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Route to Pyrazolo[5,1-*a*]isoquinolines via a Copper-Catalyzed Tandem Reaction of 2-Alkynylbromobenzene with Pyrazole

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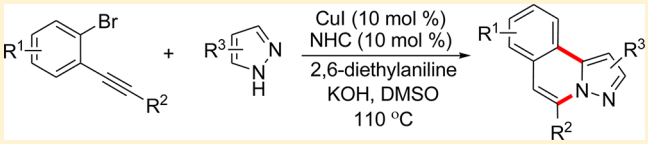
Supporting Information

ABSTRACT: A copper-catalyzed tandem reaction of 2-alkynylbromobenzene and pyrazole is described that provides a facile route to pyrazolo[5,1-*a*]isoquinolines in good yields. During the reaction process, copper(I)-catalyzed hydroamination and C−H activation are involved.



Currently, there is a great demand for access to natural product-like compounds in the field of chemical biology and drug discovery.[1,2] Among the privileged scaffolds constructed, continuous interest has been focused on pyrazolo[5,1-*a*]isoquinolines due to their promising biological activities.[3,4] For instance, pyrazolo[5,1-*a*]isoquinoline derivatives show activities for inhibition of CDC25B, TC-PTP, and PTP1B.[4b] Additionally, in our preliminary biological evaluations, several compounds were found to be active for inhibition of cervical carcinoma. In our continuous efforts for the generation of druglike small molecules, we are interested in the construction of diverse pyrazolo[5,1-*a*]isoquinolines with an expectation of finding more active compounds.

Tandem reaction is regarded as a powerful approach for the formation of complex heterocycles.[5] The advantages and efficiency of tandem reaction have been well recognized. Recently, we and others identified that 2-alkynylbromobenzene was a useful building block for the generation of polycyclic molecules.[6,7] On the basis of this result, we conceived that pyrazolo[5,1-*a*]isoquinoline would be produced via a transition-metal-catalyzed tandem reaction of 2-alkynylbromobenzene with pyrazole. The proposed synthetic route is described in Scheme 1. We hypothesized that the reaction would proceed through a transition-metal-catalyzed hydroamination and C−H activation.[8] The transformation seems feasible on the basis of the previous results, since Verma and Larock reported the generation of indolo- and pyrrolo[2,1-*a*]isoquinolines via a copper(I)-catalyzed reaction of 2-alkynylbromobenzene with indole or pyrrole.[9] However, there are still some challenges for this reaction between pyrazole and 2-alkynylbromobenzene. For instance, the direct coupling of 2-alkynylbromobenzene **1** and pyrazole **2** would easily lead to the formation of C−N bond[10] which should be excluded in our protocol. Moreover, C−H activation of pyrazole is usually catalyzed by the palladium catalyst, with only two examples of copper catalyst reported. For example, Daugulis and Xi reported the copper-catalyzed arylation of arenes via C−H bond activation independently.[11] Compared with the palladium catalyst, copper(I) salts obviously would be more attractive. We envisioned that the transformation would be possible if the copper(I) salt could serve as the catalyst for the subsequent C−H activation as well. With these results in mind, we proposed that a copper(I)-catalyzed hydroamination of 2-alkynylbromobenzene with pyrazole would occur to generate compound **A**.[12] Subsequently, an oxidative addition of Cu(I) to aryl bromide **A** would afford intermediate **B**, which would undergo intramolecular attack with the subsequent deprotonation of pyrazole

Scheme 1. Possible Mechanism for the Proposed Synthetic Route to Pyrazolo[5,1-*a*]isoquinolines via a Copper-Catalyzed Tandem Reaction of 2-Alkynylbromobenzene with Pyrazole

