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Research article

Metal-free synthesis of 4-(methylthio)-3-phenylisoquinolines

Chengqun Chen [*,a] **and Xiaosheng Xie** [a]

[a] Department of Chemical Engineering, Fuzhou University Zhicheng College, Fuzhou, PR China

E-mail: chenchq03@yeah.net (C. Chen)

Abstract. Herein, we report a straightforward protocol for synthesizing 4-(methylthio)-3-phenylisoquinolines, which are valuable compounds in medicinal chemistry for their biological activities. This method uses 1-(azidomethyl)-2-(phenylethynyl)benzenes and dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTSM) under mild, metal-free conditions. Notably, it tolerates diverse aromatic functional groups, enabling derivative preparation. The reaction proceeds smoothly, affording products in good to excellent yields. By avoiding hazardous and malodorous methylthio radical reagents as well as methylthio nucleophile precursors, this protocol provides a practical and eco-friendly route to sulfur-containing heterocycles.

Keywords. Tetrafluoroborate, Azide, Isoquinoline, Methylthio, Synthesis.

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1. Introduction

Isoquinolines, an important class of nitrogen heterocycles, exhibit diverse bioactivities and are widely present in natural products, such as isoquinoline alkaloids as key examples. As a ubiquitous motif, the isoquinoline scaffold possesses a bicyclic architecture, found in the secondary metabolites of plants (e.g., aforementioned alkaloids) and microbial natural products. Notably, these molecules show remarkable bioactivities, e.g., anti-inflammatory, antispasmodic, antiallergic, anticancer [1–6].

Alkyne annulation of nitrogen-containing arenes via C–H/N–H functionalization enables the installation of vicinal C–N and C–C bonds across an alkyne in a single transformation. This approach has emerged as a powerful tactic for step-economical assembly of diverse heterocycles, which exhibit activities relevant to medicinal chemistry and biology [7–9]. As an illustration, the Larock group reported that a broad range of 3,4-disubstituted isoquinolines can be synthesized via Pd-catalyzed annulation of alkynes (or allenes) with aldehydes and *tert*-butylamine [10–15]. Additionally, 2-alkynylbenzyl azides serve as suitable substrates for synthesizing isoquinoline derivatives [16–19]. For instance, Li et al. [16] described a PdI_2/I_2-catalyzed thiolation-annulation route involving alkynes, azides, and disulfides for the synthesis of 4-sulfenylisoquinolines. Separately, the Liang group [17] and the Yamamoto group [18] independently reported the Ag- or Au/Ag-catalyzed cyclization of 2-alkynylbenzyl azides, which affords 1,3-disubstituted isoquinolines.

Metal-free strategies have further expanded the utility of 2-alkynylbenzyl azides, particularly under mild conditions. Visible-light-promoted selenylation/cyclization of 2-alkynylbenzyl azides with selenosulfonates produces 4-selenoisoquinolines in up to 83% yield using AcOH as the solvent and 50 W

* Corresponding author

white LEDs, simultaneously forming C(sp^2)–Se and C–N bonds [20].

Nevertheless, the prevailing approaches to produce sulfur-containing groups still depend heavily on hazardous, malodorous reagents—including thiols and disulfides. As an electrophilic methylthiolating reagent, dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTSM) is particularly notable, featuring unique advantages including safety, good crystallinity, and convenient handling [21–23]. In recent years, the application of dimethyl(methylthio)sulfonium salts in organic synthesis has garnered significant attention, with their utility in direct alkylthiolation [24], cycloaddition [25–27], and C–C bond formation reactions [28] being extensively investigated. Over the past few years, the Xie group has reported a series of outstanding studies in the fields of alkene hydrofunctionalization [29], direct addition reactions of terminal alkyl alkynes [30], and intermolecular alkene arylsulfenylation via episulfonium ion intermediates using DMTSM [31–33]. Building on this body of research, we herein report a novel and practical method for the synthesis of substituted 4-(methylthio)-3-phenylisoquinolines using DMTSM as a key component under ambient temperature conditions (Scheme 1).

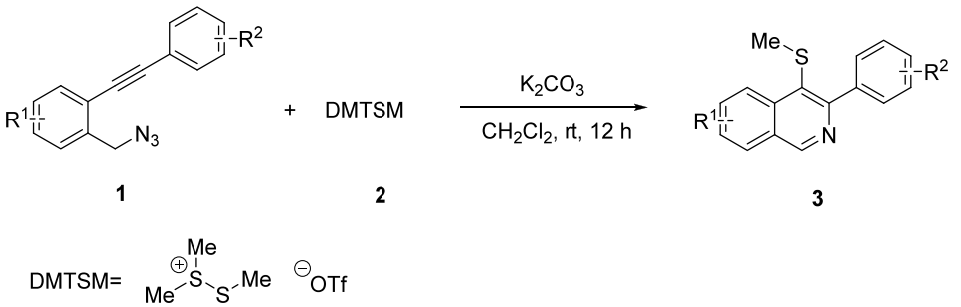
2. Results and discussion

The initial study was initiated by adding 1-(azidomethyl)-2-(phenylethynyl)benzene and dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTSM) to acetonitrile. Subsequently, the resulting substrate mixture was stirred at ambient temperature under an air atmosphere. After 12 h of reaction, the target compound, 1-(azidomethyl)-2-(phenylethynyl)benzene (**3a**), was successfully synthesized in a 21% yield. To improve the yield of this transformation, the effects of solvents, reaction temperature, bases, and catalysts were systematically investigated (Table 1).

