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$AgSbF_6$-mediated Selective Thiolation and Selenylation at C-4 Position of Isoquinolin-1(*2H*)-ones

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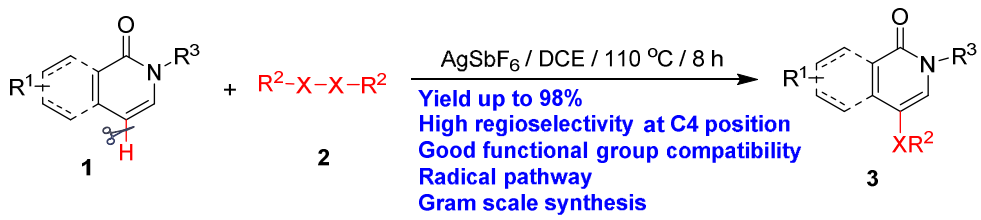


R^1 = H, 7-Cl, 6-Cl, 6-Br, 5-CH_3;
R^2 = C_6H_5, 4-ClC_6H_4, 3,5-$Cl_2C_6H_3$, 2-FC_6H_4, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, 4-CNC_6H_4, 3-FC_6H_4; C_2H_5
R^3 = H, CH_3; X = S, Se.

ABSTRACT: A new and facile $AgSbF_6$-mediated protocol for the construction of C-4 thiolated or selenylated isoquinolin-1(*2H*)-ones *via* a radical pathway was established. This reaction proceeded efficiently with excellent regioselectivity, a broad range substrate scope and good functional group tolerance. A radical reaction mechanism involving thiyl radicals as key intermediates is proposed for the present transformation.

INTRODUCTION

The isoquinolin-1(*2H*)-one scaffold has undoubtedly become a privileged structural motif within the isoquinolone family. Isoquinolin-1(*2H*)-one derivatives exhibit an amazingly wide spectrum of biological properties including anticancer,[1] steroidogenic

factor-1,[2] Rho-kinase (ROCK),[3] poly(ADP-ribose) polymerase [4] and CRTH2 inhibitory activities.[5] Accordingly, an increasing number of attentions has focused on the derivatization of isoquinolin-1(*2H*)-one, and different functional groups have been introduced into the scaffold by many methods such as transition metal-catalysis. Recently, Rode [6] and Lai [7-8] reported the nitration and chlorosulfonylation reaction at the C5 position of isoquinolin-1(*2H*)-one. With significant progress in the C-H functionalization,[9] substitutions at the C8 positions of isoquinolin-1(*2H*)-one has been reported.[10-13] Meanwhile, some approaches for the construction of bonds between carbons and carbons/heteroatoms at the C4 position of isoquinolin-1(*2H*)-one have also been developed (Figure 1). For instance, as shown in Figure 1, Sercel,[14] Austin,[15] Ansari,[16] Bach [17] and co-workers developed a route to access 4-substituted- 1(*2H*)-isoquinolinone (**5 - 7)** via bromination, lithiation, followed by electrophilic substitution or addition reactions. Kaila group realized borylation of isoquinolin-1(*2H*)-one in four steps (**8)**. [18] Fish group reported chlorination reaction with *N*-chlorosuccinimide (NCS) in CH_3CN (**9)**. [19] C4-fluorination with F-TEDA-BF_4 in CH_3CN was also developed by Price group (**10)** (Figure 1).[20] Although great progress has been achieved in this field, most of these transformations were performed in multiple steps and suffered from relatively hash reaction conditions. Except for halogenation at C4 position, the one-step method of C4 functionalization of

isoquinolin-1(*2H*)-ones is rare.

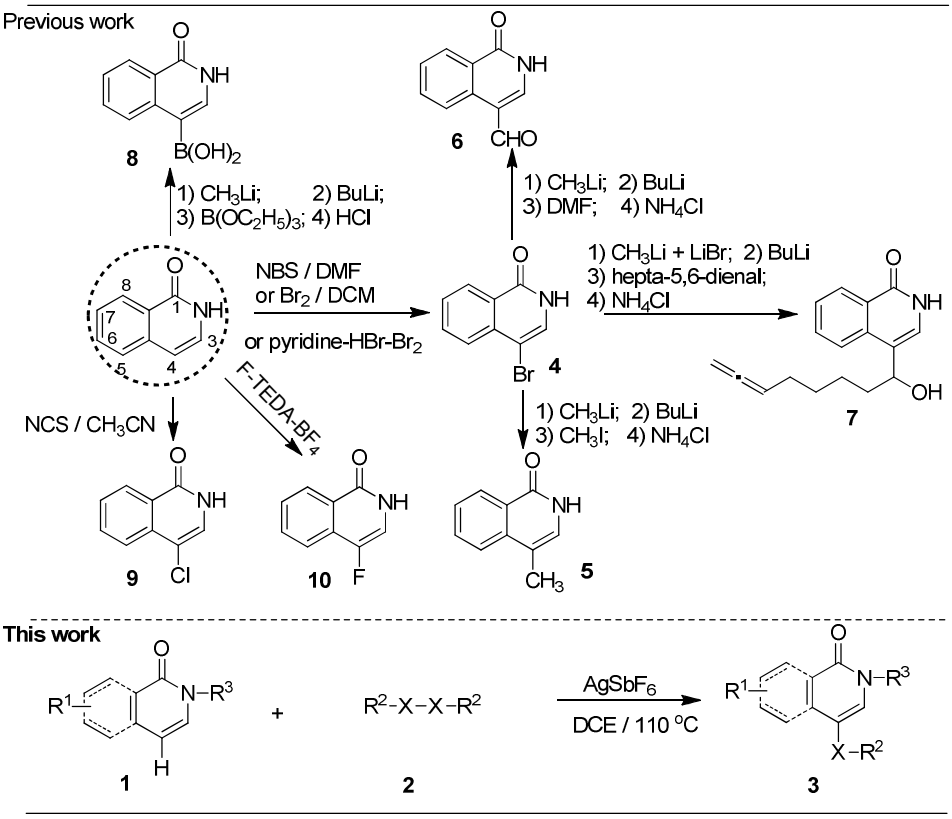


Figure 1. Some examples of functionalization at C4 position of isoquinolin-1(*2H*)-one

On the other hand, organosulfur and organoseleno compounds are of great importance in pharmaceutical industry (such as antifolates,[21] albendazole,[22] nelfinavir,[23] cimetidine [24] and omeprazole [25]) and synthetic chemistry. The development of an efficient method for the C-S and C-Se bond formation reaction has proven to be an attractive research area.[26] For instance, Jiang's group developed a method to synthesis aryl and alkyl thioethers through Cu(II)-catalyzed and chelate-directed C6-selective C-H thiolation of 2-pyridones with disulfides.[27] Rafique and the

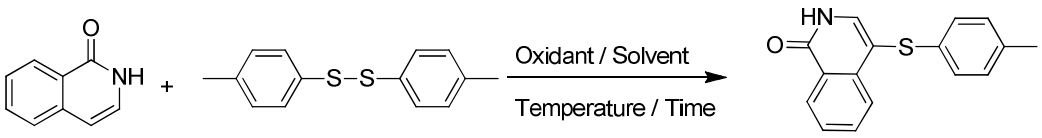
co-authors reported the chalcogenation of bicyclic arenes by using I_2/DMSO as catalytic system.[28] Herein, we wish to report a new $AgSbF_6$-mediated reaction for the synthesis of C-4 thiolated or selenylated isoquinolin-1(*2H*)-ones through the direct thiolation or selenylation of readily available isoquinolin-1(*2H*)-one with diphenyl disulfides or diselenides.

