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Synthesis of 1-Thio-Substituted Isoquinoline Derivatives by Tandem Cyclization of Isothiocyanates

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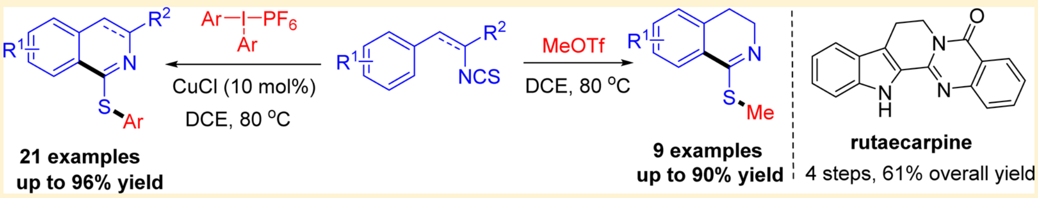
Supporting Information



ABSTRACT: A copper-catalyzed tandem arylation−cyclization process to access 1-(arylthio)isoquinolines from isothiocyanates and diaryliodonium salts is described. It is the first general method to construct the potentially useful 1-(arylthio)isoquinoline derivatives. Moreover, 1-(methylthio)isoquinoline derivatives were also achieved successfully with MeOTf instead of diaryliodonium salts under metal-free conditions. Mechanistic studies reveal that these two processes proceed in different routes. This method has been successfully applied to the synthesis of quinazolinone alkaloid rutaecarpine.

INTRODUCTION

Isoquinoline is an important heteroaromatic scaffold existing in natural products, pharmaceuticals, and functional materials,[1] such as berberine alkaloids,[2] antispasmodic drug papaverine,[3] and cytotoxic alkaloid quinocarcin (Figure 1).[4] Thus, diverse synthetic methods have been developed for constructing isoquinoline derivatives. However, classical methods of isoquinoline synthesis, involving Bischler−Napieralski[5] and Pictet−Spengler reactions,[6] require harsh acidic conditions which limited their usage. Recently, many efficient methods have been reported to construct isoquinolines through annulation reactions catalyzed by transition metals,[7] such as palladium,[8] nickel,[9] silver,[10] copper,[11] rhodium,[12] and ruthenium.[13] Although significant advances have been made toward isoquinoline construction, to the best of our knowledge, there has been no general method to synthesize 1-(arylthio)-isoquinoline derivatives. Given the increasing prevalence of sulfur-containing compounds in pharmaceuticals,[14] introducing an arylthio or methylthio group into the isoquinoline motif would be of great synthetic value.

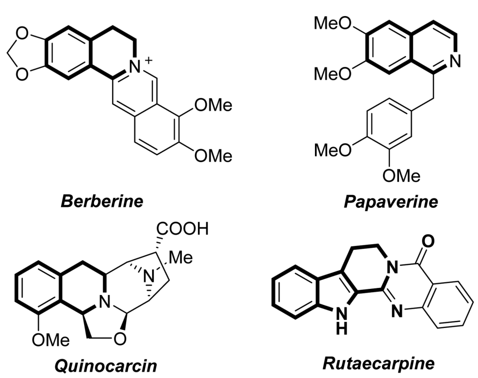


Figure 1. Representative bioactive isoquinoline natural products.

Recently, the arylation−cyclization process based on diaryliodonium salts has become a powerful strategy for the construction of heterocycles.[15] Various substrates, such as alkenes,[16] alkynes,[17] and nitriles,[18] can be easily arylated with diaryliodonium salts to generate carbocation intermediates, which undergo cyclization to obtain structure-divergent molecules. Isothiocyanates, as versatile synthetic intermediates, have been widely used in the construction of heterocyclic compounds.[19] Traditionally, reactions occurred at the C atom of isothiocyanates; i.e., the −NCS group was applied as an electrophile. Recently, tandem radical cyclization reactions involving isothiocyanates have received more attention.[20] However, reactions induced by the S atom of isothiocyanate have been much less reported.[21] Moreover, β-arylethyl isothiocyanates and vinyl isothiocyanates, as potentially synthetic useful intermediates, are seldom applied for the synthesis of heterocycles.[22] As our continuing interests in using isothiocyanates as the starting materials for the construction of heterocycles,[23] herein, we report a new efficient tandem reaction to synthesize 1-(arylthio)- and 1-(methylthio)-

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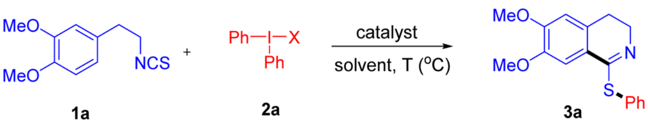
isoquinoline derivatives through isothiocyanates with diaryliodonium salts and methyl triflate, respectively.

