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Copper-Catalyzed Regioselective Coupling of Tosylhydrazones and 2-Pyridones: A Strategy for the Production of N-Alkylated Compounds

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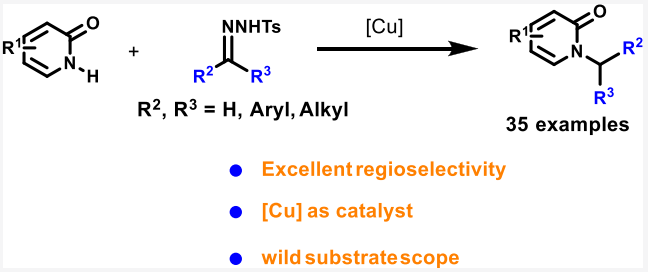
ABSTRACT: The highly regioselective N-alkylation reaction of 2-pyridones was achieved through hydrazone chemistry, especially for substrates with bulky secondary alkyl groups. Described herein is a copper-catalyzed coupling reaction of pyridone derivatives with tosylhydrazones.



N-Substituted 2-pyridones and analogues are key motifs in natural products and many active drugs (Figure 1),[1−3]

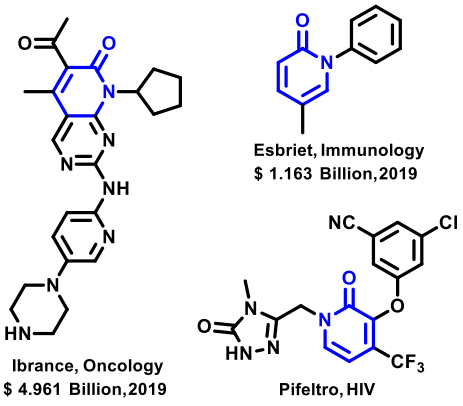


Figure 1. Drugs with pyridone-like structures.

but their synthesis is plagued by the regioselectivity control of N- and O-alkylation of 2-pyridones over the past decades.[4−6] Various modified methods have been established to enhance the regioselectivity of the N-alkylation process, and a variety of reaction parameters including solvents, bases, and temperature have been identified to be vital for its regioselectivity.[7] In 2015, Ren and co-workers reported that Tween 20 (2% w/w) was used as an effective additive to improve the N-selectivity,[8] but the regioselectivity decreases a lot in the case of bulky alkyl halides. More recently, a very impressive work reported by Xu et al. demonstrated that N-alkylation of hydroxypyridines could proceed in the absence of catalysts and bases.[9] On the other hand, it means that this type of reaction depends on the intrinsic activity of organohalides. The substrate scope is limited. Despite the considerable progress, selective N-alkylation of 2-pyridones is still a problem, especially with bulky secondary alkyl groups.

In 2018, a rhodium-catalyzed dearomatization of O-substituted pyridines to produce N-substituted 2-pyridones was developed by Sun et al.,[10] inspiring us to achieve regioselective synthesis of N-substituted 2-pyridones and analogues via the hydrazone chemistry.[11] As we all know, copper can catalyze C−N coupling between amines and tosylhydrazones, but it is hard for C−O coupling. Hence, we propose that high regioselectivity could be achieved through the hydrazone chemistry (Figure 2).

Initially, **1a** and **2a** were used as model substrates to establish the optimal reaction conditions. To our delight, the reaction proceeded smoothly under the "standard conditions", affording the desired product **3a** without O-alkylated product **3a′** (Table 1, entry 2). Upon switching the catalyst to other Cu salts, it was found that $Cu(acac)_2$ shows better performance than CuI (entries 2−7). Addition of different bases such as KOtBu, LiOH, and DIPEA led to diminished yields (entries 8−15). After screening the catalysts, bases, and solvents, the combination of $Cu(acac)_2$, Cs_2CO_3, and 1,4-dioxane gave the highest yield without O-alkylation byproducts.

With the optimized conditions in hand, the substrate scope was explored (Scheme 1). According to LCMS analysis, only

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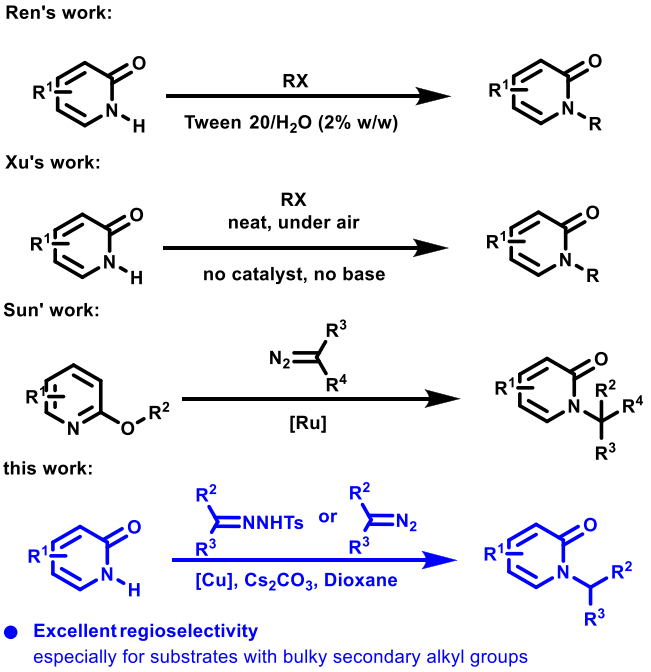

Figure 2. Previous reports and our new strategy.

N-alkylated products were detected on most substrates. Initially, a range of aryl tosylhydrazones bearing various substituents, such as methoxy, chloro, and nitro groups, at the para, meta, or ortho position of the phenyl ring, were tested, and the products were obtained in moderate yields with excellent regioselectivity. Note that the yield of tosylhydrazones with nitro groups (**3b**, **3c**) is somewhat reduced. The reaction is also amenable to other types of heteroaromatic tosylhydrazones. For instance, the use of furanyl and pyridinyl tosylhydrazones produced **3i**, **3j**, and **3n** in moderate yields. Notably, the alkyl tosylhydrazones (**3q**, **3s**) were also tolerated. Expectedly, the reaction was not limited to tosylhydrazones but also amenable to the diazoacetates (**3t**, **3u**). We think it will greatly expand the scope of application of this reaction.