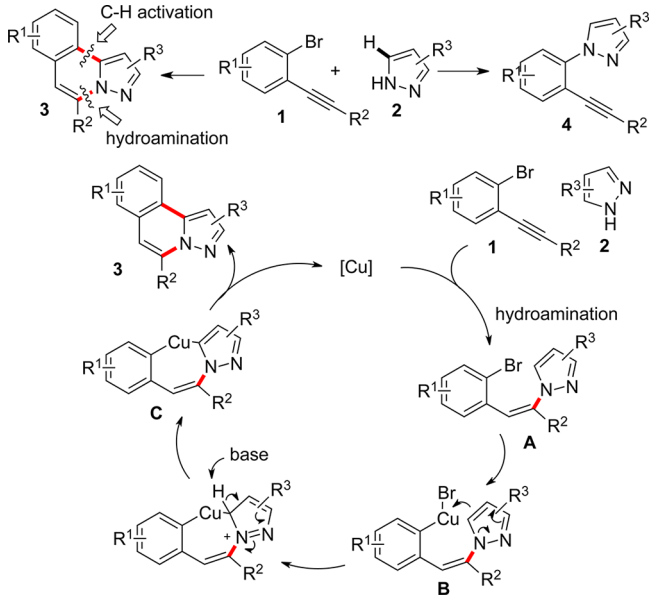


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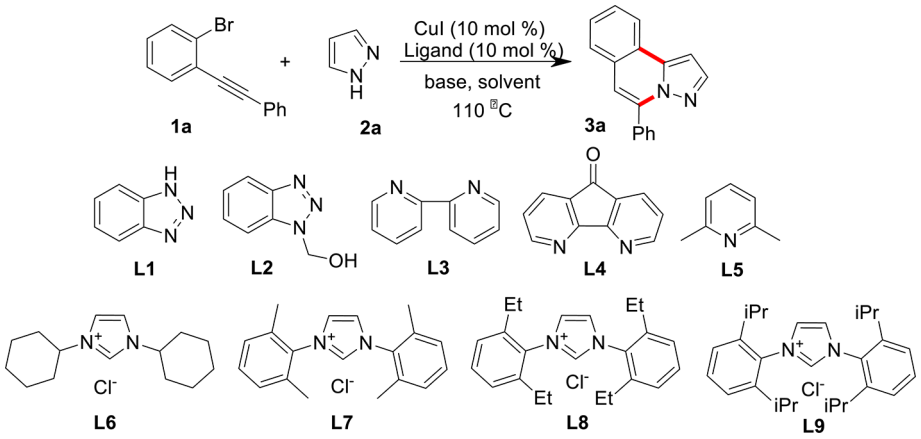
Table 1. Initial Studies for the Copper-Catalyzed Reaction of 2-Alkynylbromobenzene 1a with Pyrazole 2a



entry	[Cu]	ligand	base	solvent	yield[a] (%)
1	CuOTf	**L1**	^{t}BuOK	DMF	NR
2	Cu_2O	**L1**	^{t}BuOK	DMF	trace
3	CuCl	**L1**	^{t}BuOK	DMF	14
4	CuI	**L1**	^{t}BuOK	DMF	15
5	CuI	**L1**	^{t}BuOK	toluene	NR
6	CuI	**L1**	^{t}BuOK	dioxane	NR
7	CuI	**L1**	^{t}BuOK	NMP	NR
8	CuI	**L1**	^{t}BuOK	DMSO	34
9	CuI	**L1**	KOH	DMSO	40
10	CuI	**L1**	^{t}BuONa	DMSO	33
11	CuI	**L1**	^{t}BuOLi	DMSO	34
12	CuI	**L1**	NaH	DMSO	28
13	CuI	**L2**	KOH	DMSO	43
14	CuI	**L3**	KOH	DMSO	39
15	CuI	**L4**	KOH	DMSO	30
16	CuI	**L5**	KOH	DMSO	41
17	CuI	**L6**	KOH	DMSO	45
18	CuI	**L7**	KOH	DMSO	45
19	CuI	**L8**	KOH	DMSO	51
20	CuI	**L9**	KOH	DMSO	46
21[b]	CuI	**L8**	KOH	DMSO	65
22[b]	CuI		KOH	DMSO	40

[a]Isolated yield based on pyrazole **2a**. [b]In the presence of 2,6-diethylaniline (10 mol %).

ring to produce intermediate **C**. Reductive elimination of intermediate **C** would furnish the expected pyrazolo[5,1-*a*]isoquinoline **3**. Encouraged by the previous results as mentioned above, we began to explore this copper-catalyzed tandem reaction of 2-alkynylbromobenzene **1** and pyrazole **2**.