RESULTS AND DISCUSSION

We initially optimized the reaction of isoquinolin-1(*2H*)-one (**1a**) and di-(4-methylphenyl) disulfide (**2a**) by using various oxidants in toluene at 130 ^oC (Table 1). None of desired product was detected in the absence of oxidant (entry 1). Then, the reaction was conducted in the presence of various oxidants such as $Cu(OAc)_2$, $AgNO_3$, AgOTf, $AgSbF_6$, AgOAc, $AgBF_4$, CF_3SO_3Ag, CF_3CO_2Ag, I_2 and MnO_2 (Table 1, entries 2 - 11). To our delight, the target product (**3a**) was generated nearly in quantitative yield when $AgSbF_6$ was employed as the oxidant (entry 5). When the amount of $AgSbF_6$ was decreased to 0.15 mmol, the yield fell to 77 % (Table 1, entry 12). However, when the reaction time was shortened to 6 h, the yield was only 85 % (Table 1, entry 13). When the reaction time was prolonged to 8 h, compound **3a** was obtained in nearly quantitative (Table 1, entry 14), which suggested that the optimal time was about 8 h. It was also noticed that the temperature had obvious effection on the reaction efficiency. When the reaction was proceeded at 60 ^oC, 80 ^oC and 110 ^oC

respectively, the yields were reduced to 30 %, 48 % and 72 % (Table 1, entries 15 - 17). In order to investigate the solvent effect on the reaction, the model reaction was carried out in various solvents at 110 ^{o}C (Table 1, entries 18 - 22). The best result (99% yield) was obtained when DCE was used as solvent. When the reaction temperature was decreased to 90 ^{o}C, the yield was only 68 % (Table 1, entry 23). When the stoichiometric ratio of **1a** and **2a** was increased from 1:1 to 2:1, the yield dropped to 44 % (Table 1, entry 24). When the mixture of $AgSbF_6$ (0.03 mmol) and $K_2S_2O_8$ (0.3 mmol) was used as oxidant, little product was detected (Table 1, entry 25).

Table 1. Optimization of the reaction conditions [a]



1a **2a** **3a**

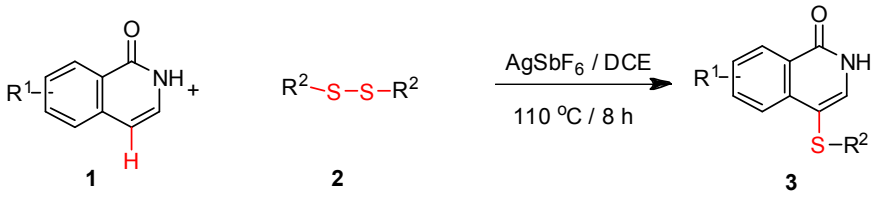
Entry	Oxidant	Solvent	Time (h)	Temp (^{o}C)	Yield (%) [b]
1	-	toluene	12	130	0
2	$Cu(OAc)_2$	toluene	12	130	40
3	$AgNO_3$	toluene	12	130	70
4	AgOTf	toluene	12	130	54
5	$AgSbF_6$	toluene	12	130	≧99
6	AgOAc	toluene	12	130	30
7	$AgBF_4$	toluene	12	130	67
8	CF_3SO_3Ag	toluene	12	130	76
9	CF_3COOAg	toluene	12	130	25
10	I_2	DMSO	12	130	25
11	MnO_2	toluene	12	130	0
12 [c]	$AgSbF_6$	toluene	12	130	77

13	$AgSbF_6$	toluene	6	130	85
14	$AgSbF_6$	toluene	8	130	≧99
15	$AgSbF_6$	toluene	8	110	72
16	$AgSbF_6$	toluene	8	80	48
17	$AgSbF_6$	toluene	8	60	30
18	$AgSbF_6$	Dioxane	8	110	10
19	$AgSbF_6$	DCE	8	110	≧99
20	$AgSbF_6$	THF	8	110	34
21	$AgSbF_6$	*o*-dichlorobenzene	8	110	89
22	$AgSbF_6$	DMF	8	110	0
23	$AgSbF_6$	DCE	8	90	68
24 [d]	$AgSbF_6$	DCE	8	110	44
25[e]	$AgSbF_6$+$K_2S_2O_8$	DCE	8	110	6

[a] **1a** (0.3 mmol), **2a** (0.3 mmol), oxidant (0.3 mmol), solvent (1.5 mL); [b] Yields were determined by the ^{1}H NMR integration method using mesitylene as the internal standard; [c] $AgSbF_6$ (0.15 mmol); [d] **2a** (0.15 mmol); [e] $AgSbF_6$ (0.03 mmol) + $K_2S_2O_8$ (0.3 mmol).

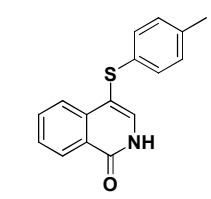
Under the optimized conditions, the scope of the reaction of **1a-1e** with diaryl or dialkyl disulfides was firstly explored (Table 2). As shown in Table 2, the diaryl disulfides with electron-donating groups (such as methoxy, methyl) showed efficient reactivity with the isoquinolin-1(*2H*)-ones, producing the desired products with excellent yields (**3a**, **3d**, **3j**, **3p** and **3s**). However, when the R^2 was *ortho*-fluorophenyl group and R^1 was H, 6-Br and 6-Cl, the yields of corresponding products were 90% (**3c**), 85% (**3m**) and 70% (**3r**) respectively, presumably because the electron-withdrawing effect of chlorine atom might result in the yield decrease. When a methyl group was introduced at the 5-position (**1e**), the yield of **3** was slightly decreased (**3v** - **3x**). This indicated that the steric effect of the C-5 substituent had certain influence on this reaction. When **1a** and **1d** were reacted with diethyl disulfide, the yields of the target product **3y** and **3z** were 45% and 30% respectively. When **1a** was reacted with 4-chlorobenzenethiol, the yield of the target product **3b** was only 35%.

Table 2. Scope of thiolation of isoquinolin-1(*2H*)-ones [a]

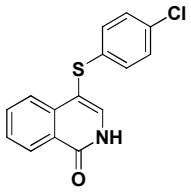


1 **2** **3**

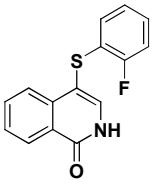
R^1 = H(**1a**), 7-Cl(**1b**), 6-Cl(**1c**), 6-Br(**1d**), 5-CH_3(**1e**); R^2 = C_6H_5, 4-ClC_6H_4, 3,5-di-ClC_6H_3, 2-FC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-CNC_6H_4, 3-FC_6H_4, C_2H_5