Considering that this reaction can be applied to the synthesis of drug molecules, many 2-pyridone derivatives with complex structures have been examined (Scheme 2). When we started exploring the compatibility of our established methods with different 2-pyridones, we found that CuI is better than $Cu(acac)_2$ (SI). For polysubstituted 2-pyridones, most of them delivered products (**4b**−**4d**, **4f**) with moderate yields. Pyridones with parallel ring structure (**4g**−**4p**) were also tested. Based on the results, high regioselectivity of this reaction is well maintained for most of these substrates with only a slight decrease in product yield. Finally, the scalability of the method was evaluated using 2-pyridinol **4q** on a gram scale to afford the corresponding product with 72.2% yield.

Since the copper-catalyzed C−N coupling reaction has been widely reported,[12] we propose that the reaction proceeded via copper carbene, followed by the chemoselectively inserted copper carbene into the N−H bond over the O−H bond.

In conclusion, we have discovered a copper-catalyzed N-alkylation of 2-pyridones with tosylhydrazones. The key advantage of the process is its excellent regioselectivity, especially for substrates with bulky secondary alkyl groups. Typically, the reaction is amenable to various pyridone derivatives. Although the yield of some 2-pyridone derivatives with complex structures is relatively low, the regioselectivity is still well maintained.

EXPERIMENTAL SECTION

General Information. All chemicals were used as received without further purification unless stated otherwise. ^1H and ^{13}C NMR spectra were collected on a Bruker AVANCE NEO (400 MHz) spectrometer using DMSO-d_6 as solvent. Chemical shifts of ^1H NMR were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ = 0.00 ppm) with the solvent resonance as the internal standard (DMSO-d_6: δ = 2.50 ppm). Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Chemical shifts of ^{13}C NMR were reported in ppm with the solvent as the internal standard (DMSO-d_6: δ = 39.52 ppm). Mass measurement was performed on a Shimadzu-2020EV mass spectrometer with electron spray ionization (ESI) as the ion source. Reverse flash chromatography was carried out to purify the products.

General Procedure for the Preparation of Starting Materials. All the compound pyridin-2(1*H*)-one derivations and tosylhydrazones are known or commercially available, and data are consistent with the literature.[13] Tosylhydrazones are obtained by condensation of 4-toluenesulfonyl hydrazide with the corresponding ketone.[14] A solution of 4-toluenesulfonyl hydrazide (0.8 equiv) in MeOH (5.0 mL) was heated in an oil bath to 60 °C and stirred for 5 min under a nitrogen atmosphere. The reaction mixture was cooled to room temperature. Ketone (1.0 equiv) was added to the mixture at room temperature. After stirring for 2 h at 60 °C, the reaction mixture was cooled to room temperature. The precipitated solids were collected by filtration and washed with a PE/EA mixture to afford the corresponding hydrazone.

Ethyl 2-diazopropanoate was obtained by condensation of ethyl 2-methyl-3-oxobutanoate with tosyl azide.[15] DBU (22.5 mmol, 1.5 equiv) was added slowly to a stirred solution of ethyl 2-methyl-3-oxobutanoate (15.0 mmol, 1.0 equiv) and tosyl azide (22.5 mmol, 1.5 equiv) in MeCN (50 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, and the reaction was quenched with H_2O and extracted with MTBE (3 × 50 mL). We combined the organic layers and washed with a saturated solution of brine (50 mL). The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (100:0−10:1 petrol ether/ethyl acetate) to afford ethyl 2-diazopropanoate.

Methyl α-diazobenzeneacetate was obtained by condensation of ethyl 2-phenylacetate with tosyl azide.[16] We charged a round-bottomed flask with methyl 2-phenylacetate (13.3 mmol, 1.0 equiv), MeCN (30 mL), and tosyl azide (20 mmol, 1.5 equiv) under nitrogen at room temperature. The reaction temperature was cooled to 0 °C, and DBU (20 mmol, 1.5 equiv) was added slowly to the reaction mixture. The reaction mixture was allowed to warm to room temperature and stirred at room temperature overnight. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The reaction mixture was extracted with MTBE (3 × 50 mL). The solvent was removed under reduced pressure and purified by flash column chromatography (100:0−10:1 petrol ether/ethyl acetate) to afford methyl α-diazobenzeneacetate.

Experimental Procedures. To a stirred mixture of 2-pyridones **1** (0.25 mmol, 1.0 equiv), tosylhydrazones ordiazoacetates **2** (0.5 mmol, 2.0 equiv), and Cs_2CO_3 (0.5 mmol, 2.0 equiv) in dioxane (2.0 mL) was added Cu salt (0.05 mmol, 0.2 equiv) at room temperature under a nitrogen atmosphere. After raising the temperature to 110 °C on a heating plate and stirring for 2 h, the reaction mixture was cooled to room temperature. The resulting mixture was diluted with DCM (20 mL). The resulting mixture was filtered, and the filter cake was washed with DCM:EA (1:1) (3 × 20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3);

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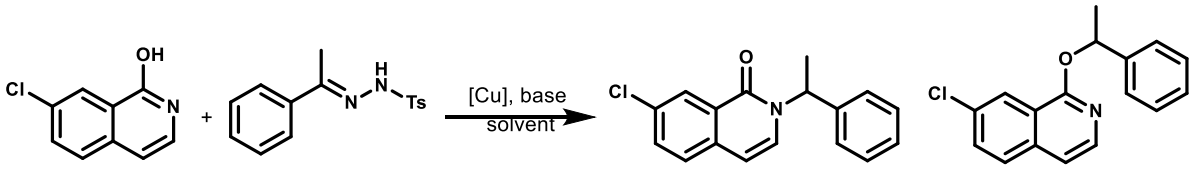
J. Org. Chem. 2021, 86, 6918−6926