An initial solvent screening was conducted, evaluating dichloromethane (CH_2Cl_2), dioxane, 1,2-dichloroethane (DCE), and tetrahydrofuran (THF) as reaction media (Table 1, entries 2–5). The reactions were conducted at room temperature without the addition of an external base. Notably, dichloromethane (CH_2Cl_2) proved to be the optimal solvent, affording the desired product in 32% yield—outperforming all other tested solvents. Specifically, 1,2-dichloroethane (DCE) gave a yield of 26%, whereas the polar aprotic solvents tetrahydrofuran (THF) and dioxane resulted in substantially lower yields at 11% and 7%, respectively. These results underscore the superior performance of CH_2Cl_2 in promoting this transformation relative to the other evaluated solvents. Furthermore, elevating the reaction temperature was found to be detrimental to the product yield (Table 1, entries 6–8). Various bases were tested to accelerate the reaction (Table 1, entries 9–11), It was found that K_2CO_3 yields better results than AcONa and *t*-BuOK. This outcome was primarily attributed to the degradation of DMTSM by the strong base. Meanwhile, catalysts including CuI, $Cu(OAc)_2$, and $FeCl_3$ exerted no significant effect on the reaction (Table 1, entries 12–14). Consequently, an optimized yield of 77% was achieved by using DMTSM (1.2 equiv) under the reaction conditions specified in Table 1, entry 11: CH_2Cl_2 as the solvent at rt, K_2CO_3 (1.5 equiv) for 12 h.

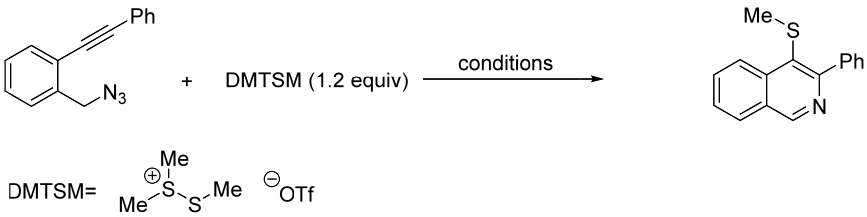
The scope of the reaction was then evaluated and various 1-(azidomethyl)-2-(phenylethynyl)benzene derivatives, bearing different groups, were treated with DMTSM(1.2 equiv), affording the 4-(methylthio)-3-phenylisoquinolines in various yields (Table 2). Generally, when R^2 was a para-alkyl-substituted phenyl group (Alkyl = Me-, Et-, and *t*-Bu-), the target products **3b–3d** were obtained in good yields. A slight decrease in the yield was observed when the methyl group was at the *meta* or *ortho* position of the aromatic ring; yields of only 69% and 67% were obtained, respectively (**3e,3f**). An 83% yield was obtained when the methoxy group was at the *para* position of the aromatic ring, and a 76% yield was reached with the methoxy group at the *meta* position. When R^2 was 3,4,5-trimethoxyphenyl, an excellent yield (81%) was still attained, demonstrating the favorable electron-donating effect of methoxy groups (**3g–3i**). However, when R^2 was a halogen at the *para* position on the aryl group, the yield decreased significantly; in contrast, a good yield was still obtained when R^2 was a biphenyl group (**3j–3m**). When R^2 was a heterocyclic group or an alkyl group, the yields of all corresponding products were less than 60% (**3n–3r**).

As expected, when the R^1 group of substrates **1** was replaced by one or two methyl groups, the



Scheme 1. Synthesis of 4-(methylthio)-3-phenylisoquinolines.

Table 1. Optimization of reaction conditions[a]



Entry	Solvent	Temp (°C)	Base (1.5 equiv)	Yield (%)[b]	Entry	Solvent	Temp (°C)	Base (1.5 equiv)	Yield (%)[b]
1	MeCN	rt	None	21	8	CH_2Cl_2	70	None	11
2	CH_2Cl_2	rt	None	32	9	CH_2Cl_2	rt	AcONa	60
3	DCE	rt	None	26	10	CH_2Cl_2	rt	*t*-BuOK	15
4	THF	rt	None	11	**11**	**CH_2Cl_2**	**rt**	**K_2CO_3**	**77**
5	Dioxane	rt	None	7	12[c]	CH_2Cl_2	rt	K_2CO_3	72
6	CH_2Cl_2	40	None	34	13[d]	CH_2Cl_2	rt	K_2CO_3	70
7	CH_2Cl_2	55	None	29	14[e]	CH_2Cl_2	rt	K_2CO_3	71

[a]Reaction conditions: **1a** (0.5 mmol), **DMTSM** (0.6 mmol), base (0.75 mmol), and solvent (2 mL) under air for 12 h.

[b]Isolated yields.

[c]CuI (0.05 mmol) was added as the catalyst.

[d]$Cu(OAc)_2$ (0.05 mmol) was added as the catalyst.

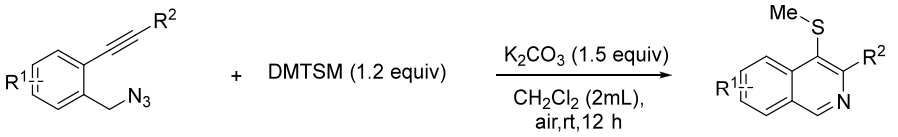
[e]$FeCl_3$ (0.05 mmol) was added as the catalyst.

CH_2Cl_2 = dichloromethane, DCE = dichloroethane, THF = tetrahydrofuran.