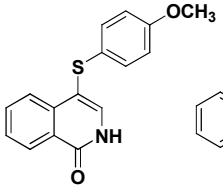
3a 96%



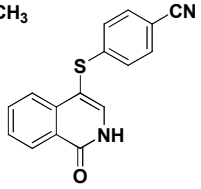
3b 90%



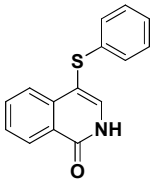
3c 90%



3d 95%

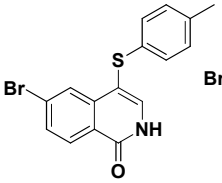


3e 70%

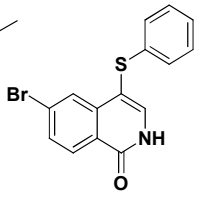


3f 98%

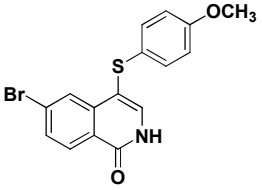
3g 90%



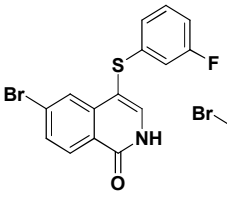
3h 90%



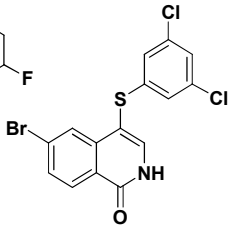
3i 90%



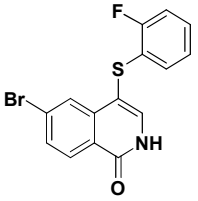
3j 95%



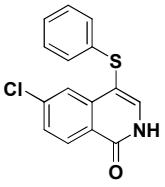
3k 90%



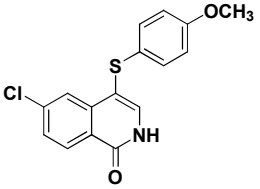
3l 75%



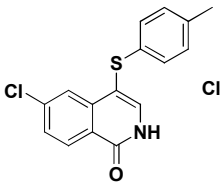
3m 85%



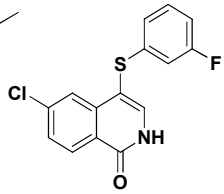
3n 80%



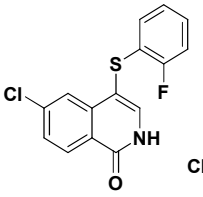
3o 87%



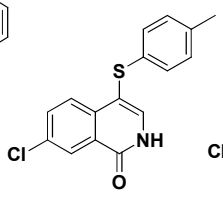
3p 90%



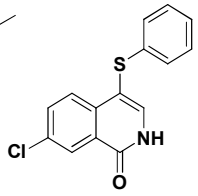
3q 88%



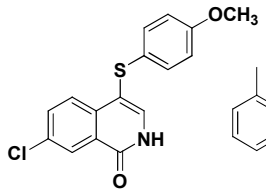
3r 70%



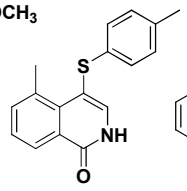
3s 95%



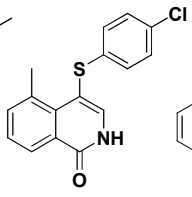
3t 95%



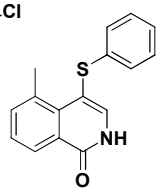
3u 90%



3v 85%



3w 75%



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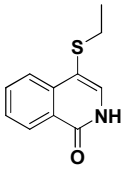
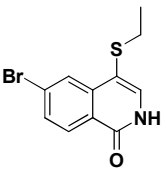


3y 45%

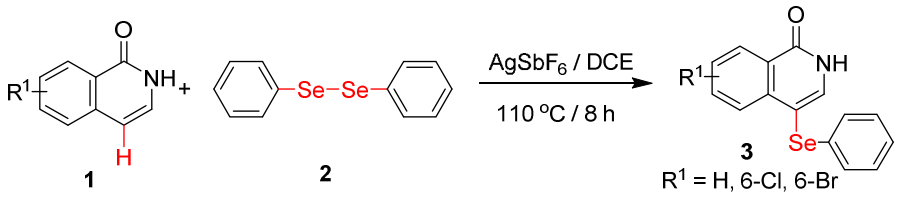


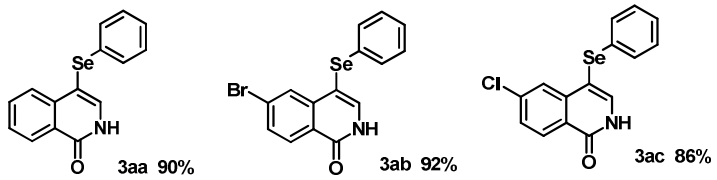
3z 30%

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), $AgSbF_6$ (0.3 mmol), DCE (1.5 mL), 8 h, 110 ^oC; Yield of purified product is reported.

These encouraging results led us to study the propensity of the methodology and explore whether seleno-functionalization of isoquinolin-1(*2H*)-ones could also be achieved to broaden the synthetic utility of this method. Fortunately, when isoquinolin-1(*2H*)-ones were subjected to the standard reaction condition in presence of $(PhSe)_2$, the reaction furnished the desired selenylated product **3aa - 3ac** in 86 - 92% yield (Table 3).

Table 3. Scope of selenylation of isoquinolin-1(*2H*)-ones [a]



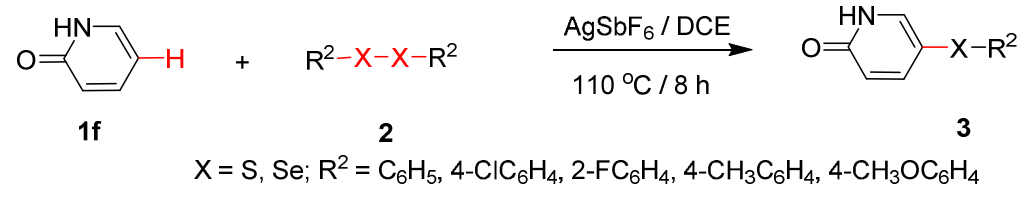


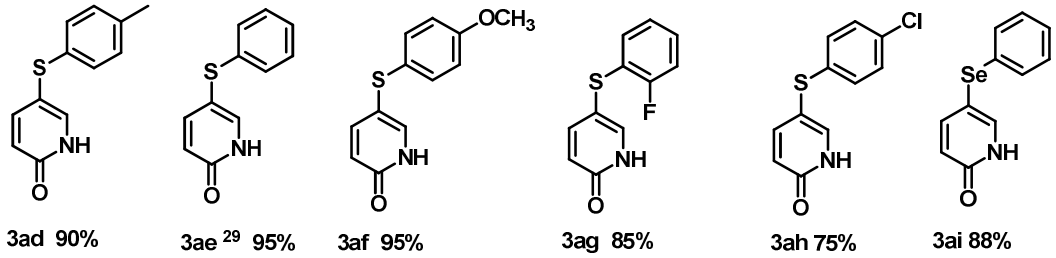
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), $AgSbF_6$ (0.3 mmol), DCE (1.5 mL), 8 h, 110 ^oC; Yield of purified product is reported.

To further demonstrate the selectivity and versatility of this reaction, additional reactions of pyridin-2(*1H*)-one (**1f**) and various quinolinones (**1g – 1j**) with $(ArS)_2$ or $(PhSe)_2$ were examined. As listed in table 4, when pyridin-2(*1H*)-one was reacted with $(ArS)_2$, products **3ad-3ai** were obtained in 70 - 95% yield (Table 4). However, when

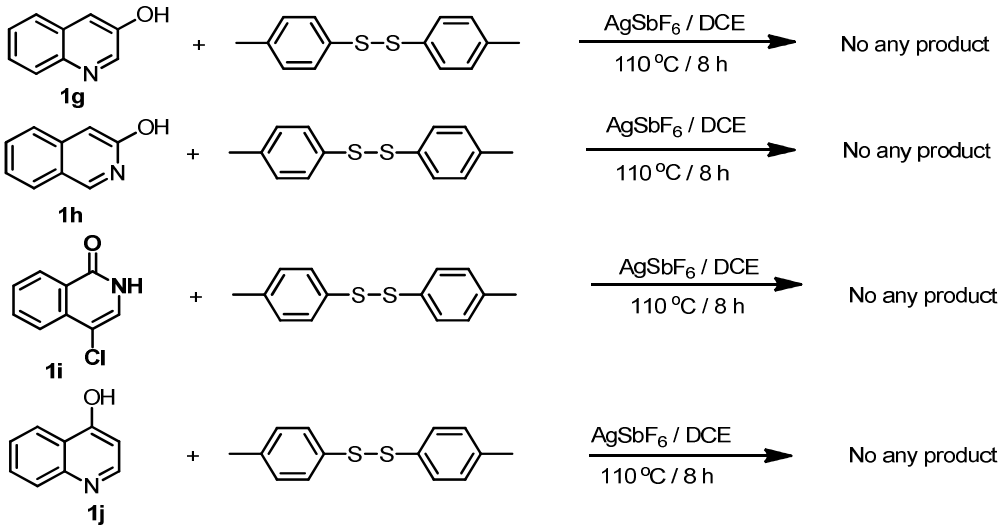
di-(4-methylphenyl) disulfide was reacted with quinolin-3-ol, isoquinolin-3-ol, 4-chloroisoquinolin-1-ol and quinolin-4-ol, respectively (Scheme 1), none of the desired products were detected and most of the starting material quinolinones were recovered. This indicated that this reaction possessed exclusive selectivity and only occurred at the *para*-position of the carbonyl group.