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a 3a'

entry	[Cu]	solvent	base	ratio of 3a/M[b]	ratio of 3a/3a'[b]
1	none	1,4-dioxane	Cs_2CO_3	no	/
2	CuI	1,4-dioxane	Cs_2CO_3	1.33	single peak
3	$Cu(OAc)_2$	1,4-dioxane	Cs_2CO_3	0.98	single peak
4	$Cu(SO_3CF_3)_2$	1,4-dioxane	Cs_2CO_3	1.28	single peak
5	$Cu(acac)_2$	1,4-dioxane	Cs_2CO_3	1.97	single peak
6	Cu_2O	1,4-dioxane	Cs_2CO_3	0.76	single peak
7	Cu	1,4-dioxane	Cs_2CO_3	0.30	single peak
8	$Cu(acac)_2$	1,4-dioxane	K_2CO_3	0.21	single peak
9	$Cu(acac)_2$	1,4-dioxane	Na_2CO_3	no	/
10	$Cu(acac)_2$	1,4-dioxane	Li_2CO_3	no	/
11	$Cu(acac)_2$	1,4-dioxane	NaOH	0.82	single peak
12	$Cu(acac)_2$	1,4-dioxane	NaOtBu	1.42	single peak
13	$Cu(acac)_2$	1,4-dioxane	KOtBu	1.57	single peak
14	$Cu(acac)_2$	1,4-dioxane	K_3PO_4	0.17	single peak
15	$Cu(acac)_2$	1,4-dioxane	DBU	trace	/
16	$Cu(acac)_2$	1,4-dioxane	LiOH	1.81	single peak
17	$Cu(acac)_2$	1,4-dioxane	DIPEA	trace	/
18[c]	$Cu(acac)_2$	THF	Cs_2CO_3	no	/
19[d]	$Cu(acac)_2$	DCE	Cs_2CO_3	trace	/
20[e]	$Cu(acac)_2$	MeCN	Cs_2CO_3	0.30	single peak
21	$Cu(acac)_2$	toluene	Cs_2CO_3	0.79	single peak
22	$Cu(acac)_2$	DMF	Cs_2CO_3	0.80	single peak
23[f]	$Cu(acac)_2$	1,4-dioxane	Cs_2CO_3	no	/
24[g]	$Cu(acac)_2$	1,4-dioxane	Cs_2CO_3	no	/
25[h]	$Cu(acac)_2$	1,4-dioxane	Cs_2CO_3	1.69	single peak
26[i]	$Cu(acac)_2$	1,4-dioxane	Cs_2CO_3	1.74	single peak

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (2 equiv), Cu salt (0.2 equiv), base (2.0 equiv), solvent (2.0 mL), and vigorous stirring under a N_2 atmosphere at 110 °C, 2 h. [b]Ratio of isomers based on LCMS and HPLC using 5-bromo-2-methyl-2*H*-indazole (M, 1.0 equiv) as an internal standard. [c]65 °C for 2 h. [d]85 °C for 2 h. [e]80 °C for 2 h. [f]Room temperature for 2 h. [g]50 °C for 2 h. [h]80 °C for 2 h. [i]80 °C for 10 h.

30% to 100% gradient in 15 min; detector, UV 254 nm to afford the corresponding products.

Gram-Scale Experiment of 4q. To a stirred mixture of 2-pyridones **1** (10.0 mmol, 1.0 equiv), tosylhydrazones **2a** (20.0 mmol, 2.0 equiv), and Cs_2CO_3 (20.0 mmol, 2.0 equiv) in dioxane (80 mL) was added CuI (2.0 mmol, 0.2 equiv) at room temperature under a nitrogen atmosphere. After stirring for 2 h at 110 °C, the reaction mixture was cooled to room temperature. The resulting mixture was diluted with DCM (20 mL). The resulting mixture was filtered, and the filter cake was washed with DCM:EA (1:1) (3 × 50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (100:0−10:3 petrol ether/ethyl acetate) to afford the corresponding product **5a** (1.66 g, 72.2%).

7-Chloro-2-(1-phenylethyl)isoquinolin-1(2H)-one (**3a**). 39.1 mg, 55.3% yield; a light yellow semisolid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23−8.17 (m, 1H), 7.80−7.69 (m, 2H), 7.44 (d, J = 7.6 Hz, 1H), 7.41−7.33 (m, 4H), 7.33−7.25 (m, 1H), 6.70 (dd, J = 7.6, 0.7 Hz, 1H), 6.30 (q, J = 7.2 Hz, 1H), 1.75 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.3, 141.4, 135.6, 133.0, 131.8, 130.2, 129.11, 128.9, 128.1, 127.4, 126.9, 126.8, 105.6, 52.9, 19.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{15}ClNO$ 284.0842; found 284.0834.

7-Chloro-2-(1-(3-nitrophenyl)ethyl)isoquinolin-1(2H)-one (**3b**). 32.5 mg, 39.6% yield; a light yellow semisolid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21−8.13 (m, 3H), 7.82−7.73 (m, 3H), 7.70−7.65 (m, 1H), 7.62 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 6.33 (q, J = 7.2 Hz, 1H), 1.83 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.3, 148.4, 143.8, 135.7, 134.2, 133.2, 131.9, 130.7, 130.2, 129.0, 126.9, 126.8, 123.0, 122.0, 105.9, 53.1, 19.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{14}ClN_2O_3$ 329.0693; found 329.0682.

7-Chloro-2-(1-(4-nitrophenyl)ethyl)isoquinolin-1(2H)-one (**3c**). 15.3 mg, 18.6% yield; a light yellow semisolid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24−8.13 (m, 3H), 7.80−7.71 (m, 2H), 7.63−7.49 (m, 3H), 6.75 (d, J = 7.5 Hz, 1H), 6.30 (q, J = 7.2 Hz, 1H), 1.81 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.3, 149.2, 147.2, 135.7, 133.2, 131.9, 130.3, 129.3, 129.0, 128.6, 126.9, 126.8, 124.2, 105.9, 53.3, 19.1;