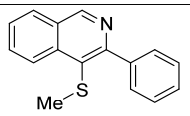
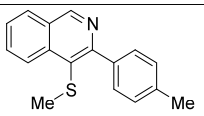
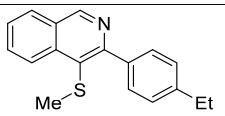
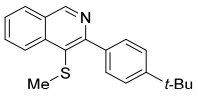
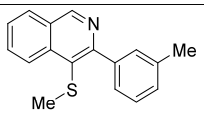
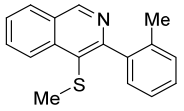
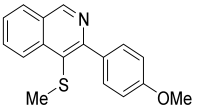
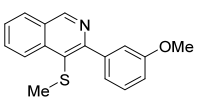
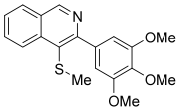
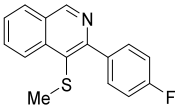
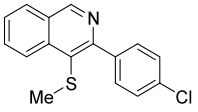
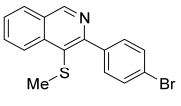
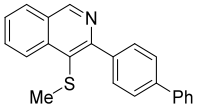
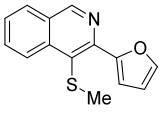
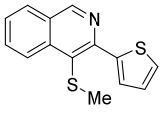
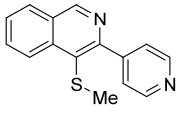
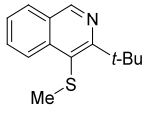
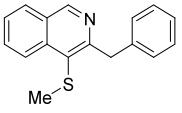
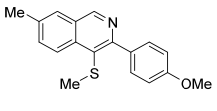
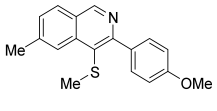
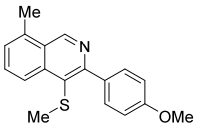
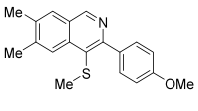
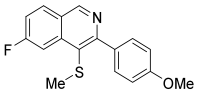
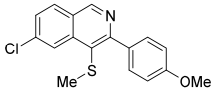
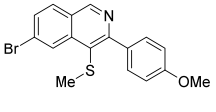
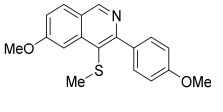
corresponding cyclized products **3s–3v** were also isolated in excellent yields. Similarly, when R^1 was an electron-withdrawing group, the cyclized products **3** were still obtained in good yields (**3w–3y**, yield up to 79%). While a methoxy group at the R^1 position also afforded excellent yields, it did not lead to any further increase in the yield (**3z**, 83%).

To gain insights into the reaction mechanism, a series of control experiments were performed. First, butylated hydroxytoluene (BHT) and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) were employed as radical inhibitors of the reaction (Scheme 2, Equations (1) and (2)), and no significant impact on the isolated yield was observed. Upon substituting

Table 2. Scope of 1-(azidomethyl)-2-(phenylethynyl)benzene olefinations



1 **2** **3**

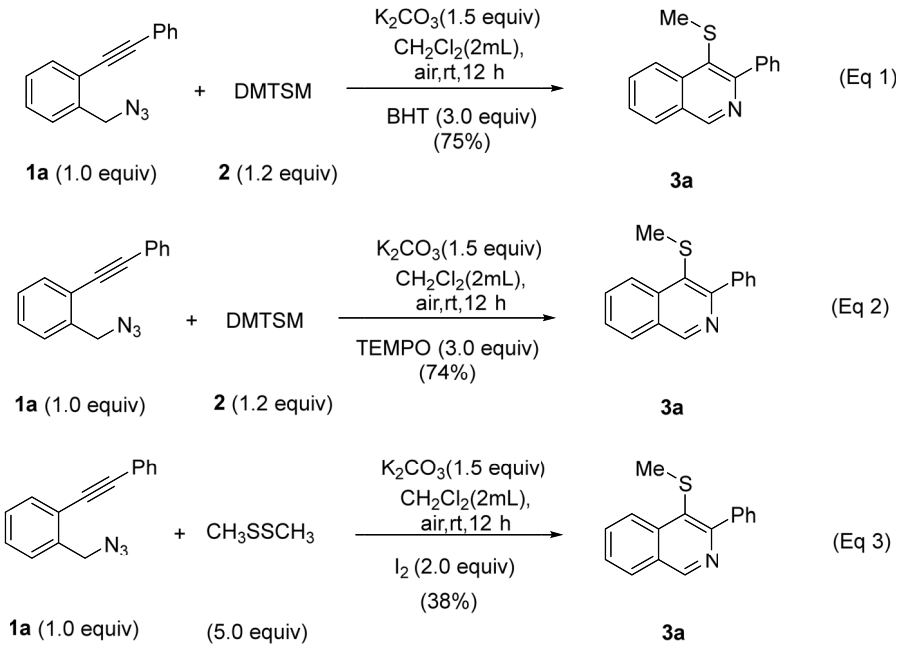
 **3a** (77%)	 **3b** (78%)	 **3c** (79%)	 **3d** (76%)	 **3e** (67%)
 **3f** (69%)	 **3g** (83%)	 **3h** (76%)	 **3i** (81%)	 **3j** (61%)
 **3k** (69%)	 **3l** (70%)	 **3m** (78%)	 **3n** (54%)	 **3o** (48%)
 **3p** (56%)	 **3q** (43%)	 **3r** (51%)		
 **3s** (81%)	 **3t** (83%)	 **3u** (82%)	 **3v** (83%)	 **3w** (76%)
 **3x** (78%)	 **3y** (79%)	 **3z** (83%)		

DMTSM with CH_3SSCH_3 in the presence of I_2, product **3a** could still be formed, yet the yield was merely 38% (Scheme 2, Equation (3)).

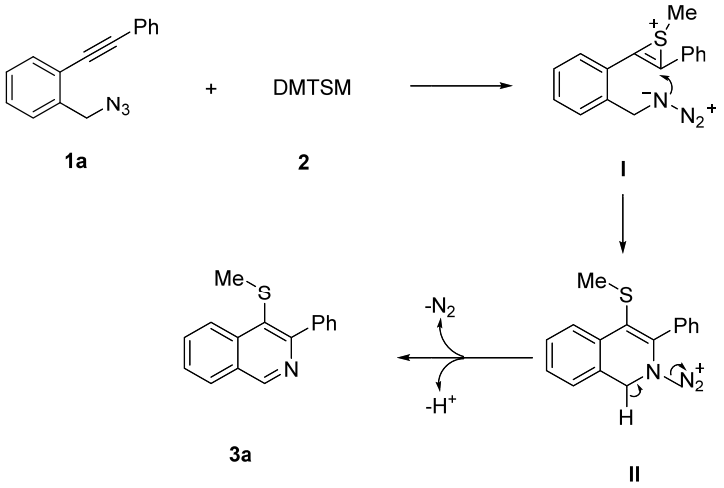
Based on these results and the literature [16,20], a reaction mechanism (Scheme 3) was proposed as follows: the sulfonium group transfer from DMTSM to 2-styrylbenzoic acid generates the intermediate episulfonium ion (**I**); subsequently, the formation of the cyclic intermediate (**II**) is achieved through intramolecular cyclization; ultimately, the anticipated product is generated when the cyclic intermediate (**II**) experiences the concomitant processes of deprotonation and N_2 elimination.