Table 4. Scope of chalcogenation of pyridin-2(*1H*)-one (1f) [a]



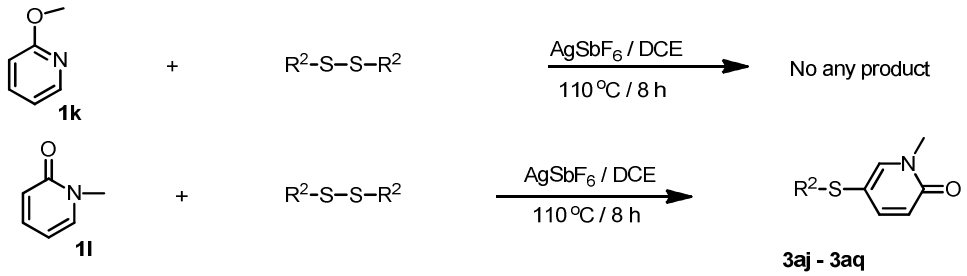


[a] Reaction conditions: **1f** (0.3 mmol), **2** (0.3 mmol), $AgSbF_6$ (0.3 mmol), DCE (1.5 mL), 8 h, 110 °C; Yield of purified product is reported.



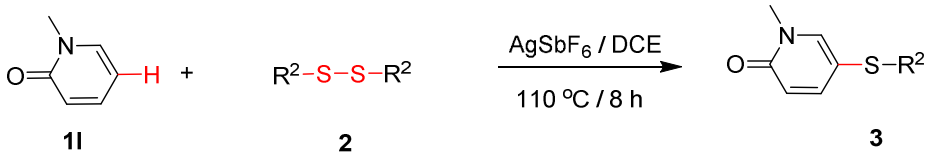
Scheme 1 Reactions between four quinolones and di-(4-methylphenyl) disulfide.

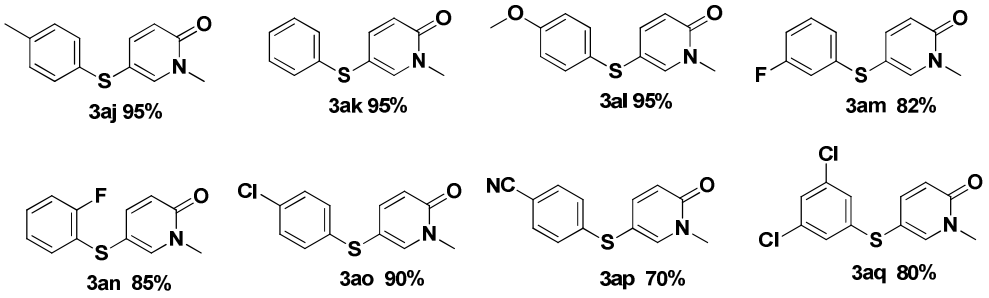
It was well known that pyridin-2(*1H*)-one (**1f**) and various quinolinones (**1a – 1e**) could exist in both keto- and enol-form in the meantime. In order to examine which form is necessary for this reaction, some control experiments were conducted (Scheme 2). When pyridin-2(*1H*)-one (**1f**) was replaced by 2-mthoxypyridine (**1k**) to react with di-aryl disulfides, no any product was detected. When the nitrogen atom of pyridin-2(*1H*)-one (**1f**) was methylated (**1l**), the thiolation reaction proceeded smoothly (Table 5). This suggested that the keto-form was responsible for the thiolation.



Scheme 2. Control experiments

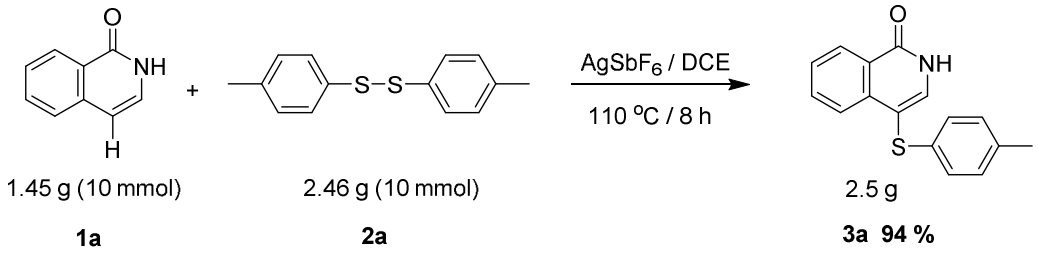
Table 5. Scope of thiolation of 1-methylpyridin-2(1H)-one (**1l**) [a]





[a] Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), $AgSbF_6$ (0.3 mmol), DCE (1.5 mL), 8 h, 110 °C; Yield of purified product is reported.

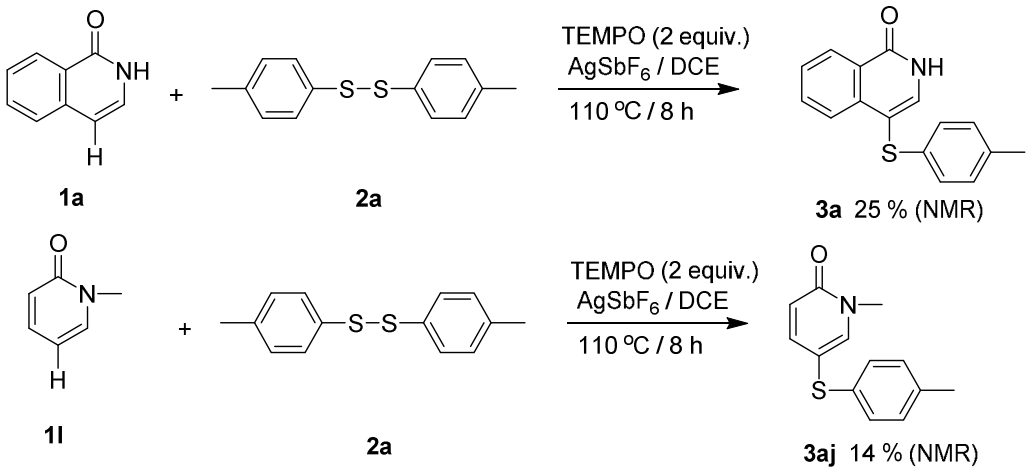
To probe the synthetic utility of this method, a scale-up reaction of 10 mmol was carried out under the optimized conditions (Scheme 3). Through the reaction of isoquinolin-1(*2H*)-one **1a** with di-(4-methylphenyl) disulfide **2a**, the pure product **3a** was obtained in 94 % yield after 8 h.



Scheme 3. Gram scale reaction.

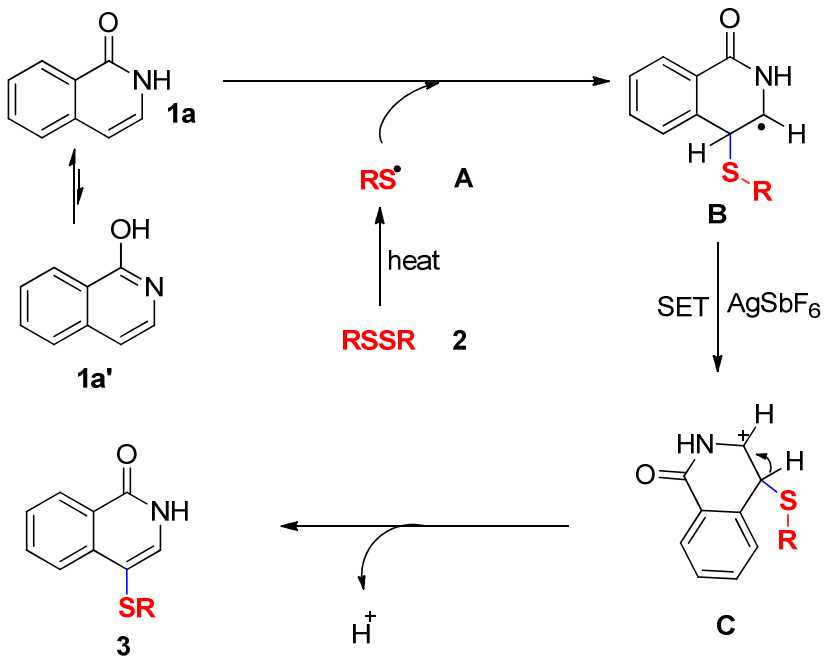
To gain further insight into the reaction mechanism, control experiments were descried under the optimized conditions (Scheme 4). The presence of a radical inhibitor (2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) inhibited the reaction and

the product **3a** and **3aj** were obtained in only 25 % and 14% yield respectively (NMR yield). This result indicates that the reaction might proceed through a radical reaction pathway.