For the model reaction, 2-alkynylbromobenzene **1a** with pyrazole **2a** was adopted. The preliminary screening for the reaction was performed in the presence of copper(I) catalyst (10 mol %) at 110 °C (Table 1). Various copper sources were screened first, but only a trace amount of product was observed when the reaction occurred in the presence of **L1** (20 mol %), Cu_2O, and *t*-BuOK in DMF at 110 °C (Table 1, entry 2). No reaction took place when the copper salt was changed to CuOTf (Table 1, entry 1). The reaction could proceed leading to the desired product **3a** in 14% yield catalyzed by copper(I) chloride in the presence of ligand **L1** and *t*-BuOK in DMF (Table 1, entry 3). No reaction occurred in a control experiment without the addition of ligand **L1** (data not shown in Table 1). A similar yield was obtained when the catalyst was changed to copper(I) iodide (Table 1, entry 4). The reaction could not proceed when the solvent was changed to toluene, 1,4-dioxane, or NMP (Table 1, entries 5−7). Interestingly, the yield was improved when the reaction was performed in DMSO, giving rise to the corresponding product **3a** in 34% yield (Table 1, entry 8). Subsequently, different bases were examined, which identified that potassium hydroxide was the best choice (40% yield, Table 1, entry 9). With these results in hand, we next screened various ligands. To our delight, the desired product **3a** was obtained in 51% yield when *N*-heterocyclic carbene **L8** was employed in the reaction as a ligand (Table 1, entry 19). However, other ligands (such as X-Phos) were ineffective in this reaction. After careful investigation, we found that the addition of 10 mol % of 2,6-diethylaniline would increase the final outcome of the reaction, which afforded compound **3a** in 65% yield (Table 1, entry 21). The yield was reduced to 40% without the addition of ligand **L8** in the presence of 10 mol % of 2,6-diethylaniline (Table 1, entry22). However, the role of 2,6-diethylaniline remains uncertain. The presence of other anilines could not improve the yield. The reaction became complex when the temperature

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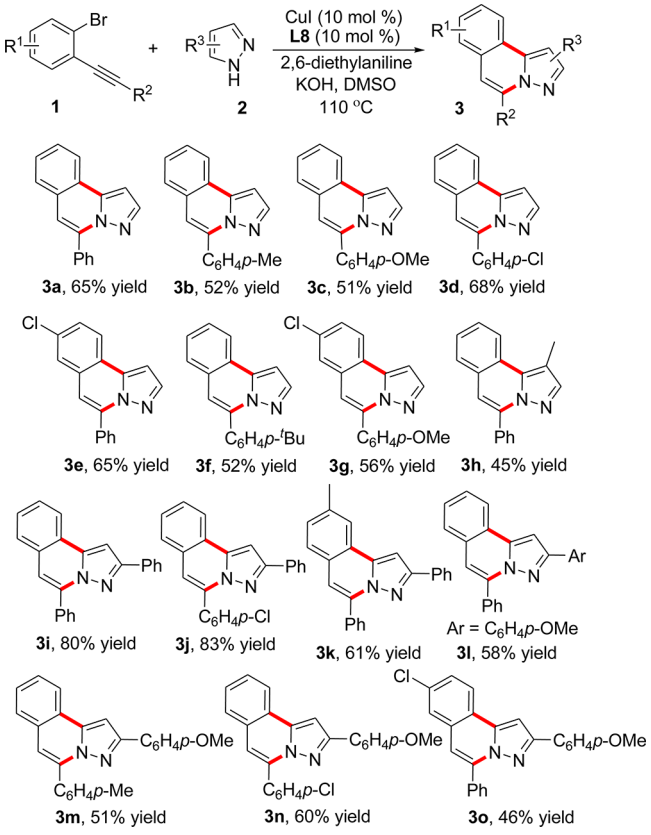
was lowered, while higher temperature could not enhance the yield. Furthermore, other additive such as silver salts and other amines could not improve the final outcome.