3. Conclusion

In conclusion, we herein report a straightforward and efficient protocol for the synthesis of 4-(methylthio)-3-phenylisoquinolines. This protocol involves the reaction of 1-(azidomethyl)-2-(phenylethynyl)benzene



Scheme 2. Control experiments.



Scheme 3. Proposed mechanism.

with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSM) under mild, metal-free conditions, and exhibits good tolerance toward a diverse range of functional groups on the aromatic ring, thus affording the corresponding products in good to excellent yields.

4. Experimental part

4.1. *General information*

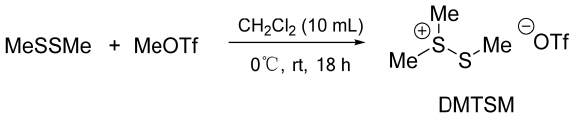
All reagents were purchased from Aladdin, Macklin, or Merck and directly used without further

purification. Column chromatography separations were carried out on silica gel (200–300 mesh).

NMR spectra were performed on a Bruker 400MHz (^{1}H: 400 MHz; ^{13}C: 100 MHz; ^{19}F: 376 MHz) spectrometer, using $CDCl_3$ as a solvent and TMS as the internal standard. Melting points are uncorrected. The NMR results were processed using the MestReNova program. HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF) by Agilent 7890 LECO PEGASUS HRT 4D.

4.2. *Experimental procedures*

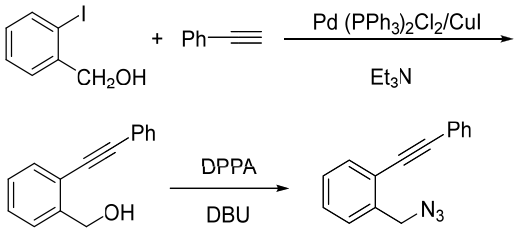
4.2.1. *General procedure for the synthesis of DMTSM [30]*



DMTSM

At 0 °C (ice bath), to a solution of methyl trifluoromethanesulfonate (12 mmol, 1.36 mL, 1.2 equiv) in CH_2Cl_2 (10 mL), Me_2S_2 (10 mmol, 0.89 mL, 1.0 equiv) was added dropwise in 30 min. The mixture was stirred for 1 h at that temperature, followed by 18 h at room temperature. Upon completion, the resulting white solid was collected by filtration and washed with fresh distilled Et_2O under nitrogen atmosphere, affording dimethyl(methylthio)sulfonium trifluoromethanesulfonate (2.27 g, 88% yield) as a white solid.

4.2.2. *Synthesis of 1-(azidomethyl)-2-(phenylethynyl) benzene [20]*

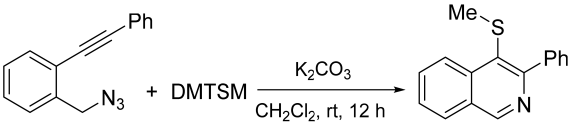


$Pd(PPh_3)_2Cl_2$ (0.03 mmol, 1 mol%) and CuI (0.06 mmol, 2 mol%) were sequentially added to a stirred solution of phenylacetylene (3.6 mmol, 1.2 equiv) in Et_3N (10 mL) under an argon atmosphere at rt. The mixture was stirred for 10 min. Then (2-iodophenyl)methanol (3.0 mmol, 1.0 equiv) was added. The mixture was stirred overnight. An aqueous saturated solution of NH_4Cl (8 mL) was added to the resulting mixture, and the mixture was extracted with EtOAc (2 × 10 mL). The organic layers were combined to be washed with brine and dried over Na_2SO_4 for 20 min. The solution was then concentrated under reduced pressure. The obtained residue was further purified by flash column chromatography on silica gel to give (2-(phenylethynyl)phenyl) methanol.

DBU (1.3 mmol, 1.3 equiv) and diphenyl phosphoryl azide (DPPA, 1.2 mmol, 1.2 equiv) were sequentially added portionwise to a solution of (2-(phenylethynyl)phenyl)methanol (1.0 mmol, 1.0 equiv) in toluene (2 mL) at rt. The mixture was stirred overnight. After completion of the reaction, determined by TLC analysis, the reaction mixture was extracted with EtOAc (2 × 5 mL). The organic layers were combined, then washed with brine and dried over Na_2SO_4 for 20 min. The solution was concentrated under reduced pressure. The obtained residue was further purified by flash column chromatography on silica gel to give pale yellow oil 1-(azidomethyl)-2-(phenylethynyl)-benzene.

Other compounds **1** were synthesized according to the above procedures.

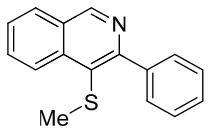
4.2.3. *General procedure for the synthesis of 4-(methylthio)-3-phenylisoquinolines*



To a solution of 1-(azidomethyl)-2-(phenylethynyl)benzene (0.5 mmol, 1 equiv) at rt in CH_2Cl_2 (2 mL), DMTSM (0.6 mmol, 1.2 equiv) and K_2CO_3 (0.75 mmol, 1.5 equiv) were added to the solvent. The mixture was stirred for 12 h (TLC-monitored). The reaction mixture was extracted with CH_2Cl_2 after adding the saturated brine. Then the organic phases were combined and dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo, the crude product was purified by column chromatography on silica gel, eluting with petroleum ether/EtOAc to afford the desired products.