Scheme 4. Control experiments.

On the basis of the preliminary experimental results above and the knowledge of analogous reactions,[30 - 33] a possible reaction pathway was thus proposed as shown in Scheme 5. Initially, a RS radical was generated through homolysis of a disulifide **2** under thermolysis. After that, it underwent addition to **1a** to generate intermediate **B**. Single electron oxidation of this radical intermediate by $AgSbF_6$ afforded carbon cation intermediate **C**, the following deprotonation gave product **3**.



Scheme 5. Postulated reaction pathway.

Conclusion

We have developed a direct and efficient $AgSbF_6$-mediated thiolation or selenylation of isoquinolin-1(*2H*)-ones or pyridin-2(*1H*)-ones with diaryl disulfide or 1,2-diphenyldiselane at the C4-position. This reaction has a broad scope of substrates and affords the target product in high yield with excellent regioselectivity and good functional group tolerance. Mechanistic studies revealed that the present reaction might involve a radical process.

Experimental Section

Solvents and reagents were purchased from Sigma-Aldrich and were used without further purification unless otherwise specified. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometers; internal reference of δ = 7.28 or 77.0

$CHCl_3$ as standard. HRMS was conducted using electro-spraying ionization (ESI), and was performed on a Thermo-Scientific Exactive Orbitrap. Deprotonated molecular ions $[M - H]^-$, protonated molecular ions $[M + H]^+$ or sodium adducts $[M + Na]^+$ were used for empirical formula confirmation.

General Synthetic Procedure for Compounds 3

An oven-dried reaction vessel was charged with isoquinolin-1(*2H*)-one **1** (0.3 mmol), disulfide **2** (0.3 mmol), $AgSbF_6$ (0.3 mmol), DCE (1.5 mL). The mixture was stirred at 110 ^oC (oil bath temperature) for 8 h. After this time, the resulting mixture was cooled down to room temperature, filtered through a short pad of silica gel, and then concentrated under vacuum. The residue was purified by preparative TLC (eluent: hexane/ethyl acetate = 1 : 1) to afford the corresponding product.

4-(*p*-Tolylthio)isoquinolin-1(*2H*)-one (3a). White solid, mp 165 - 167 ^oC; yield 77.0 mg, 96 %; ^1H NMR (400 MHz, $CDCl_3$) δ 11.74 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.71 (s, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.03 (dd, J = 20.6, 8.1 Hz, 4H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 138.3, 135.8, 135.2, 133.4, 130.8, 129.8, 127.8, 127.4, 127.1, 126.1, 125.5, 109.1, 20.9; HRMS (ESI) m/z calcd for $C_{16}H_{12}NOS$ $[M - H]^-$ 266.0645, found 266.0644.

4-((4-Chlorophenyl)thio)isoquinolin-1(*2H*)-one (3b). White solid, mp 158 - 160 ^oC; yield 77.7 mg, 90%; ^1H NMR (400 MHz, $CDCl_3$) δ 11.36 (s, 1H), 8.46 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 9.0 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.17

(d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 137.9, 135.9, 135.8, 133.6, 131.6, 129.2, 128.0, 127.7, 126.4, 125.4, 107.5, 100.0; HRMS (ESI) m/z calcd for $C_{15}H_9ClNOS$ $[M - H]^-$ 286.0099, found 286.0109.

4-((2-Fluorophenyl)thio)isoquinolin-1(*2H*)-one (3c). Pale yellow solid, mp 175 - 177 ^oC; yield 73.3 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 8.46 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 7.71 (ddd, J = 8.3, 7.3, 1.4 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.19 – 7.03 (m, 2H), 6.95 – 6.84 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 159.5 (d, J_{C-F} = 244.8 Hz), 138.1, 136.4, 133.6, 128.7 (d, J_{C-F} = 1.5 Hz), 127.9, 127.7, 127.4 (d, J_{C-F} = 7.5 Hz), 126.3, 125.3, 124.6 (d, J_{C-F} = 3.3 Hz), 115.7, 115.5, 106.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.2; HRMS (ESI) m/z calcd for $C_{15}H_9FNOS$ $[M - H]^-$ 270.0394, found 270.0387.

4-((4-Methoxyphenyl)thio)isoquinolin-1(*2H*)-one (3d). Red solid, mp 185 - 187 ^oC; yield 80.8 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.68 (s, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.65 (s, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.22 – 7.15 (m, 2H), 6.82 – 6.74 (m, 2H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 158.5, 138.2, 134.7, 133.3, 129.6, 127.8, 127.4, 127.2, 126.3, 125.5, 114.8, 109.9, 55.3; HRMS (ESI) m/z calcd for $C_{16}H_{12}NO_2S$ $[M - H]^-$ 282.0594, found 282.0602.

4-((4-Cyanophenyl)thio)isoquinolin-1(*2H*)-one (3e). Pale yellow solid, mp 185 - 186 ^oC; yield 58.5 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.48 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 9.0 Hz, 2H), 7.59 (t, J = 8.4 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 163.7, 137.5, 136.6, 133.8, 132.5, 128.2, 128.1, 126.5, 125.8, 125.1, 108.8, 105.3, 100.0; HRMS (ESI) m/z calcd for $C_{16}H_9N_2OS$ $[M - H]^-$ 277.0441, found 277.0442.

4-(Phenylthio)isoquinolin-1(*2H*)-one (3f). Yellow solid, mp 225 - 227 °C; yield 74.5 mg, 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (s, 1H), 8.46 (d, J = 7.3 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.71 (s, 1H), 7.71 – 7.66 (m, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.12 (dd, J = 15.6, 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 138.3, 137.3, 135.9, 133.5, 129.1, 127.8, 127.5, 126.5, 126.4, 125.7, 125.6, 107.9; HRMS (ESI) m/z calcd for $C_{15}H_{10}NOS$ $[M - H]^-$ 252.0489, found 252.0487.

4-((3-Fluorophenyl)thio)isoquinolin-1(*2H*)-one (3g). White solid, mp 186 - 188 °C; yield 73.3 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.94 (s, 1H), 8.47 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.74 (s, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.17 (dd, J = 13.9, 6.9 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.80 (d, J = 8.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 163.1 (d, J_{C-F} = 248.5 Hz), 139.9, 138.0, 136.4, 133.6, 130.3 (d, J_{C-F} = 8.5 Hz), 127.9, 127.7, 126.4, 125.4, 121.8, 113.2 (d, J_{C-F} = 24.1 Hz), 112.6 (d, J_{C-F} = 21.6 Hz), 107.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.8; HRMS (ESI) m/z calcd for $C_{15}H_9FNOS$ $[M - H]^-$ 270.0394, found 270.0382.

6-Bromo-4-(p-tolylthio)isoquinolin-1(*2H*)-one (3h). White solid, mp 221 - 223 °C; yield 93.5 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.27 (d, J = 8.6 Hz, 1H), 8.17 (d, J = 1.8 Hz, 1H), 7.63 (dd, J = 8.5, 1.9 Hz, 2H), 7.11 – 7.00 (m, 4H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 139.9, 136.5, 136.2, 132.8, 131.0, 130.0, 129.6, 128.3, 127.3, 125.0, 107.9, 100.0, 20.9; HRMS (ESI) m/z calcd for $C_{16}H_{11}BrNOS$ $[M - H]^-$ 343.9750, found 343.9740.

6-Bromo-4-(phenylthio)isoquinolin-1(*2H*)-one (3i). White solid, mp 225 - 227 °C; yield 89.7 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.74 (s, 1H), 8.21 (d, J = 8.5 Hz, 1H), 8.09 (s, 1H), 7.64 (s, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.20 – 7.13 (m, 2H), 7.08 (d, J = 5.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 140.0, 137.2, 136.7, 131.0,

129.6, 129.2, 129.2, 128.2, 126.6, 126.0, 124.9, 107.2; HRMS (ESI) m/z calcd for $C_{15}H_9BrNOS$ $[M - H]^-$ 329.9594, found 329.9595 .