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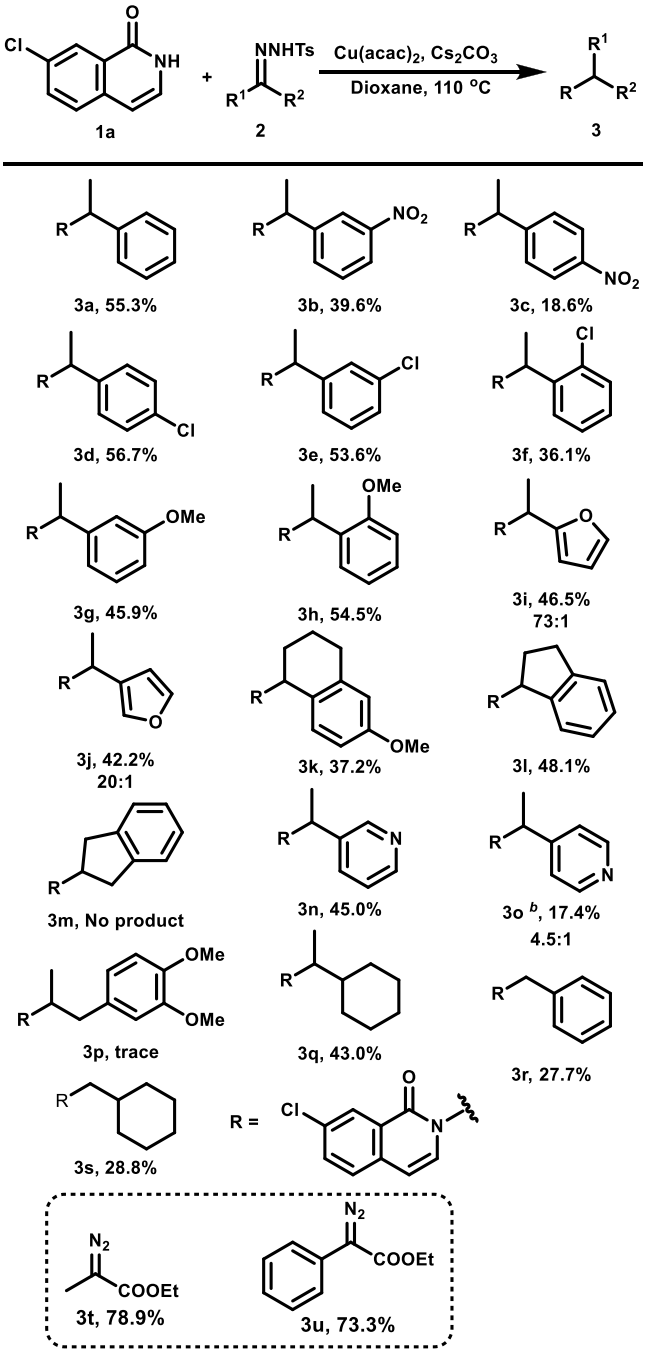
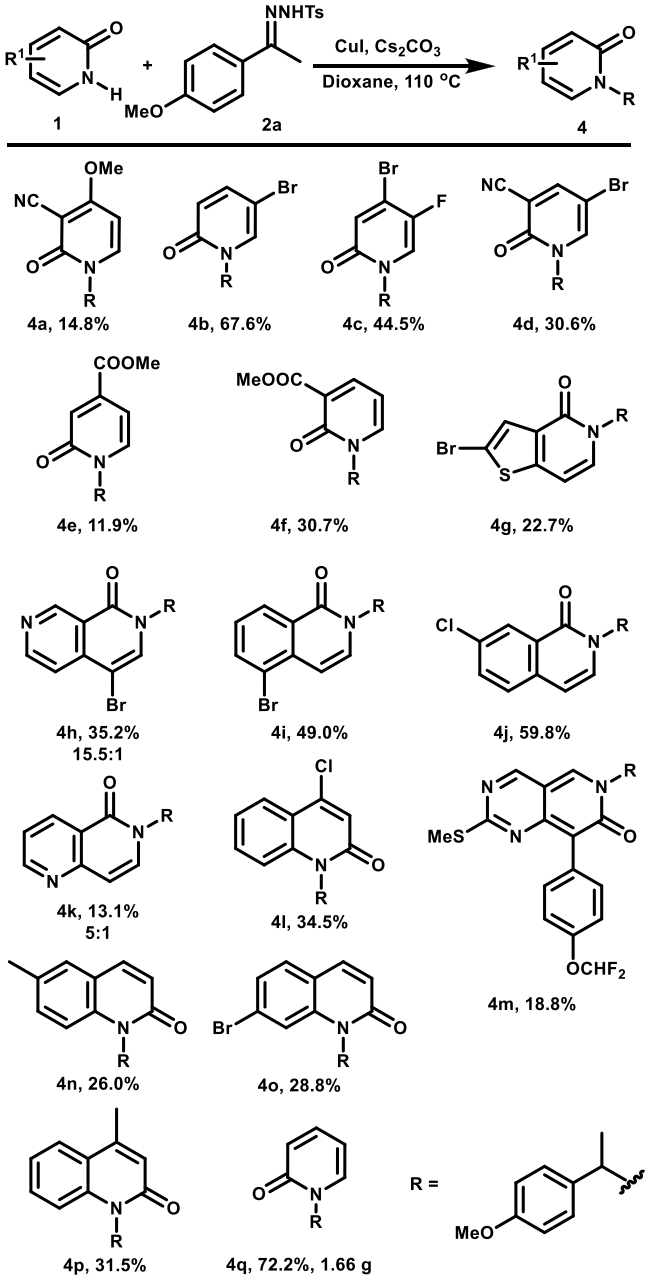
Scheme 1. Scope of Tosylhydrazones[a]



[a]Reaction conditions: **1a** (0.25 mmol), **2** (2.0 equiv), $Cu(acac)_2$ (0.2 equiv), Cs_2CO_3 (2.0 equiv), 1,4-dioxane (2.0 mL), vigorous stirring under N_2 atmosphere at 110 °C, 2 h. If not noted, only N-alkylated products are detected in LCMS. [b]CuI as catalyst.

Scheme 2. Scope of Pyridones[a]



[a]Reaction conditions: **1a** (0.25 mmol), **2** (2 equiv), CuI_2 (0.2 equiv), Cs_2CO_3 (2.0 equiv), 1,4-dioxane (2.0 mL), vigorous stirring under N_2 atmosphere at 110 °C, 2 h. If not noted, only N-alkylated products are detected in LCMS.

HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{14}ClN_2O_3$ 329.0693; found 329.0682.

7-Chloro-2-(1-(4-chlorophenyl)ethyl)isoquinolin-1(2H)-one (**3d**). 44.9 mg, 56.7% yield; a light yellow semisolid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 8.21−8.16 (m, 1H), 7.81−7.69 (m, 2H), 7.49−7.33 (m, 5H), 6.71 (dd, J = 7.6, 0.7 Hz, 1H), 6.25 (q, J = 7.2 Hz, 1H), 1.74 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 160.3, 140.5, 135.6, 133.1, 132.7, 131.8, 130.1, 129.3, 129.0, 128.95, 126.9, 126.8, 105.8, 52.6, 19.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{14}Cl_2NO$ 318.0452; found 318.0441.