The reaction scope was then examined under the optimized conditions (10 mol % of CuI, 10 mol % of ligand **L8**, 10 mol % of 2,6-diethylaniline, 2.0 equiv of KOH, DMSO, 110 °C). The results are summarized in Scheme 2 for the evaluation of

Scheme 2. Copper-Catalyzed Tandem Reaction of 2-Alkynylbromobenzenes 1 with Pyrazoles 2[a]



[a]Isolated yield based on pyrazole **2**.

various substituted 2-alkynylbromobenzenes **1** with pyrazoles **2**. These reactions proceeded well, leading to the corresponding pyrazolo[5,1-*a*]isoquinolines **3** in good yields. A better result was obtained when 2-alkynylbromobenzene **1** with an electron-withdrawing aryl groups attached on the triple bond (R^2 position) was employed in the reaction. Various substrates with different substituents on the aromatic ring of 2-alkynylbromobenzene **1** or attached on the pyrazole **2** worked well under the standard conditions, giving rise to the desired products in moderate to good yields. Unfortunately, only a trace amount of the corresponding products were detected when the terminal alkyne or alkyl-substituted alkynes (*n*-butyl or cyclopropyl) were used as the substrates in the transformation.

In summary, we have described a copper-catalyzed tandem reaction of 2-alkynylbromobenzene with pyrazole, providing a facile route for the synthesis of pyrazolo[5,1-*a*]isoquinolines. The reaction involves copper(I)-catalyzed hydroamination and C−H activation during the process.

EXPERIMENTAL SECTION

General Experimental Procedure for the Copper-Catalyzed Tandem Reaction of 2-Alkynylbromobenzene with Pyrazole. 2-Alkynylbromobenzene **1** (0.25 mmol) was added to a mixture of CuI (10 mol %), NHC **L8** (10 mol %), 2,6-diethylbenzeneamine (10 mol %), pyrazole **2** (0.2 mmol), and KOH (2.0 equiv) in DMSO (2.0 mL) under nitrogen atmosphere. The mixture was heated at 110 °C. After consumption of the starting material as indicated by TLC, the reaction mixture was cooled to room temperature. The solvent was diluted by EtOAc (10 mL), washed with saturated brine (2 × 10 mL), and dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel (petroleum ether/ethyl acetate = 16:1) provided the product **3**.

5-Phenylpyrazolo[5,1-a]isoquinoline (**3a**).[4a] Yellow solid. Mp: 145.2−146.0 °C. Weight: 32.0 mg. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 6.9 Hz, 1H), 7.99 (s, 1H), 7.87 (d, J = 6.9 Hz, 2H), 7.72−7.70 (m, 1H), 7.52−7.48 (m, 5H), 7.07−7.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 139.2, 138.3, 133.7, 129.3, 129.2, 128.8, 128.3, 127.8, 127.2, 127.0, 123.9, 123.4, 112.5, 97.7.

5-(p-Tolyl)pyrazolo[5,1-a]isoquinoline (**3b**). Yellow solid. Mp: 134.8−135.2 °C. Weight: 26.9 mg. Yield: 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10−8.09 (m, 1H), 7.98 (s, 1H), 7.78−7.70 (m, 3H), 7.54−7.52 (m, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.07−7.01 (m, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 139.3, 138.6, 130.9, 129.3, 129.2, 129.0, 127.8, 127.1, 127.0, 125.9, 123.9, 123.5, 112.1, 97.7, 21.4. HRMS (ESI): calcd for $C_{18}H_{15}N_2$ 259.1230 (M + H^+), found 259.1247.

5-(4-Methoxyphenyl)pyrazolo[5,1-a]isoquinoline (**3c**). Yellow solid. Mp: 138.5−139.2 °C. Weight: 28.1 mg. Yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08−8.07 (m, 1H), 7.99 (s, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.70−7.65 (m, 2H), 7.52−7.50 (m, 2H), 7.05−7.00 (m, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 140.7, 139.3, 138.2, 130.7, 129.2, 127.8, 127.0, 126.9, 126.1, 123.8, 123.4, 113.7, 111.8, 97.7, 29.6. HRMS (ESI): calcd for $C_{18}H_{15}N_2O$ 275.1179 (M + H^+), found 275.1185.

5-(4-Chlorophenyl)pyrazolo[5,1-a]isoquinoline (**3d**). White solid.Mp: 173.9−174.8 °C. Weight: 38.2 mg. Yield: 68%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 7.3 Hz, 1H), 7.98 (s, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.73−7.71 (m, 1H), 7.58−7.48 (m, 4H), 7.08−7.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 139.3, 137.2, 135.2, 132.1, 130.7, 128.9, 128.6, 128.0, 127.5, 127.1, 124.0, 123.5, 112.6, 97.9. HRMS (ESI): calcd for $C_{17}H_{12}ClN_2$ 279.0684 (M + H^+), found 279.0688.