6-Bromo-4-((4-methoxyphenyl)thio)isoquinolin-1(*2H*)-one (3j). White solid, mp 223 - 225 ^oC; yield 103.3 mg, 95%; ^1H NMR (400 MHz, $CDCl_3$) δ 11.73 (s, 1H), 8.24 (s, 1H), 8.22 (d, J = 4.5 Hz, 1H), 7.64 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 7.1 Hz, 2H), 6.80 (d, J = 7.2 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 158.8, 139.8, 135.9, 130.8, 130.1, 129.5, 129.1, 128.2, 126.5, 124.8, 114.9, 109.4, 55.4; HRMS (ESI) m/z calcd for $C_{16}H_{11}BrNO_2S$ $[M - H]^-$ 361.9673, found 361.9654.

6-Bromo-4-((3-fluorophenyl)thio)isoquinolin-1(*2H*)-one (3k). White solid, mp 224 - 226 ^oC; yield 94.6 mg, 90%; ^1H NMR (400 MHz, $CDCl_3$) δ 11.58 (s, 1H), 8.29 (d, J = 8.5 Hz, 1H), 8.10 (s, 1H), 7.72 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.20 (dd, J = 14.1, 7.9 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.81 (dd, J = 21.9, 8.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 162.8 (d, J_{C-F} = 177.3 Hz), 139.6, 137.6, 131.2, 130.5 (d, J_{C-F} = 8.6 Hz), 129.7, 129.4, 128.0, 125.0, 121.8 (d, J_{C-F} = 3.1 Hz), 113.2 (d, J_{C-F} = 25.0 Hz), 112.9, 106.1, 100.00; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.5; HRMS (ESI) m/z calcd for $C_{15}H_8BrFNOS$ $[M - H]^-$ 347.9499 , found 347.9494.

6-Bromo-4-((3,5-dichlorophenyl)thio)isoquinolin-1(*2H*)-one (3l). White solid, mp 230 - 232 ^oC; yield 90.2mg, 75%; ^1H NMR (400 MHz, $CDCl_3$) δ 11.41 (s, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.06 (s, 1H), 7.69 (d, J = 9.2 Hz, 2H), 7.13 (s, 1H), 6.96 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 140.7, 139.3, 138.2, 135.7, 131.5, 129.9, 129.6, 127.7, 126.2, 125.1, 123.9, 104.8; HRMS (ESI) m/z calcd for $C_{15}H_7BrCl_2NOS$ $[M - H]^-$ 397.8814, found 397.8799 .

6-Bromo-4-((2-fluorophenyl)thio)isoquinolin-1(*2H*)-one (3m). White solid, mp 230 - 232 ^oC; yield 89.3 mg, 85%; ^1H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.87 (s, 1H), 7.83 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.33 – 7.17 (m,

2H), 7.05 (t, J = 7.3 Hz, 1H), 6.93 (t, J = 7.7 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 158.6 (d, J_{C-F} = 242.6 Hz), 140.1, 139.2, 130.2, 130.0, 128.3, 127.9 (d, J_{C-F} = 7.4 Hz), 127.5, 126.4, 125.5, 125.4 (d, J_{C-F} = 3.2 Hz), 123.6 (d, J_{C-F} = 16.8 Hz), 115.6 (d, J_{C-F} = 20.9 Hz), 100.7; ^{19}F NMR (376 MHz, DMSO-d_6) δ -112.9; HRMS (ESI) m/z calcd for $C_{15}H_8BrFNOS$ $[M - H]^-$ 347.9499, found 347.9495.

6-Chloro-4-(phenylthio)isoquinolin-1(*2H*)-one (3n). White solid, mp 226 - 228 °C; yield 69.0 mg, 80%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 8.25 (d, J = 8.3 Hz, 1H), 7.79 (s, 1H), 7.72 (s, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.16 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 140.1, 139.7, 138.8, 137.1, 130.4, 129.8, 127.8, 126.5, 126.3, 125.7, 124.0, 103.3; HRMS (ESI) m/z calcd for $C_{15}H_9ClNOS$ $[M - H]^-$ 286.0099, found 286.0109.

6-Chloro-4-((4-methoxyphenyl)thio)isoquinolin-1(*2H*)-one (3o). White solid, mp 214 - 216 °C; yield 82.9 mg, 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 7.64 (s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 6.80 (d, J = 8.3 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 140.3, 139.7, 135.8, 130.0, 129.6, 128.1, 126.5, 125.0, 115.0, 113.7, 109.4, 100.0, 55.4; HRMS (ESI) m/z calcd for $C_{16}H_{11}ClNO_2S$ $[M - H]^-$ 316.0205, found 316.0212.

6-Chloro-4-(*p*-tolylthio)isoquinolin-1(*2H*)-one (3p). White solid, mp 228 - 230 °C; yield 81.5 mg, 90%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 5.5 Hz, 1H), 7.72 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.08 (s, 4H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 139.7, 139.7, 138.7, 135.9, 133.4, 130.5, 130.4, 127.8, 127.0, 125.6, 124.1, 104.0, 20.9; HRMS (ESI) m/z calcd for $C_{16}H_{11}ClNOS$ $[M - H]^-$ 300.0255 , found 300.0248.

6-Chloro-4-((3-fluorophenyl)thio)isoquinolin-1(*2H*)-one (3q). White solid, mp 231 - 233 °C; yield 80.7 mg, 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (s, 1H), 8.38 (d, J

= 8.6 Hz, 1H), 7.93 (s, 1H), 7.74 (s, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.20 (dd, J = 14.0, 7.9 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 6.81 (dd, J = 18.9, 9.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 162.7 (d, J_{C-F} = 150.6 Hz), 140.7, 139.5, 137.6, 130.6 (d, J_{C-F} = 8.6 Hz), 129.8, 128.4, 124.9, 124.7, 121.8 (d, J_{C-F} = 3.0 Hz), 113.3, 113.1, 112.9, 106.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.1; HRMS (ESI) m/z calcd for $C_{15}H_8ClFNOS$ $[M - H]^-$ 304.0005, found 304.0015 .

6-Chloro-4-((2-fluorophenyl)thio)isoquinolin-1(*2H*)-one (3r). White solid, mp 210 - 212 °C; yield 64.2 mg, 70%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.32 – 7.18 (m, 2H), 7.05 (t, J = 7.4 Hz, 1H), 6.93 (t, J = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.5, 160.9 (d, J_{C-F} = 138.7 Hz), 140.8, 139.6, 138.9, 130.5, 128.7 (d, J_{C-F} = 2.7 Hz), 128.4 (d, J_{C-F} = 7.7 Hz), 128.0, 125.9 (d, J_{C-F} = 3.7 Hz), 125.7, 123.7, 116.3, 116.1, 101.2; ^{19}F NMR (376 MHz, DMSO-d_6) δ -108.9; HRMS (ESI) m/z calcd for $C_{15}H_8ClFNOS$ $[M - H]^-$ 304.0005, found 304.0014 .

7-Chloro-4-(*p*-tolylthio)isoquinolin-1(*2H*)-one (3s). White solid, mp 225 - 227 °C; yield 86.0 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (s, 1H), 8.40 (d, J = 1.6 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.64 (s, 1H), 7.60 (dd, J = 8.7, 1.8 Hz, 1H), 7.11 – 7.00 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 136.7, 136.1, 135.3, 133.8, 133.7, 132.9, 130.8, 129.9, 127.4, 127.3, 127.2, 108.5, 20.9; HRMS (ESI) m/z calcd for $C_{16}H_{11}ClNOS$ $[M - H]^-$ 300.0255, found 300.0256.