7-Chloro-2-(1-(3-chlorophenyl)ethyl)isoquinolin-1(2H)-one (**3e**). 42.5 mg, 53.6% yield; a light yellow oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 2.1 Hz, 1H), 7.81−7.70 (m, 2H), 7.53 (d, J = 7.5 Hz, 1H), 7.44−7.33 (m, 3H), 7.34−7.26 (m, 1H), 6.76−6.69 (m, 1H), 6.25 (q, J = 7.2 Hz, 1H), 1.76 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 160.3, 144.1, 135.6, 133.8, 133.1, 131.8, 131.0, 130.1, 129.0, 128.1,

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127.2, 126.9, 126.8, 126.2, 105.8, 52.8, 19.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{14}Cl_2NO$ 318.0452; found 318.0442.

7-Chloro-2-(1-(2-chlorophenyl)ethyl)isoquinolin-1(2H)-one (**3f**). 28.6 mg, 36.1% yield; a light yellow oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 2.3 Hz, 1H), 7.7 (d, J = 2.2 Hz, 1H), 7.73 (s, 1H), 7.60−7.56 (m, 1H), 7.50−7.47 (m, 1H), 7.43−7.38 (m, 2H), 7.24 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.32 (q, J = 6.8 Hz, 1H), 1.71 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 159.9, 138.2, 135.6, 133.6, 133.1, 131.8, 130.3, 130.2, 129.8, 129.2, 129.0, 128.1, 126.8, 126.7, 105.5, 51.8, 18.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{14}Cl_2NO$ 318.0452; found 318.0437.

7-Chloro-2-(1-(3-methoxyphenyl)ethyl)isoquinolin-1(2H)-one (**3g**). 35.9 mg, 45.9% yield; a light yellow oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 2.2 Hz, 1H), 7.80−7.69 (m, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 8.2 Hz, 1H), 6.93−6.84 (m, 3H), 6.69 (dd, J = 7.6, 0.7 Hz, 1H), 6.26 (q, J = 7.2 Hz, 1H), 3.74 (s, 3H), 1.73 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.2, 159.9, 143.0, 135.6, 133.1, 131.7, 130.2, 130.2, 129.0, 126.9, 126.8, 119.6, 113.5, 113.2, 105.6, 55.5, 52.8, 19.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{17}ClNO_2$ 314.0948; found 314.0941.

7-Chloro-2-(1-(2-methoxyphenyl)ethyl)isoquinolin-1(2H)-one (**3h**). 42.7 mg, 54.5% yield; a light yellow oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 2.6 Hz, 1H), 7.80−7.65 (m, 2H), 7.40−7.29 (m, 2H), 7.24 (dd, J = 7.5, 2.8 Hz, 1H), 7.05−6.96 (m, 2H), 6.61 (dd, J = 7.6, 2.6 Hz, 1H), 6.37−6.26 (m, 1H), 3.67 (d, J = 2.7 Hz, 3H), 1.72−1.75 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 159.9, 157.4, 135.7, 132.8, 131.5, 130.2, 129.8, 128.8, 128.7, 127.9, 127.0, 126.7, 120.8, 111.8, 104.8, 56.0, 49.3, 18.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{17}ClNO_2$ 314.0948; found 314.0938.

7-Chloro-2-(1-(furan-2-yl)ethyl)isoquinolin-1(2H)-one (**3i**). 31.7 mg, 46.5% yield; a light yellow oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23−8.18 (m, 1H), 7.81−7.74 (m, 1H), 7.74−7.65 (m, 1H), 7.63 (dd, J = 1.9, 0.8 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 6.69 (dd, J = 7.6, 0.7 Hz, 1H), 6.61 (dt, J = 3.3, 1.0 Hz, 1H), 6.49 (dd, J = 3.3, 1.8 Hz, 1H), 6.34−6.24 (m, 1H), 1.66 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 159.9, 153.5, 143.8, 135.7, 133.2, 131.9, 129.4, 129.0, 126.9, 126.8, 111.0, 109.2, 105.8, 47.6, 18.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{13}ClNO_2$ 274.0635; found 274.0630.

7-Chloro-2-(1-(furan-3-yl)ethyl)isoquinolin-1(2H)-one (**3j**). 28.8 mg, 42.2% yield; a light yellow oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 2.2 Hz, 1H), 7.79−7.68 (m, 3H), 7.66 (t, J = 1.7 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 6.43 (dd, J = 1.8, 0.9 Hz, 1H), 6.23−6.13 (m, 1H), 1.64 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.0, 144.6, 141.4, 135.7, 133.0, 131.7, 129.7, 128.9, 126.9, 126.8, 126.3, 110.3, 105.6, 46.2, 19.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{13}ClNO_2$ 274.0635; found 274.0629.

7-Chloro-2-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-isoquinolin-1(2H)-one (**3k**). 31.5 mg, 37.2% yield; a light yellow oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 2.3 Hz, 1H), 7.79−7.68 (m, 2H), 7.02 (d, J = 7.5 Hz, 1H), 6.78 (s, 1H), 6.70 (d, J = 1.5 Hz, 2H), 6.62 (d, J = 7.5 Hz, 1H), 6.14 (dd, J = 8.5, 5.9 Hz, 1H), 3.73 (s, 3H), 2.98−2.88 (m, 1H), 2.82−2.72 (m, 1H), 2.15−2.05 (m, 1H), 2.04−1.68 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.7, 158.8, 140.5, 135.7, 133.0, 131.7, 131.1, 129.4, 129.0, 127.0, 126.8, 126.8, 114.0, 113.5, 105.3, 55.5, 53.4, 29.9, 29.5, 20.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{19}ClNO_2$ 340.1104; found 340.1101.

7-Chloro-2-(2,3-dihydro-1H-inden-1-yl)isoquinolin-1(2H)-one (**3l**). 35.5 mg, 48.1% yield; a light yellow oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 2.3 Hz, 1H), 7.80−7.70 (m, 2H), 7.39 (d, J = 7.5 Hz, 1H), 7.32 (t, J = 7.4 Hz, 1H), 7.22 (td, J = 7.5, 1.2 Hz, 1H), 7.03 (dd, J = 17.8, 7.5 Hz, 2H), 6.65 (d, J = 7.5 Hz, 1H), 6.53 (t, J = 7.7 Hz, 1H), 3.20−3.10 (m, 1H), 3.04−2.94 (m, 1H), 2.75−2.56 (m, 2H), 2.14−2.03 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.7, 144.5, 141.7, 135.7, 133.0, 131.8, 130.1, 129.0, 128.8, 127.5, 126.8, 125.5, 124.6, 105.9, 60.1, 32.5, 30.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{15}ClNO$ 296.0842; found 296.0835.