8-Chloro-5-phenylpyrazolo[5,1-a]isoquinoline (**3e**). White solid. Mp: 114.3−115.1 °C. Weight: 36.3 mg. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99−7.97 (m, 2H), 7.84 (d, J = 6.4 Hz, 2H), 7.66 (s, 1H), 7.52−7.45 (m, 4H), 7.02−7.82 (s, 1H), 6.9 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 139.6, 138.7, 133.6, 133.4, 130.3, 129.5, 129.3, 128.4, 127.7, 126.2, 124.9, 122.3, 111.3, 98.1. HRMS (ESI): calcd for $C_{17}H_{12}ClN_2$ 279.0684 (M + H^+), found 279.0694.

5-(4-(tert-Butyl)phenyl)pyrazolo[5,1-a]isoquinoline (**3f**). Yellow solid. Mp: 96.1−97.1 °C. Weight: 31.2 mg. Yield: 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11−8.09 (m, 1H), 8.01 (s, 1H), 7.83 (d, J = 7.8 Hz, 2H), 7.72−7.70 (m, 1H), 7.56−7.52 (m, 4H), 7.07−7.03 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 140.8, 139.3, 138.5, 130.9, 129.2, 129.1, 127.8, 127.1, 125.3, 123.9, 123.5, 112.3, 97.8, 37.8, 31.3 HRMS (ESI): calcd for $C_{21}H_{21}N_2$ 301.1699 (M + H^+), found 301.1699.

8-Chloro-5-(4-methoxyphenyl)pyrazolo[5,1-a]isoquinoline (**3g**). Yellow solid. Mp: 134.5−135.0 °C. Weight: 34.7 mg. Yield: 56%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98−7.96 (m, 2H), 7.81 (d, J = 8.7 Hz, 2H), 7.65 (m, 1H), 7.45−7.43 (m, 1H), 7.05−7.01 (m, 3H), 6.87 (s, 1H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 141.0, 139.3, 138.7, 133.5, 130.7, 130.4, 127.4, 126.0, 125.7, 124.9, 122.1, 113.8, 110.6, 98.0, 29.6. HRMS (ESI): calcd for $C_{18}H_{14}ClN_2O$ 309.0789 (M + H^+), found 309.0796.

1-Methyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3h**).[4a] White solid. Mp: 130.5−131.4 °C. Weight: 23.4 mg. Yield: 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 7.8 Hz, 1H), 7.85−7.80 (m, 3H),

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7.70 (d, J = 7.3 Hz, 1H), 7.57−7.46 (m, 5H), 6.95 (s, 1H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 138.5, 135.1, 134.0, 129.4, 129.3, 129.1, 128.3, 127.1, 126.0, 125.6, 123.1, 112.3, 110.0, 11.8.

*2,5-Diphenylpyrazolo[5,1-a]isoquinoline (**3i**).*[13] Yellow solid. Mp: 140.8−141.5 °C. Weight: 51.4 mg. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 6.8 Hz, 1H), 7.01−7.97 (m, 3H), 7.68−7.66 (m, 1H), 7.53−7.47 (m, 5H), 7.42−7.39 (m, 2H), 7.36−7.30 (m, 3H), 7.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 138.3, 133.7, 133.3, 129.7, 129.5, 129.2, 128.6, 128.1, 127.9, 127.2, 126.4, 126.3, 123.9, 123.5, 123.3, 112.5, 94.7.

*5-(4-Chlorophenyl)-2-phenylpyrazolo[5,1-a]isoquinoline (**3j**).* Yellow solid. Mp: 159.8−160.2 °C. Weight: 58.8 mg. Yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98−7.91 (m, 3H), 7.85 (d, J = 7.3 Hz, 2H), 7.55 (d, J = 6.9 Hz, 1H), 7.44−7.45 (m, 6H), 7.31−7.27 (m, 1H), 7.23 (s, 1H), 6.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 140.5, 136.9, 134.9, 133.1, 132.0, 130.9, 130.7, 128.9, 128.5, 128.2, 127.8, 127.3, 126.3, 123.8, 123.4, 123.2, 112.4, 94.8. HRMS (ESI): calcd for $C_{23}H_{16}ClN_2$ 355.0997 (M + H$^+$), found: 355.0990.