4.3. *Characterization data of products*

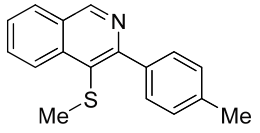
4.3.1. *4-(Methylthio)-3-phenylisoquinoline (3a)*



Brown solid (97 mg, 77%); mp = 129–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1H), 8.29 (d, J = 7.5 Hz, 1H), 8.24 (dd, J = 8.8, 3.2 Hz, 2H), 8.07 (d, J = 7.4 Hz, 1H), 7.80 (dd, J = 6.8, 1.2 Hz, 1H), 7.65–7.58 (m, 3H), 7.57–7.52 (m, 1H), 2.79 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 155.9, 146.8, 139.6, 138.8, 130.0, 129.2, 129.1, 128.6 (2C), 127.4 (2C), 127.1, 125.9, 124.6, 120.8, 18.9; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{16}H_{14}NS^+$: 252.0841, found: 252.0841.

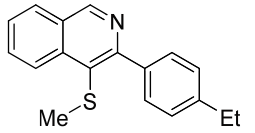
4.3.2. *4-(Methylthio)-3-(p-tolyl)isoquinoline (3b)*



Brown solid (103 mg, 78%); mp = 125–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.90 (dd, J = 7.8, 1.6 Hz, 1H), 7.65–7.60 (m, 1H), 7.47–7.42 (m, 1H), 7.24 (d, J = 8.3 Hz, 2H), 2.59 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 158.5, 150.2, 144.7, 139.2, 135.0, 130.0, 129.4 (2C), 129.2, 127.3 (2C), 127.1, 125.8, 124.5, 121.1, 23.2, 19.0; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{16}NS^+$: 266.0998, found: 266.0996.

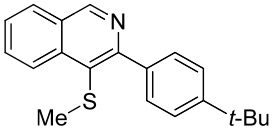
4.3.3. *3-(4-Ethylphenyl)-4-(methylthio)isoquinoline (3c)*



Pale yellow solid (110 mg, 79%); mp = 130–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1H), 8.22 (d, J = 5.2 Hz, 1H), 8.12 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 4.8 Hz, 1H), 7.77–7.72 (m, 1H), 7.58–7.53 (m, 1H), 7.39 (t, J = 7.6 Hz, 2H), 2.76–2.69 (m, 5H), 1.29 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 157.4, 148.5, 145.1, 144.2, 136.0, 129.6, 128.7, 127.8 (2C), 127.0 (2C), 126.6, 125.3, 124.2, 120.6, 28.2, 17.1, 15.1; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{18}H_{18}NS^+$: 280.1154, found: 280.1153.

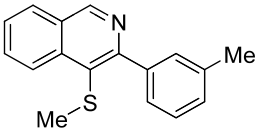
4.3.4. *3-(4-(tert-Butyl)phenyl)-4-(methylthio) isoquinoline (3d)*



White solid (117 mg, 76%); mp = 138–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.34 (s, 1H), 8.13 (d, J = 7.2 Hz, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 6.0 Hz, 1H), 7.68–7.63 (m, 1H), 7.50–7.45 (m, 1H), 7.34 (t, J = 8.4 Hz, 2H), 2.70 (s, 3H), 1.40 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 156.3, 150.4, 149.5, 144.9, 136.7, 130.4, 129.5, 127.7 (2C), 127.4 (2C), 127.1, 126.0, 124.8, 121.0, 32.3, 24.1 (3C), 18.0; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{20}H_{22}NS^+$: 308.1467, found: 308.1468.

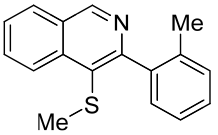
4.3.5. *4-(Methylthio)-3-(m-tolyl)isoquinoline (3e)*



Yellow solid (89 mg, 67%); mp = 124–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1H), 8.18 (d, J = 6.4 Hz, 1H), 8.01–7.97 (m, 2H), 7.78 (d, J = 5.4 Hz, 1H), 7.71–7.68 (m, 1H), 7.56–7.51 (m, 1H), 7.42–7.37 (m, 1H), 7.26 (d, J = 8.4 Hz, 1H), 2.80 (s, 3H), 2.47 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.1, 149.9, 146.1, 137.6, 137.0, 130.6, 130.4, 129.8, 129.1, 128.7, 127.7, 126.4, 125.1, 124.0, 121.1, 22.0, 18.4; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{16}NS^+$: 266.0998, found: 266.0999.

4.3.6. *4-(Methylthio)-3-(o-tolyl)isoquinoline (3f)*

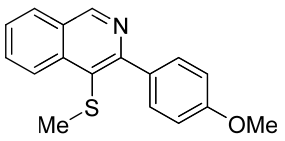


Brown solid (91 mg, 69%); mp = 131–133 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1H), 8.16 (d, J = 7.2 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.74–7.69 (m, 1H), 7.59–7.54 (m, 1H), 7.48–7.44 (m, 1H), 7.34–7.26 (m, 3H), 2.68 (s, 3H), 2.30(s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.4, 149.0, 145.8, 142.2,

136.4, 131.7, 131.0, 130.5, 130.3, 129.4, 127.8, 127.1, 126.9, 125.6, 125.1, 19.8, 17.5; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{16}NS^+$: 266.0998, found: 266.1000.

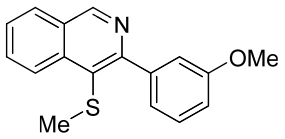
4.3.7. *3-(4-Methoxyphenyl)-4-(methylthio) isoquinoline (3g)*



White solid (117 mg, 83%); mp = 126–129 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (s, 1H), 8.16–8.09 (m, 3H), 7.82 (t, J = 4.4 Hz, 1H), 7.71–7.66 (m, 1H), 7.52–7.47 (m, 1H), 7.03 (d, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.68(s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.1, 158.9, 151.1, 144.1, 133.5, 131.2, 130.5, 130.1 (2C), 128.2, 126.9, 124.8, 122.4, 114.1 (2C), 55.4, 18.4; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{16}NOS^+$: 282.0947, found: 282.0949.