7-Chloro-2-(1-(pyridin-3-yl)ethyl)isoquinolin-1(2H)-one (**3n**). 32.0 mg, 45.0% yield; a brown oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (br, 2H), 8.18 (d, J = 2.2 Hz, 1H), 7.77 (dd, J = 8.4, 2.3 Hz, 2H), 7.73 (d, J = 8.5 Hz, 1H), 7.64−7.33 (m, 2H), 6.73 (d, J = 7.5 Hz, 1H), 6.30 (q, J = 7.2 Hz, 1H), 1.80 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.3, 135.6, 133.1, 131.8, 130.1, 129.0, 126.9, 126.8, 105.9, 19.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{14}ClN_2O$ 285.0795; found 285.0789.

7-Chloro-2-(1-(pyridin-4-yl)ethyl)isoquinolin-1(2H)-one (**3o**). 12.4 mg, 17.4% yield; a brown oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68−8.54 (m, 2H), 8.32 (d, J = 2.2 Hz, 1H), 8.00−7.92 (m, 2H), 7.80 (dd, J = 8.8, 2.2 Hz, 1H), 7.55−7.49 (m, 2H), 7.41 (d, J = 5.8 Hz, 1H), 6.45 (q, J = 6.6 Hz, 1H), 1.72 (d, J = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 158.2, 140.5, 136.6, 132.1, 132.1, 129.3, 122.9, 119.9, 115.5, 72.5, 22.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{14}ClN_2O$ 285.0795; found 285.0788.

7-Chloro-2-(1-cyclohexylethyl)isoquinolin-1(2H)-one (**3q**). 31.1 mg, 43% yield; a brown oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22−8.09 (m, 1H), 7.78−7.67 (m, 2H), 7.49 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 4.79 (s, 1H), 1.87 (d, J = 12.8 Hz, 1H), 1.71 (d, J = 17.9 Hz, 2H), 1.58 (d, J = 9.2 Hz, 2H), 1.33 (d, J = 6.9 Hz, 3H), 1.27−0.96 (m, 5H), 0.87−0.76 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.4, 135.5, 132.8, 131.5, 130.2, 128.8, 126.9, 126.8, 105.3, 41.8, 30.0, 29.5, 26.2, 26.1, 25.9, 25.7, 17.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{21}ClNO$ 290.1312; found 290.1303.

2-Benzyl-7-chloroisoquinolin-1(2H)-one (**3r**). 18.3 mg, 27.2% yield; an off-white solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 2.2 Hz, 1H), 7.79−7.70 (m, 2H), 7.62 (d, J = 7.4 Hz, 1H), 7.44−7.21 (m, 6H), 6.70 (d, J = 7.4 Hz, 1H), 5.20 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.5, 137.9, 136.2, 134.1, 133.0, 131.8, 129.1, 129.1, 128.1, 128.0, 127.1, 126.6, 105.3,

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J. Org. Chem. 2021, 86, 6918−6926

51.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{13}ClNO$ 270.0686; found 270.0680.

*7-Chloro-2-(cyclohexylmethyl)isoquinolin-1(2H)-one (**3s**).* 19.8 mg, 28.8% yield; an off-white solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 8.15 (dd, J = 2.0, 0.9 Hz, 1H), 7.78−7.68 (m, 2H), 7.47 (d, J = 7.3 Hz, 1H), 6.65 (dd, J = 7.4, 0.7 Hz, 1H), 3.82 (d, J = 7.3 Hz, 2H), 1.79 (ddt, J = 11.1, 7.2, 3.6 Hz, 1H), 1.72−1.64 (m, 2H), 1.64−1.52 (m, 3H), 1.21−1.09 (m, 3H), 1.07−0.95 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 160.5, 136.1, 134.7, 132.8, 131.5, 128.9, 127.0, 126.5, 104.4, 54.6, 37.2, 30.4, 26.4, 25.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{19}ClNO$ 276.1155; found 276.1148.

*Ethyl 2-(7-Chloro-1-oxoisoquinolin-2(1H)-yl)propanoate (**3t**).* 55.0 mg, 78.9% yield; a white solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 2.2 Hz, 1H), 8.02−7.95 (m, 2H), 7.83 (dd, J = 8.7, 2.2 Hz, 1H), 7.47 (d, J = 5.8 Hz, 1H), 5.43 (q, J = 7.0 Hz, 1H), 4.17−4.07 (m, 2H), 1.66 (d, J = 7.0 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 171.7, 158.2, 140.3, 136.6, 132.1, 132.1, 129.4, 122.7, 119.4, 115.7, 70.6, 61.0, 17.8, 14.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{15}ClNO_3$ 280.0740; found 280.0730.

*Methyl 2-(7-Chloro-1-oxoisoquinolin-2(1H)-yl)-2-phenylacetate (**3u**).* 60 mg, 73.3% yield; a light yellow solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 2.2 Hz, 1H), 8.08−8.01 (m, 2H), 7.86 (dd, J = 8.7, 2.2 Hz, 1H), 7.74−7.69 (m, 2H), 7.56−7.47 (m, 4H), 6.44 (s, 1H), 3.65 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.3, 158.1, 140.3, 136.7, 135.1, 132.3, 132.3, 129.7, 129.4, 129.4, 128.2, 122.6, 119.4, 116.1, 76.0, 52.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{15}ClNO_3$ 328.0740, found 328.0731.

*4-Methoxy-1-(1-(4-methoxyphenyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**4a**).* 10.5 mg, 14.8% yield; a white solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 8.0 Hz, 1H), 7.30−7.23 (m, 2H), 6.96−6.89 (m, 2H), 6.41 (d, J = 7.9 Hz, 1H), 6.05 (q, J = 7.2 Hz, 1H), 3.97 (s, 3H), 3.75 (s, 3H), 1.67 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 172.6, 160.9, 159.4, 142.7, 128.8, 115.1, 114.5, 95.2, 86.4, 58.1, 55.6, 53.2, 19.3; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{16}N_2O_3Na$ 307.1059; found 307.1051.