7-Chloro-4-(phenylthio)isoquinolin-1(*2H*)-one (3t). Yellow solid, mp 215 - 217 °C; yield 82.0 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.61 (s, 1H), 8.42 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.69 (s, 1H), 7.61 (dd, J = 8.7, 2.1 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.13 (t, J = 5.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 136.8, 136.7, 135.8,

133.9, 133.8, 129.2, 127.4, 127.3, 126.5, 125.9, 107.7, 100.0; HRMS (ESI) m/z calcd for $C_{15}H_9ClNOS$ $[M - H]^-$ 286.0099, found 286.0108.

7-Chloro-4-((4-methoxyphenyl)thio)isoquinolin-1(*2H*)-one (3u). White solid, mp 226 - 228 ^oC; yield 85.8 mg, 90%; ^1H NMR (400 MHz, $CDCl_3$) δ 11.94 (s, 1H), 8.39 (s, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.63 (s, 1H), 7.61 (s, 1H), 7.18 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 158.7, 136.6, 134.7, 133.8, 133.7, 129.8, 127.3, 127.2, 126.7, 114.9, 109.8, 100.0, 55.4; HRMS (ESI) m/z calcd for $C_{16}H_{11}ClNO_2S$ $[M - H]^-$ 316.0205, found 316.0191.

5-Methyl-4-(*p*-tolylthio)isoquinolin-1(*2H*)-one (3v). Red solid, mp 235 - 237 ^oC; yield 71.7 mg, 85%; ^1H NMR (400 MHz, $CDCl_3$) δ 11.89 (s, 1H), 8.43 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.46 (d, J = 6.8 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.1 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 2.86 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 135.7, 135.1, 134.6, 134.3, 133.4, 132.6, 127.5, 125.2, 124.7, 124.2, 123.0, 104.7, 21.0, 18.4; HRMS (ESI) m/z calcd for $C_{17}H_{14}NOS$ $[M - H]^-$ 280.0802, found 280.0795.

4-((4-Chlorophenyl)thio)-5-methylisoquinolin-1(*2H*)-one (3w). Red solid, mp 224 - 226 ^oC; yield 67.9 mg, 75%; ^1H NMR (400 MHz, $CDCl_3$) δ 11.78 (s, 1H), 8.38 (d, J = 8.8 Hz, 1H), 7.67 (s, 1H), 7.47 (d, J = 6.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 2.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 139.0, 138.6, 137.7, 136.6, 135.6, 131.0, 129.3, 127.7, 127.3, 126.8, 126.3, 106.1, 23.3; HRMS (ESI) m/z calcd for $C_{16}H_{11}ClNOS$ $[M - H]^-$ 300.0255, found 300.0250.

5-Methyl-4-(phenylthio)isoquinolin-1(*2H*)-one (3x). Red solid, mp 212 - 214 ^oC; yield 68.2 mg, 85%; ^1H NMR (400 MHz, $CDCl_3$) δ 12.09 (s, 1H), 8.34 (d, J = 7.1 Hz, 1H), 7.62 (s, 1H), 7.37 (s, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.13 (s, 2H), 6.98 (dd, J =

26.5, 6.7 Hz, 3H), 2.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 140.4, 138.5, 137.5, 137.1, 135.8, 129.2, 127.6, 127.1, 126.7, 125.2, 106.7, 100.0, 23.3; HRMS (ESI) m/z calcd for $C_{16}H_{12}NOS$ $[M - H]^-$ 266.0645, found 266.0635.

4-(Ethylthio)isoquinolin-1(2H)-one (3y). Yellow solid, mp 112 - 114 ^oC; yield 30.8 mg, 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 8.45 (d, J = 7.9 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.58 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 2.71 (q, J = 7.3 Hz, 2H), 1.20 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 134.3, 133.2, 127.8, 127.2, 126.1, 125.4, 110.1, 29.6, 14.8; HRMS (ESI) m/z calcd for $C_{11}H_{12}NOS$ $[M + H]^+$ 206.0634, found 206.0638.

6-Bromo-4-(ethylthio)isoquinolin-1(2H)-one (3z). Yellow solid, mp 162 - 164 ^oC; yield 25.6 mg, 30%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.35 (s, 1H), 8.28 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.53 (s, 1H), 2.70 (q, J = 7.3 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 140.3, 135.4, 130.7, 129.7, 129.0, 128.1, 124.8, 109.1, 29.8, 14.7; HRMS (ESI) m/z calcd for $C_{11}H_{11}BrNOS$ $[M + H]^+$ 283.9739, found 283.9742.

4-(Phenylselanyl)isoquinolin-1(*2H*)-one (3aa). Yellow solid, mp 198 - 200 ^oC; yield 81.1 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.83 (s, 1H), 8.52 (d, J = 7.9 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.86 (s, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.29 – 7.19 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 138.7, 136.3, 133.5, 132.0, 129.4, 129.3, 127.7, 127.6, 127.5, 126.5, 126.4, 105.3; HRMS (ESI) m/z calcd for $C_{15}H_{10}NOSe$ $[M - H]^-$ 299.9933, found 299.9932.

6-Bromo-4-(phenylselanyl)isoquinolin-1(*2H*)-one (3ab). Yellow solid, mp 220 - 222 ^oC; yield 104.6 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (s, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.21 (s, 1H), 7.77 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.29 (d, J = 6.7 Hz, 2H), 7.21 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 140.4, 137.5,

131.5, 130.9, 130.3, 129.7, 129.5, 129.4, 129.2, 126.8, 125.1, 104.4; HRMS (ESI) m/z calcd for $C_{15}H_9BrNOSe$ $[M - H]^-$ 377.9038 , found 377.9041.

6-Chloro-4-(phenylselanyl)isoquinolin-1(*2H*)-one (3ac). Yellow solid, mp 211 - 213 ^oC; yield 86.3 mg, 86%; ^1H NMR (400 MHz, $CDCl_3$) δ 11.47 (s, 1H), 8.35 (d, J = 8.6 Hz, 1H), 8.03 (s, 1H), 7.77 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 6.8 Hz, 2H), 7.20 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 140.4, 140.3, 137.5, 131.5, 129.6, 129.5, 128.2, 127.1, 126.8, 124.7, 104.5, 90.9; HRMS (ESI) m/z calcd for $C_{15}H_9ClNOSe$ $[M - H]^-$ 333.9543, found 333.9527.

5-(*p*-Tolylthio)pyridin-2(*1H*)-one (3ad). Yellow solid, mp 153 - 155 ^oC; yield 58.7 mg, 90%; ^1H NMR (400 MHz, $CDCl_3$) δ 13.36 (s, 1H), 7.56 (s, 1H), 7.49 (d, J = 9.4 Hz, 1H), 7.11 (dd, J = 18.4, 8.2 Hz, 4H), 6.56 (d, J = 9.4 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 146.0, 137.9, 135.9, 131.7, 129.0, 128.1, 120.1, 111.8, 20.0; HRMS (ESI) m/z calcd for $C_{12}H_{10}NOS$ $[M - H]^-$ 216.0489, found 216.0477.

5-(phenylthio)pyridin-2(*1H*)-one (3ae). Brown solid, mp 151 - 153 ^oC（Reference value [29]: 180-181.5 ^oC）; yield 58.0 mg, 95%; ^1H NMR (400 MHz, $CDCl_3$) δ 13.18 (s, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.51 (dd, J = 9.5, 2.6 Hz, 1H), 7.29 (d, J = 7.7 Hz, 2H), 7.19 (dd, J = 6.7, 4.8 Hz, 3H), 6.59 (d, J = 9.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 147.5, 139.8, 136.8, 129.2, 128.0, 126.5, 121.3, 111.5; HRMS (ESI) m/z calcd for $C_{11}H_8NOS$ $[M - H]^-$ 202.0332, found 202.0319 .

5-((4-Methoxyphenyl)thio)pyridin-2(*1H*)-one (3af). Brown solid, mp 135 - 137 ^oC; yield 66.5 mg, 95%; ^1H NMR (400 MHz, $CDCl_3$) δ 13.48 (s, 1H), 7.50 (d, J = 5.1 Hz, 1H), 7.47 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.55 (d, J = 9.4 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 159.3, 146.3, 137.7,

132.3, 126.1, 120.9, 115.0, 114.4, 55.4; HRMS (ESI) m/z calcd for $C_{12}H_{10}NO_2S$ [M - H]$^-$ 232.0438, found 232.0433 .