■ RESULTS AND DISCUSSION

Considering many natural isoquinoline alkaloids containing 3,4-dimethoxy or 3,4-methylenedioxy groups (Figure 1), 4-(2-isothiocyanatoethyl)-1,2-dimethoxybenzene **1a** was chosen as a model substrate to react with diphenyliodonium salt **2a** (Table 1). Initially, our previous optimized conditions[23a] were used, and the desired product 1-(phenylthio)-3,4-dihydroisoquinoline **3a** was obtained in 34% yield (entry 1). This result motivated us to test different copper catalysts. However, other copper salts such as $Cu(OTf)_2$, $Cu(OAc)_2$, CuBr, CuTC, and CuI did not improve the yield of **3a** (entries 2–6). In addition, compound **3a** was not observed in the absence of copper salt (entry 7). When hexafluorophosphate (PF_6^-) was used as an anion instead of OTf^-, **3a** was obtained in excellent yield (entry 8), whereas lower yield was provided with tetrafluoroborate (BF_4^-) (entry 9), which showed that the anions of diaryliodonium salts had dramatic influence on the reaction. Additionally, screening some other solvents, such as THF and toluene, revealed that DCE was the best choice (entries 10 and 11). The yield of **3a** decreased with elevating the temperature to 100 °C or decreasing to 60 °C (entries 12 and 13). When 5 mol % CuCl was used as catalyst, the yield of **3a** dropped to 39% (entry 14). A slightly lower yield was observed when the reaction was conducted under the air atmosphere. Finally, the optimal conditions were established as follows: **1a** and **2a** (X = PF_6) in a ratio of 1:1.5, CuCl (10 mol %), DCE (0.2 M) at 80 °C for 2 h.

Table 1. Optimization of the Reaction Conditions[a]

