1-*a*]isoquinoline 3h′

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3H), 1.53–1.60 (m, 2H), 1.94–2.01 (m, 2H), 3.38–3.42 (m, 2H), 7.41 (s, 1H), 7.44–7.48 (m, 1H), 7.81 (d, J = 6.0 Hz, 1H), 7.91–7.94 (m, 1H), 8.31 (d, J = 7.3 Hz, 1H), 8.55 (d, J = 5.0 Hz, 1H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 28.8, 31.1, 108.5 (d, $^{2}J_{CF}$ = 24 Hz), 110.9, 114.8, 117.9 (d, $^{2}J_{CF}$ = 24 Hz), 125.1 (d, $^{3}J_{CF}$ = 9 Hz), 126.1, 129.8 (d, $^{3}J_{CF}$ = 9 Hz), 131.7, 139.4, 143.4, 145.1, 146.2, 150.1, 162.0 (d, $^{1}J_{CF}$ = 247 Hz); HRMS calcd for $C_{18}H_{17}FN_3$ (M^+ + H): 294.1407, found: 294.1412.

2-Chloro-6-phenylpyrido[3′,4′:3,4]pyrazolo[5,1-*a*]isoquinoline 3i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.62 (m, 5H), 7.86 (d, J = 8.7 Hz, 1H), 7.96–7.97 (m, 2H), 8.23 (d, J = 5.5 Hz, 1H), 8.46 (s, 1H), 8.57 (s, 1H), 9.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.1, 118.1, 119.0, 122.1, 126.6, 126.8, 128.5, 128.7, 129.3, 129.7, 130.1, 130.3, 133.0, 134.8, 138.3, 139.0, 144.5, 145.1; HRMS calcd for $C_{20}H_{13}ClN_3$ (M^+ + H): 330.0798, found: 330.0796.

2-Chloro-6-phenylpyrido[4′,3′:3,4]pyrazolo[5,1-*a*]isoquinoline 3i′

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.35 (m, 1H), 7.59–7.62 (m, 3H), 7.69 (d, J = 8.3 Hz, 1H), 7.73–7.77 (m, 1H), 7.84 (d, J = 7.3 Hz, 1H), 7.92–7.97 (m, 2H), 8.53 (s, 1H), 8.72 (s, 1H), 9.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.7, 120.5, 122.9, 127.9, 128.2, 128.7, 129.4, 129.8, 130.1, 130.2, 130.3, 133.1, 135.1, 139.0, 143.4, 146.3, 151.2; HRMS calcd for $C_{20}H_{13}ClN_3$ (M^+ + H): 330.0798, found: 330.0792.

1-Chloro-13-phenyl-5-tosyl-6,11-dihydro-5*H*-11,6-(azenometheno)benzo[*e*]pyrido[4,3-*b*]azepine 4a

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 6.76 (s, 1H), 7.01 (d, J = 8.3 Hz, 2H), 7.08 (s, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 6.0 Hz, 1H), 7.40–7.57 (m, 6H), 7.72 (d, J = 6.9 Hz, 1H), 7.80 (d, J = 6.0 Hz, 1H), 8.08–8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 53.2, 62.0, 114.7, 120.5, 125.0, 127.4, 127.5, 127.6, 128.6, 129.1, 129.3, 129.9, 131.6, 131.9, 134.5, 135.5, 141.9, 145.1, 145.5, 147.9, 150.9, 167.0; HRMS calcd for $C_{27}H_{21}ClN_3O_2S$ (M^+ + H): 486.1043, found: 486.1043.

13-Butyl-1-chloro-5-tosyl-6,11-dihydro-5*H*-11,6-(azenometheno)-benzo[*e*]pyrido[4,3-*b*]azepine 4b

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 1.28–1.37 (m, 2H), 1.65–1.72 (m, 2H), 2.29 (s, 3H), 2.61–2.79 (m, 2H), 6.19 (s, 1H), 6.49 (s, 1H), 7.07 (d, J = 7.8 Hz, 2H), 7.21 (t, J = 7.3 Hz, 3H), 7.37–7.45 (m, 2H), 7.49 (d, J = 6.9 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.81 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.5, 22.4, 27.7, 37.9, 55.6, 61.4, 114.7, 121.0, 124.9, 127.3, 127.5, 128.4, 129.2, 129.9, 131.7, 134.7, 142.3, 145.1, 145.4, 147.8, 150.7, 172.7; HRMS calcd for $C_{25}H_{25}ClN_3O_2S$ (M^+ + H): 466.1356, found: 466.1345.