5-((2-Fluorophenyl)thio)pyridin-2(*1H*)-one (3ag). White solid, mp 124 - 126 ^oC; yield 56.4 mg, 85%; ^1H NMR (400 MHz, $CDCl_3$) δ 13.29 (s, 1H), 7.64 (s, 1H), 7.54 (d, J = 9.4 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.06 (t, J = 8.0 Hz, 2H), 6.58 (d, J = 9.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 160.3 (d, J_{C-F} = 246.1 Hz), 147.4, 140.3, 130.7, 128.8 (d, J_{C-F} = 7.8 Hz), 124.8 (d, J_{C-F} = 3.7 Hz), 121.2, 116.1, 115.8, 110.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.5; HRMS (ESI) m/z calcd for $C_{11}H_7FNOS$ [M - H]$^-$ 220.0238, found 220.0228.

5-((4-Chlorophenyl)thio)pyridin-2(*1H*)-one (3ah). White solid, mp 159 - 161 ^oC; yield 53.5 mg, 75%; ^1H NMR (400 MHz, $CDCl_3$) δ 12.88 (s, 1H), 7.63 (s, 1H), 7.50 (d, J = 9.5 Hz, 1H), 7.28 (s, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.62 (d, J = 9.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2, 138.9, 134.4, 131.5, 128.3, 128.2, 120.6, 109.9, 99.0; HRMS (ESI) m/z calcd for $C_{11}H_7ClNOS$ [M - H]$^-$ 235.9942, found 235.9925.

5-(Phenylselanyl)pyridin-2(*1H*)-one (3ai). Black solid, mp 145 - 147 ^oC; yield 66.0 mg, 88%; ^1H NMR (400 MHz, $CDCl_3$) δ 13.20 (s, 1H), 7.70 (s, 1H), 7.64 (d, J = 9.4 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.32 – 7.25 (m, 3H), 6.57 (d, J = 9.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 148.5, 140.6, 131.6, 130.9, 129.5, 127.2, 121.3, 106.2; HRMS (ESI) m/z calcd for $C_{11}H_8NOSe$ [M - H]$^-$ 249.9777, found 249.9763.

1-Methyl-5-(*p*-tolylthio)pyridin-2(*1H*)-one (3aj). Yellow liquid; yield 65.9 mg, 95%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 2.5 Hz, 1H), 7.34 (dd, J = 9.4, 2.5 Hz, 1H), 7.12 – 7.05 (m, 4H), 6.54 (d, J = 9.4 Hz, 1H), 3.53 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 145.1, 143.0, 136.6, 133.4, 123.0, 128.4, 121.3, 110.5, 37.8, 21.0; HRMS (ESI) m/z calcd for $C_{13}H_{13}NNaOS$ [M + Na]$^+$ 254.0610 , found 254.0612.

1-Methyl-5-(phenylthio)pyridin-2(*1H*)-one (3ak). Yellow liquid; yield 61.9 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 2.5 Hz, 1H), 7.38 (dd, J = 9.4, 2.5 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.21 – 7.14 (m, 3H), 6.58 (d, J = 9.4 Hz, 1H), 3.56 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 145.4, 143.7, 137.3, 129.2, 127.4, 126.3, 121.5, 109.4, 37.8; HRMS (ESI) m/z calcd for $C_{12}H_{11}NNaOS$ $[M + Na]^+$ 240.0454 , found 240.0465.

5-((4-Methoxyphenyl)thio)-1-methylpyridin-2(*1H*)-one (3al). Yellow liquid; yield 70.5 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 2.5 Hz, 1H), 7.30 (dd, J = 9.4, 2.5 Hz, 1H), 7.24 – 7.17 (m, 2H), 6.86 – 6.77 (m, 2H), 6.50 (d, J = 9.4 Hz, 1H), 3.76 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 159.1, 144.5, 141.9, 131.5, 126.8, 121.2, 114.9, 112.0, 55.4, 37.7; HRMS (ESI) m/z calcd for $C_{13}H_{13}NNaO_2S$ $[M + Na]^+$ 270.0559 , found 270.0561.

5-((3-Fluorophenyl)thio)-1-methylpyridin-2(*1H*)-one (3am). Yellow liquid; yield 57.9 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 9.4, 2.4 Hz, 1H), 7.28 – 7.18 (m, 1H), 6.93 – 6.78 (m, 3H), 6.60 (d, J = 9.4 Hz, 1H), 3.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (d, J = 248.9 Hz), 162.2, 145.4, 144.4, 140.1 (d, J_{C-F} = 7.7 Hz), 130.5 (d, J_{C-F} = 8.8 Hz), 122.4 (d, J_{C-F} = 3.3 Hz), 121.7, 113.8 (d, J_{C-F} = 24.0 Hz), 113.0 (d, J_{C-F} = 21.4 Hz), 108.0, 37.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.2. HRMS (ESI) m/z calcd for $C_{12}H_{10}FNNaOS$ $[M + Na]^+$ 258.0359 , found 258.0372.

5-((2-Fluorophenyl)thio)-1-methylpyridin-2(*1H*)-one (3an). Yellow liquid; yield 60.0 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 2.5 Hz, 1H), 7.38 (dd, J = 9.5, 2.5 Hz, 1H), 7.23 – 7.15 (m, 1H), 7.12 – 7.01 (m, 3H), 6.56 (d, J = 9.5 Hz, 1H), 3.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 160.1 (d, J_{C-F} = 245.6 Hz), 145.3, 144.1, 130.2, 128.5 (d, J_{C-F} = 7.7 Hz), 124.8 (d, J_{C-F} = 3.7 Hz), 121.4, 116.0, 115.8,

108.0, 37.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.0. HRMS (ESI) m/z calcd for $C_{12}H_{10}FNNaOS$ $[M + Na]^+$ 258.0359 , found 258.0378.

5-((4-Chlorophenyl)thio)-1-methylpyridin-2(*1H*)-one (3ao). Yellow liquid; yield 68.0 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 2.5 Hz, 1H), 7.35 (dd, J = 9.4, 2.5 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.12 – 7.07 (m, 2H), 6.59 (d, J = 9.4 Hz, 1H), 3.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 145.2, 143.9, 135.9, 132.2, 129.3, 128.7, 121.7, 108.9, 37.9; HRMS (ESI) m/z calcd for $C_{12}H_{10}ClNNaOS$ $[M + Na]^+$ 274.0064, found 274.0056.

4-((4-Cyanophenyl)thio)-1-methylpyridin-2(*1H*)-one (3ap). White solid, mp 166 - 168 ^{o}C; yield 50.9 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.52 (d, J = 6.8 Hz, 2H), 7.35 (d, J = 9.4 Hz, 1H), 7.15 (d, J = 6.8 Hz, 2H), 6.64 (d, J = 8.0 Hz, 1H), 3.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 145.3, 145.2, 132.6, 126.0, 122.1, 118.6, 110.0, 109.0, 106.0, 38.0; HRMS (ESI) m/z calcd for $C_{13}H_{10}N_2NaOS$ $[M + Na]^+$ 265.0406, found 265.0423.

5-((3,5-Dichlorophenyl)thio)-1-methylpyridin-2(*1H*)-one (3aq). Yellow liquid; yield 68.7 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 2.5 Hz, 1H), 7.35 (dd, J = 9.5, 2.5 Hz, 1H), 7.14 (t, J = 1.7 Hz, 1H), 6.96 (d, J = 1.7 Hz, 2H), 6.63 (d, J = 9.5 Hz, 1H), 3.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 145.2, 145.0, 141.5, 135.6, 126.1, 124.5, 122.0, 106.8, 38.0; HRMS (ESI) m/z calcd for $C_{12}H_9Cl_2NNaOS$ $[M + Na]^+$ 307.9674, found 307.9670 .

ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra for all compounds are prepared. This information 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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