*9-Methyl-2,5-diphenylpyrazolo[5,1-a]isoquinoline (**3k**).*[3f] Yellow solid. Mp: 125.8−126.5 °C. Weight: 40.9 mg. Yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02−7.98 (m, 3H), 7.91 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.51−7.49 (m, 3H), 7.43−7.39 (m, 2H), 7.33−7.31 (m, 4H), 6.99 (s, 1H), 2.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 140.5, 137.5, 137.3, 133.8, 133.4, 129.6, 129.5, 129.0, 128.5, 128.1, 127.0, 126.4, 126.2, 123.9, 123.3, 112.5, 94.5. HRMS (ESI): calcd for $C_{24}H_{19}N_2$ 335.1543 (M + H$^+$), found 335.1538.

*2-(4-Methoxyphenyl)-5-phenylpyrazolo[5,1-a]isoquinoline (**3l**).*[3f] Yellow solid. Mp: 128.9−129.9 °C. Weight: 40.8 mg. Yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 6.9 Hz, 1H), 8.02 (d, J = 6.9 Hz, 2H), 7.91 (d, J = 8.7 Hz, 2H), 7.71−7.69 (m, 1H), 7.52−7.48 (m, 5H), 7.29 (s, 1H), 7.02 (s, 1H), 6.95 (d, J = 8.7 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 152.1, 140.7, 138.4, 133.8, 129.6, 129.3, 129.1, 128.1, 127.8, 127.6, 127.1, 126.2, 123.8, 123.5, 114.5, 112.2, 94.3, 29.7. HRMS (ESI): calcd for $C_{24}H_{19}N_2O$ 351.1492 (M + H$^+$), found 351.1500.

*2-(4-Methoxyphenyl)-5-(p-tolyl)pyrazolo[5,1-a]isoquinoline (**3m**).* Yellow solid. Mp: 120.4−121.0 °C. Weight: 37.1 mg. Yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 6.9 Hz, 1H), 7.93−7.90 (m, 3H), 7.70−7.68 (m, 1H), 7.50−7.49 (m, 2H), 7.34−7.28 (m, 3H), 7.00−6.93 (m, 4H), 3.82 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 152.0, 140.7, 139.1, 138.4, 130.9, 129.5, 129.4, 128.8, 127.8, 127.6, 127.0, 126.2, 123.7, 123.4, 118.3, 113.9, 111.8, 94.2, 29.7, 21.4. HRMS (ESI): calcd for $C_{25}H_{21}N_2O$ 365.1648 (M + H$^+$), found 365.1630.

*5-(4-Chlorophenyl)-2-(4-methoxyphenyl)pyrazolo[5,1-a]isoquinoline (**3n**).* Yellow solid. Mp: 143.4−144.2 °C. Weight: 46.4 mg. Yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 7.3 Hz, 1H), 7.94−7.87 (m, 4H), 7.65 (d, J = 7.8 Hz, 1H), 7.51−7.45 (m, 4H), 7.24 (s, 1H), 6.95−6.93 (m, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 152.1, 140.7, 137.1, 135.0, 132.2, 130.9, 129.1, 128.3, 127.9, 127.6, 127.3, 127.2, 126.0, 123.9, 123.4, 114.1, 112.1, 94.3, 29.7. HRMS (ESI): calcd for $C_{24}H_{18}ClN_2O$: 385.1102 (M + H$^+$), found 385.1099.

*8-Chloro-2-(4-methoxyphenyl)-5-phenylpyrazolo[5,1-a]isoquinoline (**3o**).* Yellow solid. Mp: 163.6−164.4 °C. Weight: 35.3 mg. Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.00−7.98 (m, 2H), 7.89 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 1H), 7.52−7.50 (m, 3H), 7.46−7.43 (m, 1H), 7.25−7.24 (m, 1H), 6.96−6.94 (m, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 152.4, 139.7, 138.6, 133.5, 132.8, 129.6, 129.3, 128.6, 128.3, 128.2, 127.7, 125.9, 124.8, 122.9, 114.1, 111.3, 94.7, 29.7. HRMS (ESI): calcd for $C_{24}H_{18}ClN_2O$ 385.1102 (M + H$^+$), found 385.1085.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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