1-Chloro-9-methyl-13-phenyl-5-tosyl-6,11-dihydro-5*H*-11,6-(azenometheno)benzo[*e*]pyrido[4,3-*b*]azepine 4c

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.42 (s, 3H), 6.70 (s, 1H), 7.02–7.05 (m, 3H), 7.22–7.26 (m, 4H), 7.37 (s, 1H), 7.48–7.50 (m, 3H), 7.59 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 6.0 Hz, 1H), 8.07–8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 53.1, 62.0, 114.6, 120.6, 125.6, 127.4, 127.6, 128.8, 129.0, 129.1, 129.9, 131.5, 134.6, 135.6, 139.5, 142.0, 145.0, 145.5, 147.8, 150.9, 167.3; HRMS calcd for $C_{28}H_{23}ClN_3O_2S$ (M^+ + H): 500.1200, found: 500.1218.

1-Chloro-8-fluoro-13-phenyl-5-tosyl-6,11-dihydro-5*H*-11,6-(azenometheno)benzo[*e*]pyrido[4,3-*b*]azepine 4d

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 6.75 (s, 1H), 7.03–7.13 (m, 4H), 7.23–7.26 (m, 3H), 7.42–7.54 (m, 5H), 7.83 (d, J = 5.5 Hz, 1H), 8.06 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 52.9, 61.4, 114.8 (d, $^{2}J_{CF}$ = 23 Hz), 114.9, 116.0 (d, $^{2}J_{CF}$ = 22 Hz), 120.5, 126.7 (d, $^{3}J_{CF}$ = 8 Hz), 127.4, 127.5, 129.1, 130.0, 131.7, 133.9 (d, $^{3}J_{CF}$ = 8 Hz), 134.5, 135.3, 137.7, 145.3, 145.5, 148.0, 150.8, 162.8 (d, $^{1}J_{CF}$ = 247 Hz), 166.4; HRMS calcd for $C_{27}H_{20}ClFN_3O_2S$ (M^+ + H): 504.0949, found: 504.0968.

1-Chloro-9-fluoro-13-phenyl-5-tosyl-6,11-dihydro-5*H*-11,6-(azenometheno)benzo[*e*]pyrido[4,3-*b*]azepine 4e

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 6.75 (s, 1H), 7.03–7.13 (m, 4H), 7.23–7.26 (m, 3H), 7.42–7.54 (m, 5H), 7.83 (d, J = 6.0 Hz, 1H), 8.06 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 52.9, 61.4, 114.8 (d, $^{2}J_{CF}$ = 23 Hz), 114.9, 116.0 (d, $^{2}J_{CF}$ = 21 Hz), 126.7 (d, $^{3}J_{CF}$ = 8 Hz), 127.4, 127.5, 129.0, 129.1, 130.0, 131.7, 133.9 (d, $^{3}J_{CF}$ = 8 Hz), 134.5, 135.3, 137.7, 145.3, 145.5, 148.0, 150.8, 162.8 (d, $^{1}J_{CF}$ = 247 Hz), 166.4; HRMS calcd for $C_{27}H_{20}ClFN_3O_2S$ (M^+ + H): 504.0949, found: 504.0974.

13-Butyl-1-chloro-9-fluoro-5-tosyl-6,11-dihydro-5*H*-11,6-(azenometheno)benzo[*e*]pyrido[4,3-*b*]azepine 4f

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.28–1.37 (m, 2H), 1.64–1.71 (m, 2H), 2.32 (s, 3H), 2.61–2.79 (m, 2H), 6.17 (s, 1H), 6.46 (s, 1H), 7.11–7.13 (m, 3H), 7.20–7.28 (m, 4H), 7.57–7.60 (m, 1H), 7.83 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.5, 22.3, 27.6, 37.8, 54.9, 61.2, 112.5 (d, $^2J_{CF}$ = 22 Hz), 114.7, 115.3 (d, $^2J_{CF}$ = 22 Hz), 120.4, 127.4, 129.1 (d, $^3J_{CF}$ = 8 Hz), 130.1, 134.7, 144.6 (d, $^3J_{CF}$ = 8 Hz), 145.3, 145.4, 148.0, 150.8, 162.9 (d, $^1J_{CF}$ = 250 Hz), 172.9; HRMS calcd for $C_{25}H_{24}ClFN_3O_2S$ (M^+ + H): 484.1262, found: 484.1252.

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