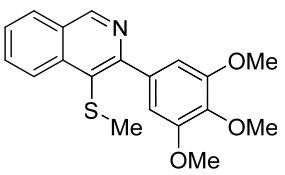
4.3.8. *3-(3-Methoxyphenyl)-4-(methylthio) isoquinoline (3h)*



Pale yellow solid (107 mg, 76%); mp = 122–124 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (s, 1H), 8.19 (d, J = 7.2 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.73–7.65 (m, 3H), 7.55–7.50 (m, 1H), 7.43–7.38 (m, 1H), 7.05 (dd, J = 7.0, 3.2 Hz, 1H), 3.91 (s, 3H), 2.57 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 161.9, 156.6, 147.8, 144.2, 141.1, 130.7, 130.3, 129.9, 129.0, 126.6, 123.1, 120.5, 120.4, 115.9, 112.3, 54.2, 19.6; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{16}NOS^+$: 282.0947, found: 282.0944.

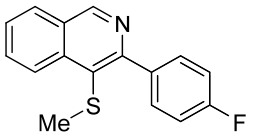
4.3.9. *4-(Methylthio)-3-(3,4,5-trimethoxyphenyl) isoquinoline (3i)*



White solid (138 mg, 81%); mp = 136–139 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.4 Hz, 1H), 7.75–7.70 (m, 1H), 7.58–7.53 (m, 1H), 7.36 (s, 2H), 3.98 (s, 6H), 3.89 (s, 3H), 2.67 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 157.6, 154.1 (2C), 150.3, 147.5, 141.9, 136.1, 131.6, 131.0, 128.7, 127.6, 125.2, 122.6, 104.4 (2C), 61.0, 56.3 (2C), 19.4; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{19}H_{20}NO_3S^+$: 342.1158, found: 342.1161.

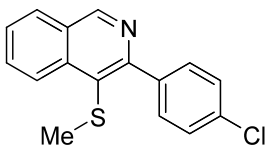
4.3.10. *3-(4-Fluorophenyl)-4-(methylthio) isoquinoline (3j)*



Yellow solid (82 mg, 61%); mp = 124–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1H), 8.24–8.17 (m, 3H), 7.88 (d, J = 6.8 Hz, 1H), 7.80–7.75 (m, 1H), 7.62–7.57 (m, 1H), 7.28–7.22 (m, 2H), 2.78 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 161.7 (d, J = 244 Hz), 156.3, 148.4, 144.9, 135.2 (d, J = 244 Hz) 129.0, 128.3 (d, J = 8 Hz, 2C), 128.2, 126.0, 125.0, 123.6, 118.8, 115.7 (d, J = 17 Hz, 2C), 17.9; **^{19}F NMR** (100 MHz, $CDCl_3$): δ = −113.2; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{16}H_{13}FNS^+$: 270.0747, found: 270.0744.

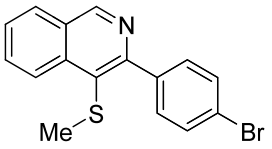
4.3.11. *3-(4-Chlorophenyl)-4-(methylthio) isoquinoline (3k)*



Brown solid (98 mg, 69%); mp = 123–127 °C.

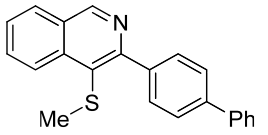
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1H), 8.24 (t, J = 7.2 Hz, 1H), 8.12 (d, J = 6.8 Hz, 1H), 7.95 (d, J = 6.2 Hz, 1H), 7.89–7.83 (m, 1H), 7.71–7.66 (m, 1H), 7.62 (d, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 158.1, 151.5, 147.3, 138.6, 135.9, 131.4, 130.7, 130.1 (2C), 130.0 (2C), 128.5, 127.4, 126.1, 124.8, 18.2; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{16}H_{13}ClNS^+$: 286.0452, found: 286.0457.

4.3.12. *3-(4-Bromophenyl)-4-(methylthio) isoquinoline (3l)*



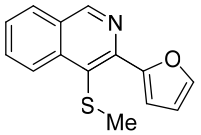
Dark brown solid (115 mg, 70%); mp = 132–134 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.29 (s, 1H), 8.12 (d, J = 7.8 Hz, 2H), 7.95 (d, J = 6.6 Hz, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.70–7.65 (m, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.53–7.48 (m, 1H), 2.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 156.4, 148.3, 143.2, 136.7, 132.1 (2C), 129.0, 128.5, 128.0 (2C), 126.2, 124.1, 122.7, 122.5, 120.8, 17.9; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{16}H_{13}BrNS^+$: 329.9947, found: 329.9946.

4.3.13. *3-([1,1'-Biphenyl]-4-yl)-4-(methylthio) isoquinoline (3m)*



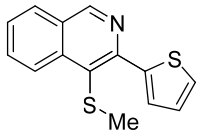
White solid (128 mg, 78%); mp = 142–145 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.31 (s, 1H), 8.35 (d, J = 7.2 Hz, 2H), 8.12 (d, J = 6.8 Hz, 1H), 7.81 (d, J = 7.0 Hz, 1H), 7.72 (d, J = 7.2 Hz, 2H), 7.66–7.61 (m, 3H), 7.55–7.50 (m, 1H), 7.46–7.41 (m, 2H), 7.36–7.31 (m, 1H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 155.4, 149.4, 141.9, 141.3, 140.1, 135.5, 132.4, 129.5 (2C), 128.4 (2C), 128.3, 128.2 (2C), 128.1 (2C), 128.0, 127.8, 127.8, 127.6, 125.2, 28.4; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{22}H_{18}NS^+$: 328.1154, found: 328.1157.