*5-Bromo-1-(1-(4-methoxyphenyl)ethyl)pyridin-2(1H)-one (**4b**).* 51.9 mg, 67.6% yield; a white solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 2.8 Hz, 1H), 7.47 (dd, J = 9.7, 2.8 Hz, 1H), 7.33−7.27 (m, 2H), 6.96−6.90 (m, 2H), 6.41 (d, J = 9.6 Hz, 1H), 6.09 (q, J = 7.2 Hz, 1H), 3.74 (s, 3H), 1.67 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 160.2, 159.3, 142.4, 135.7, 132.8, 128.9, 121.7, 114.5, 97.5, 55.6, 53.0, 19.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{15}BrNO_2$ 310.0266; found 310.0257.

*4-Bromo-5-fluoro-1-(1-(4-methoxyphenyl)ethyl)pyridin-2(1H)-one (**4c**).* 36.2 mg, 44.5% yield; a white solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 5.4 Hz, 1H), 7.32−7.27 (m, 2H), 6.95−6.89 (m, 3H), 6.02 (q, J = 7.2 Hz, 1H), 3.74 (s, 3H), 1.67 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 159.3, 158.7, 144.3 (d, J = 228.3 Hz), 132.6, 128.8, 126.0 (d, J = 23.2 Hz), 122.6, 122.0 (d, J = 38.4 Hz), 114.5, 55.6, 53.2, 19.1; ^{19}F NMR (377 MHz, DMSO-d_6) δ −145.20; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{14}BrFNO_2$ 326.0192; found 326.0186.

*5-Bromo-1-(1-(4-methoxyphenyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**4d**).* 25.4 mg, 30.6% yield; a light yellow solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J = 2.7 Hz, 1H), 8.24 (d, J = 2.8 Hz, 1H), 7.40−7.30 (m, 2H), 6.98−6.90 (m, 2H), 6.04 (q, J = 7.2 Hz, 1H), 3.75 (s, 3H), 1.73 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 159.5, 158.3, 150.1, 142.2, 131.8, 129.1, 115.7, 114.6, 105.1, 96.6, 55.6, 55.3, 19.0; HRMS (ESI) m/z $[M + K]^+$ calcd for $C_{15}H_{13}BrN_2O_2K$ 372.9777; found 372.9762.

*Methyl 1-(1-(4-Methoxyphenyl)ethyl)-2-oxo-1,2-dihydropyridine-4-carboxylate (**4e**).* 8.5 mg, 11.9% yield; a colorless oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 7.97 (dd, J = 7.1, 2.2 Hz, 1H), 7.88 (dd, J = 6.8, 2.2 Hz, 1H), 7.32−7.24 (m, 2H), 6.97−6.89 (m, 2H), 6.32 (t, J = 6.9 Hz, 1H), 6.17 (q, J = 7.2 Hz, 1H), 3.74 (s, 6H), 1.67 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 165.8, 159.3, 158.4, 143.7, 140.9, 132.9, 128.9, 120.3, 114.5, 105.1, 55.6, 53.0, 52.2, 19.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{18}NO_4$ 288.1236; found 288.1225.

*Methyl 1-(1-(4-Methoxyphenyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**4f**).* 22.0 mg, 30.7% yield; a colorless oil. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 7.71 (dd, J = 7.1, 0.6 Hz, 1H), 7.31−7.23 (m, 2H), 6.97−6.92 (m, 1H), 6.92−6.86 (m, 2H), 6.55 (dd, J = 7.2, 2.0 Hz, 1H), 6.13 (q, J = 7.2 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 2.47 (s, 1H), 1.67 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 165.1, 161.3, 159.3, 140.0, 136.9, 132.7, 128.9, 121.1, 114.5, 104.1, 55.6, 53.3, 52.8, 19.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{18}NO_4$ 288.1236; found 288.1229.

*2-Bromo-5-(1-(4-methoxyphenyl)ethyl)thieno[3,2-c]pyridin-4(5H)-one (**4g**).* 20.6 mg, 22.7% yield; a pink semisolid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, J = 0.6 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.32−7.24 (m, 2H), 6.95−6.86 (m, 3H), 6.23 (q, J = 7.2 Hz, 1H), 3.73 (s, 3H), 1.69 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 159.2, 156.9, 148.5, 133.3, 130.9, 130.4, 128.8, 127.7, 114.5, 112.5, 101.8, 55.6, 52.0, 19.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{15}BrNO_2S$ 364.0007; found 364.0000.

*4-Bromo-2-(1-(4-methoxyphenyl)ethyl)-2,7-naphthyridin-1(2H)-one (**4h**).* 31.5 mg, 35.2% yield; a light yellow solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^1H NMR (400 MHz, DMSO-d_6) δ 9.40 (d, J = 0.8 Hz, 1H), 8.88 (d, J = 5.5 Hz, 1H), 7.96 (s, 1H), 7.61 (dd, J = 5.6, 0.8 Hz, 1H), 7.42−7.33 (m, 2H), 6.97−6.89 (m, 2H), 6.21 (q, J = 7.1 Hz, 1H), 3.75 (s, 3H), 1.77 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 159.9, 159.4, 152.6, 151.2, 140.8, 135.4, 132.5, 129.0, 121.0, 118.5, 114.5, 97.0, 55.6, 53.0, 18.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{16}BrN_2O_2$ 359.0395; found 359.0389.

*5-Bromo-2-(1-(4-methoxyphenyl)ethyl)isoquinolin-1(2H)-one (**4i**).* 43.7 mg, 49% yield; an off-white solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV

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J. Org. Chem. 2021, 86, 6918−6926

254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (dt, J = 8.1, 1.0 Hz, 1H), 8.03 (dd, J = 7.7, 1.2 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.33−7.27 (m, 2H), 6.95−6.90 (m, 2H), 6.73 (dd, J = 7.8, 0.7 Hz, 1H), 6.24 (q, J = 7.1 Hz, 1H), 3.74 (s, 3H), 1.71 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.5, 159.2, 136.5, 135.8, 133.1, 131.4, 128.8, 128.2, 127.9, 127.4, 120.3, 114.5, 104.0, 55.6, 52.5, 19.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{17}BrNO_2$ 358.0443; found 358.0437.

7-Chloro-2-(1-(4-methoxyphenyl)ethyl)isoquinolin-1(2H)-one (**4j**). 46.8 mg, 59.8% yield; an off-white solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 2.2 Hz, 1H), 7.75 (dd, J = 8.5, 2.2 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.34−7.26 (m, 2H), 6.96−6.88 (m, 2H), 6.67 (d, J = 7.5 Hz, 1H), 6.26 (q, J = 7.2 Hz, 1H), 3.74 (s, 3H), 1.71 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.2, 159.2, 135.6, 133.2, 133.0, 131.7, 130.0, 128.9, 128.8, 126.9, 126.8, 114.5, 105.5, 55.6, 52.3, 19.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{17}ClNO_2$ 314.0948; found 314.0941.