4.3.14. *3-(Furan-2-yl)-4-(methylthio)isoquinoline (3n)*



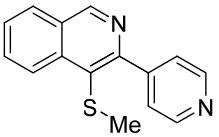
Pale yellow oil (65 mg, 54%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.23 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.75–7.70 (m, 1H), 7.60–7.55 (m, 1H), 7.54 (d, J = 7.0 Hz, 1H), 7.12–7.08 (m, 1H), 2.76 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.9, 147.2, 143.7, 143.0, 135.0, 134.7, 126.7, 126.3, 125.6, 124.2, 124.0, 114.9, 109.5, 17.2; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{14}H_{12}NOS^+$: 242.0634, found: 242.0636.

4.3.15. *4-(Methylthio)-3-(thiophen-2-yl)isoquinoline (3o)*



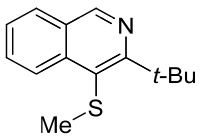
Yellow solid (62 mg, 48%); mp = 101–103 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.31 (s, 1H), 8.10 (d, J = 7.4 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.68–7.64 (m, 1H), 7.63 (d, J = 4.0 Hz, 1H), 7.49–7.44 (m, 1H), 7.17 (d, J = 5.2 Hz, 1H), 6.88–6.85 (m, 1H), 2.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 155.9, 147.5, 146.7, 142.0, 141.1, 128.7, 128.4, 127.2, 124.8, 122.5, 120.0, 116.9, 114.9, 17.8; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{14}H_{12}NS_2^+$: 258.0406, found: 258.0401.

4.3.16. *4-(Methylthio)-3-(pyridin-4-yl)isoquinoline (3p)*



Orange yellow solid (71 mg, 56%); mp = 111–114 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.33 (s, 1H), 8.73 (d, J = 4.8 Hz, 2H), 8.02–7.99 (m, 3H), 7.80 (d, J = 7.2 Hz, 1H), 7.75–7.69 (m, 1H), 7.66–7.61 (m, 1H), 2.54 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.7, 151.3 (2C), 145.1, 143.6, 137.1, 133.9, 129.4, 129.0, 128.5, 128.1, 124.7, 122.0 (2C), 20.9; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{15}H_{13}N_2S^+$: 253.0794, found: 253.0799.

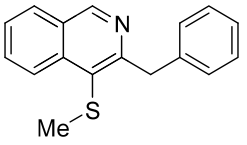
4.3.17. *3-(tert-Butyl)-4-(methylthio)isoquinoline (3q)*



Colorless oil (50 mg, 43%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.96 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 7.4 Hz, 1H), 7.66–7.61 (m, 1H), 7.49–7.44 (m, 1H), 2.65 (s, 3H),

1.47 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 165.4, 151.8, 146.4, 131.4, 131.0, 130.0, 127.4, 125.6, 124.1, 37.5, 28.6 (3C), 24.8; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{14}H_{18}NS^+$: 232.1154, found: 232.1156.

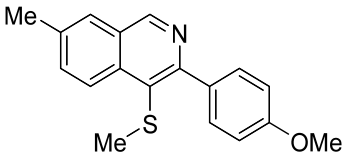
4.3.18. *3-Benzyl-4-(methylthio)isoquinoline (3r)*



Pale yellow solid (68 mg, 51%); mp = 125–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 1H), 8.16 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.79–7.74 (m, 1H), 7.51–7.46 (m, 1H), 7.31–7.25 (m, 4H), 7.22–7.17 (m, 1H), 4.27 (s, 2H), 2.58 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 153.7, 146.7, 141.7, 140.1, 128.7, 128.5, 128.4 (2C), 127.8 (2C), 126.1, 125.7, 125.0, 123.9, 122.9, 41.5, 20.6; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{16}NS^+$: 266.0998, found: 266.0993.

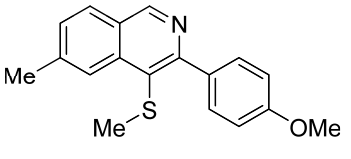
4.3.19. *3-(4-Methoxyphenyl)-7-methyl-4-(methylthio)isoquinoline (3s)*



White solid (120 mg, 81%); mp = 133–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.22 (s, 1H), 8.07 (d, J = 7.2 Hz, 2H), 7.89 (s, 1H), 7.81 (d, J = 6.8 Hz, 1H), 7.65 (d, J = 6.8 Hz, 1H), 7.99 (d, J = 7.2 Hz, 2H), 3.83 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.2, 158.0, 151.3, 145.3, 140.8, 135.3, 130.4, 130.2 (2C), 129.2, 127.7, 126.4, 124.7, 115.5 (2C), 55.3, 23.1, 20.3; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{18}H_{18}NOS^+$: 296.1104, found: 296.1102.

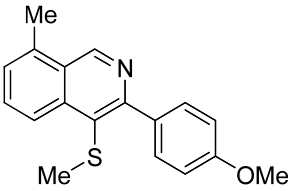
4.3.20. *3-(4-Methoxyphenyl)-6-methyl-4-(methylthio)isoquinoline (3t)*



White solid (122 mg, 83%); mp = 132–134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1H), 8.05 (d, J = 7.0 Hz, 2H), 7.99 (d, J = 6.6 Hz, 1H), 7.48 (d, J = 6.6 Hz, 1H), 7.41(s, 1H), 6.98 (d, J = 7.0 Hz, 2H), 3.82 (s, 3H), 2.61 (s, 3H), 2.46 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.7, 155.3, 149.1, 144.6, 137.7, 133.5, 132.5, 130.7, 129.8 (2C), 128.0, 126.0, 123.7, 114.2 (2C), 55.4, 22.9, 20.1; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{18}H_{18}NOS^+$: 296.1104, found: 296.1108.

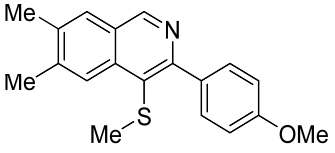
4.3.21. *3-(4-Methoxyphenyl)-8-methyl-4-(methylthio)isoquinoline (3u)*



Pale yellow solid (121 mg, 82%); mp = 129–131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1H), 8.24 (d, J = 7.8 Hz, 2H), 7.87 (d, J = 7.4 Hz, 1H), 7.81 (d, J = 7.0 Hz, 1H), 7.58–7.53 (m, 1H), 7.04 (d, J = 7.8 Hz, 2H), 3.88 (s, 3H), 2.74 (s, 3H), 2.55 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 162.8, 146.9, 146.0, 141.5, 138.2, 133.5, 131.2, 130.7 (2C), 130.0, 128.7, 127.0, 121.3, 114.2 (2C), 55.4, 21.0, 19.3; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{18}H_{18}NOS^+$: 296.1104, found: 296.1101.

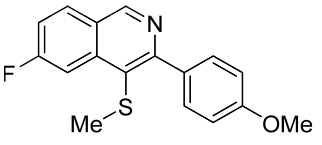
4.3.22. *3-(4-Methoxyphenyl)-6,7-dimethyl-4-(methylthio)isoquinoline (3v)*



White solid (128 mg, 83%); mp = 137–139 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.26 (s, 1H), 8.03 (d, J = 7.6 Hz, 2H), 7.85 (s, 1H), 7.51 (s, 1H), 7.05 (d, J = 7.6 Hz, 2H), 3.90 (s, 3H), 2.64 (s, 3H), 2.41 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.9, 153.8, 147.8, 142.9, 140.4, 135.9, 133.7, 130.5, 129.8 (2C), 128.3, 124.2, 122.8, 114.1 (2C), 55.4, 21.4, 21.4, 20.1; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{19}H_{20}NOS^+$: 310.1260, found: 310.1261.

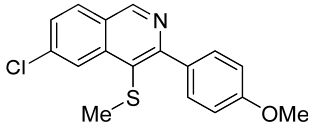
4.3.23. *6-Fluoro-3-(4-methoxyphenyl)-4-(methylthio)isoquinoline (3w)*



Yellow solid (114 mg, 76%); mp = 129–131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 1H), 8.09–8.02 (m, 3H), 7.49 (dd, J = 7.2, 3.2 Hz, 1H), 7.43–7.37 (m, 1H), 6.98 (d, J = 7.6 Hz, 2H), 3.82(s, 3H), 2.62 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 162.8, 162.2 (d, J = 196.3 Hz), 158.0, 149.5, 146.2 (d, J = 4.4 Hz), 134.4 (d, J = 7.3 Hz), 134.0, 129.7 (d, J = 7.3 Hz), 127.7 (2C), 121.9, 121.3 (d, J = 20.5 Hz), 117.9 (2C), 107.3 (d, J = 17.1 Hz), 55.4, 21.1; **^{19}F NMR** (100 MHz, $CDCl_3$): δ = −106.7; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{15}FNOS^+$: 300.0853, found: 300.0851.

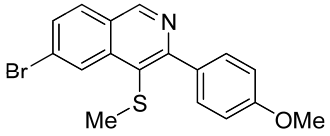
4.3.24. *6-Chloro-3-(4-methoxyphenyl)-4-(methylthio)isoquinoline (3x)*



Brown solid (123 mg, 78%); mp = 142–144 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (s, 1H), 8.10–8.04 (m, 3H), 7.88 (s, 1H), 7.60 (d, J = 6.4 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 3.89 (s, 3H), 2.65 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 158.8, 152.5, 148.6, 144.1, 133.9, 133.7, 133.5, 132.2, 130.9 (2C), 129.8, 126.7, 124.9, 114.2 (2C), 55.4, 21.1; **HRMS** (ESI) (m/z): $[M+H]^+$ calcd. for $C_{17}H_{15}ClNOS^+$: 316.0557, found: 316.0551.

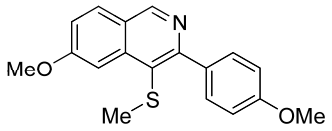
4.3.25. *6-Bromo-3-(4-methoxyphenyl)-4-(methylthio)isoquinoline (3y)*



Dark brown solid (142 mg, 79%); mp = 144–146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.24 (s, 1H), 8.14 (d, J = 6.4 Hz, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.52 (d, J = 6.4 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 3.91 (s, 3H), 2.66 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.3, 150.7, 146.7, 142.9, 136.0, 135.6, 130.9, 130.8 (2C), 127.5, 126.9, 125.2, 123.4, 114.2 (2C), 55.4, 20.8; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{17}H_{15}BrNOS^+$: 360.0052, found: 360.0048.

4.3.26. *6-Methoxy-3-(4-methoxyphenyl)-4-(methylthio)isoquinoline (3z)*



White solid (129 mg, 83%); mp = 129–131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1H), 8.03 (d, J = 7.8 Hz, 2H), 7.78 (d, J = 7.4 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.10 (d, J = 7.8 Hz, 2H), 6.96 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 2.63 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 161.7, 161.6, 151.0, 145.6, 140.4, 133.6 (2C), 129.9, 127.7, 123.1, 119.6, 118.6, 114.3 (2C), 108.0, 55.5, 55.4, 20.1; **HRMS (ESI)** (m/z): $[M+H]^+$ calcd. for $C_{18}H_{18}NO_2S^+$: 312.1053, found: 312.1051.

Declaration of interests

The authors do not work for, advise, own shares in, or receive funds from any organization that could benefit from this article, and have declared no affiliations other than their research organization.

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Supplementary materials

Supporting information for this article is available on the journal's website under https://doi.org/10.5802/crchim.447 or from the author.

Use of artificial intelligence techniques

No artificial intelligence was used in the preparation of this manuscript.

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