6-(1-(4-Methoxyphenyl)ethyl)-1,6-naphthyridin-5(6H)-one (**4k**). 9.2 mg, 13.1% yield; a light yellow semisolid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (dd, J = 4.5, 1.8 Hz, 1H), 8.58 (ddd, J = 8.1, 1.9, 0.7 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.53 (dd, J = 8.1, 4.5 Hz, 1H), 7.36−7.24 (m, 2H), 6.97−6.89 (m, 2H), 6.70 (dd, J = 7.8, 0.7 Hz, 1H), 6.25 (q, J = 7.2 Hz, 1H), 3.74 (s, 3H), 1.73 (d, J = 7.2 Hz, 3H), 1.33−1.22 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.5, 159.2, 155.2, 153.2, 136.2, 133.5, 133.1, 128.9, 122.5, 121.4, 114.5, 107.6, 55.6, 52.4, 19.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_2$ 281.1290; found 281.1282.

4-Chloro-1-(1-(4-methoxyphenyl)ethyl)quinolin-2(1H)-one (**4l**). 27.0 mg, 34.5% yield; an off-white solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (dd, J = 8.1, 1.6 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.35−7.22 (m, 2H), 7.20−7.13 (m, 2H), 7.05 (s, 1H), 6.93−6.86 (m, 2H), 6.84−6.70 (s, 1H), 3.72 (s, 3H), 1.86 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.8, 158.5, 143.8, 138.2, 132.4, 131.7, 127.3, 127.3, 126.2, 126.2, 122.9, 121.1, 119.6, 117.5, 114.6, 114.6, 55.5, 16.7; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{17}ClNO_2$ 314.0948; found 314.0939.

8-(4-(Difluoromethoxy)phenyl)-6-(1-(4-methoxyphenyl)ethyl)-2-(methylthio)pyrido[4,3-d]pyrimidin-7(6H)-one (**4m**). 22.1 mg, 18.8% yield; a yellow solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.99 (s, 1H), 7.74−7.61 (m, 2H), 7.41−7.31 (m, 2H), 7.29 (t, J = 74 Hz, 1H), 7.23−7.13 (m, 2H), 7.01−6.89 (m, 2H), 6.36 (q, J = 7.1 Hz, 1H), 3.75 (s, 3H), 2.37 (s, 3H), 1.83 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 173.5, 163.3, 161.0, 159.4, 150.0, 148.2, 144.7, 133.4, 132.6, 130.8, 129.0, 127.9, 117.5, 116.9 (t, J = 258.6 Hz), 114.6, 108.5, 55.6, 55.1, 20.4, 14.1; ^{19}F NMR (377 MHz, DMSO-d_6) δ −81.72; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{24}H_{22}F_2N_3O_3S$ 470.1350; found 470.1346.

1-(1-(4-Methoxyphenyl)ethyl)-6-methylquinolin-2(1H)-one (**4n**). 19.1 mg, 26% yield; a light yellow semisolid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 9.4 Hz, 1H), 7.50−7.45 (m, 1H), 7.19−6.99 (m, 4H), 6.93−6.76 (m, 3H), 6.66 (d, J = 9.4 Hz, 1H), 3.72 (s, 3H), 2.28 (s, 3H), 1.83 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.1, 158.4, 140.0, 136.2, 132.9, 131.3, 131.2, 129.3, 127.3, 121.7, 121.4, 116.9, 114.5, 55.5, 20.3, 16.7; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{20}NO_2$ 294.1494; found 294.1487.

7-Bromo-1-(1-(4-methoxyphenyl)ethyl)quinolin-2(1H)-one (**4o**). 25.7 mg, 28.8% yield; a light yellow solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 9.5 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 8.4, 1.7 Hz, 2H), 7.18−7.11 (m, 2H), 6.97−6.89 (m, 2H), 6.72 (d, J = 9.5 Hz, 2H), 3.73 (s, 3H), 1.83 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.0, 158.6, 139.8, 132.4, 131.5, 127.3, 125.1, 123.5, 122.0, 120.8, 119.1, 114.7, 55.5, 16.5; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{17}BrNO_2$ 358.0443; found 358.0435.

1-(1-(4-Methoxyphenyl)ethyl)-4-methylquinolin-2(1H)-one (**4p**). 23.1 mg, 31.5% yield; a light yellow solid. The title compound was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.05% NH_4HCO_3), 30% to 100% gradient in 15 min; detector, UV 254 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (dd, J = 8.1, 1.6 Hz, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.22−7.08 (m, 4H), 6.93−6.78 (m, 3H), 6.62 (s, 1H), 3.72 (s, 3H), 2.46 (d, J = 1.2 Hz, 3H), 1.84 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.9, 158.4, 147.4, 137.9, 133.0, 130.0, 127.2, 126.2, 122.2, 122.0, 120.7, 117.2, 114.5, 55.5, 18.9, 16.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{20}NO_2$ 294.1494; found 294.1486.

1-(1-(4-Methoxyphenyl)ethyl)pyridin-2(1H)-one (**4q**). 1.66 g, 72.2% yield. The title compound was isolated as a light yellow solid after flash chromatography on silica gel (100:0−10:3 petrol ether/ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (ddd, J = 7.0, 2.1, 0.7 Hz, 1H), 7.35 (ddd, J = 8.9, 6.5, 2.1 Hz, 1H), 7.28−7.22 (m, 2H), 6.95−6.88 (m, 2H), 6.39 (ddd, J = 9.2, 1.4, 0.7 Hz, 1H), 6.24−6.12 (m, 2H), 3.73 (s, 3H), 1.64 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 159.1, 139.7, 135.7, 133.3, 128.8, 119.9, 114.4, 106.2, 55.6, 51.9, 19.5; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{16}NO_2$ 230.1181; found 230.1174.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00009.

Experimental procedures and spectral data (PDF)

FAIR data, including the primary NMR FID files, for compounds **3a−3l**, **3n−3o**, **3q−3u**, and **4a−4q** (ZIP)

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Notes

The authors declare no competing financial interest.

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