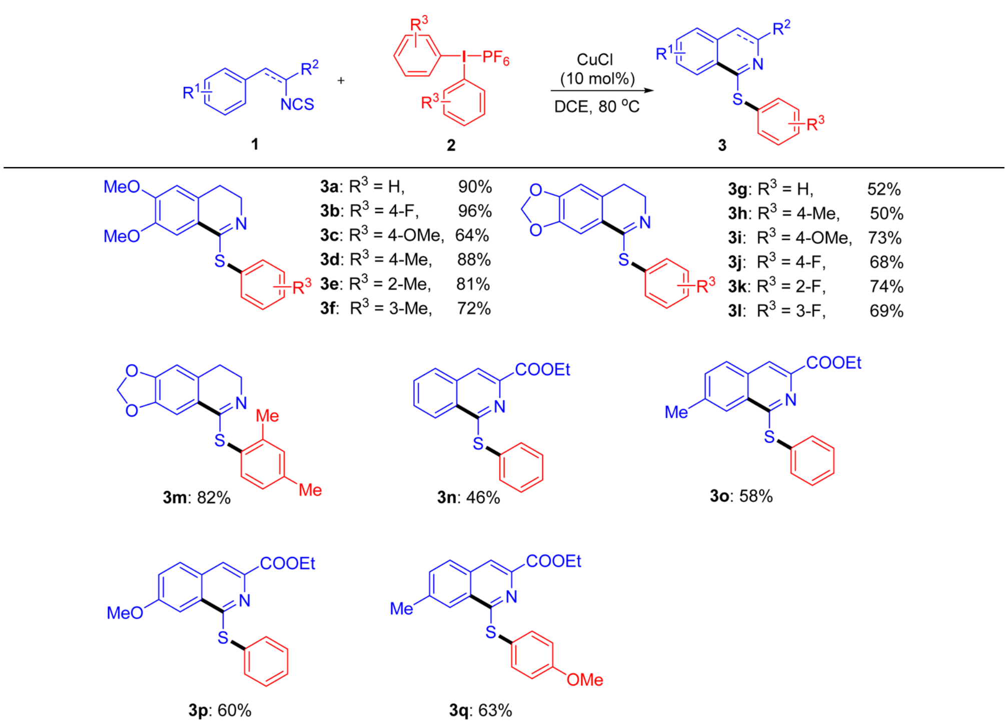


entry	catalyst (mol %)	X	solvent	T [°C]	yield [%][b]
1	CuCl (10)	OTf	DCE	80	34
2	$Cu(OTf)_2$ (10)	OTf	DCE	80	28
3	$Cu(OAc)_2$ (10)	OTf	DCE	80	12
4	CuBr (10)	OTf	DCE	80	26
5	CuTC (10)	OTf	DCE	80	28
6	CuI (10)	OTf	DCE	80	32
7	none	OTf	DCE	80	0
8	**CuCl (10)**	**PF_6**	**DCE**	**80**	**90**
9	CuCl (10)	BF_4	DCE	80	18
10	CuCl (10)	PF_6	THF	80	50
11	CuCl (10)	PF_6	toluene	80	83
12	CuCl (10)	PF_6	DCE	100	77
13	CuCl (10)	PF_6	DCE	60	75
14	CuCl (5)	PF_6	DCE	80	39
15[c]	CuCl (10)	PF_6	DCE	80	78

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), solvent (1 mL), 2 h, N_2. [b]Isolated yield based on **3a**. [c]Under an air atmosphere.

Under the optimized reaction conditions, the scope of substrates was investigated (Table 2). The 1-(arylthio)-3,4-dihydroisoquinolines **3a–f** were generated in good to excellent yields (72–96%) from isothiocyanate **1a** and diaryliodonium salts **2**, except the *para*-OMe substrate **2c** (64% yield). The desired products **3g–l** were also formed in moderated to good yields when 3,4-methylenedioxy-substituted isothiocyanate **1b** was used instead of **1a**. In addition, disubstituted diaryliodonium salts, such as 2,4-dimethyl-substituted compound **2m**, were also compatible to the reaction, and product **3m** was obtained in 82% yield. Disappointingly, no cyclization products were formed when monosubstituted substrates **1** (4-Me, 4-OMe, 4-F-phenyl) were used. To further extend the scope of

Table 2. Synthesis of Isoquinoline Derivatives 3[a,b]



[a]Reaction conditions: **1** (0.4 mmol), **2** (0.6 mmol), CuCl (0.04 mmol), DCE (2 mL), 2 h, N_2. [b]Isolated yield

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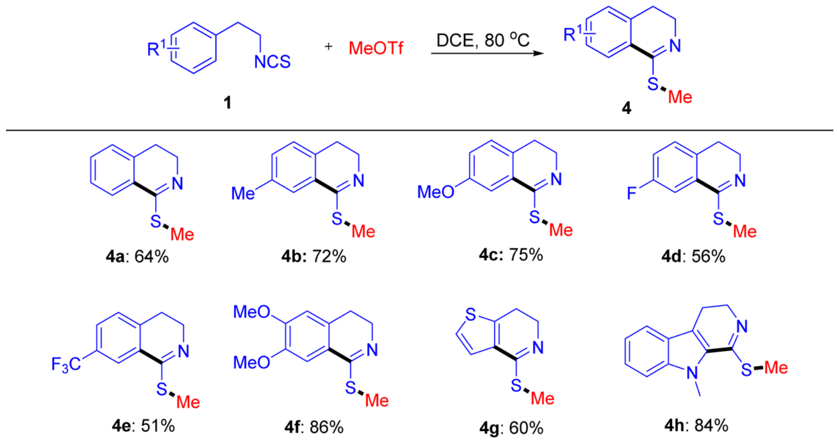
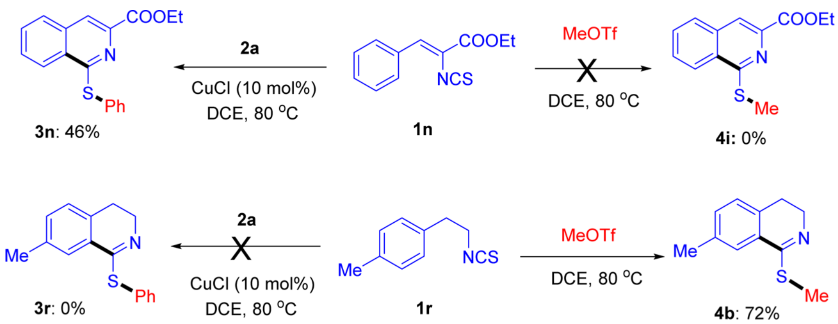
J. Org. Chem. 2017, 82, 1428–1436

Table 3. Synthesis of Isoquinoline Derivatives 4[a,b]



[a]Reaction conditions: **1** (0.4 mmol), MeOTf (0.6 mmol), DCE (2 mL), 2 h, N_2. [b]Isolated yield.

Scheme 1. Comparative Experiments of Diphenyliodonium Salt and MeOTf



Scheme 2. Control Experiments

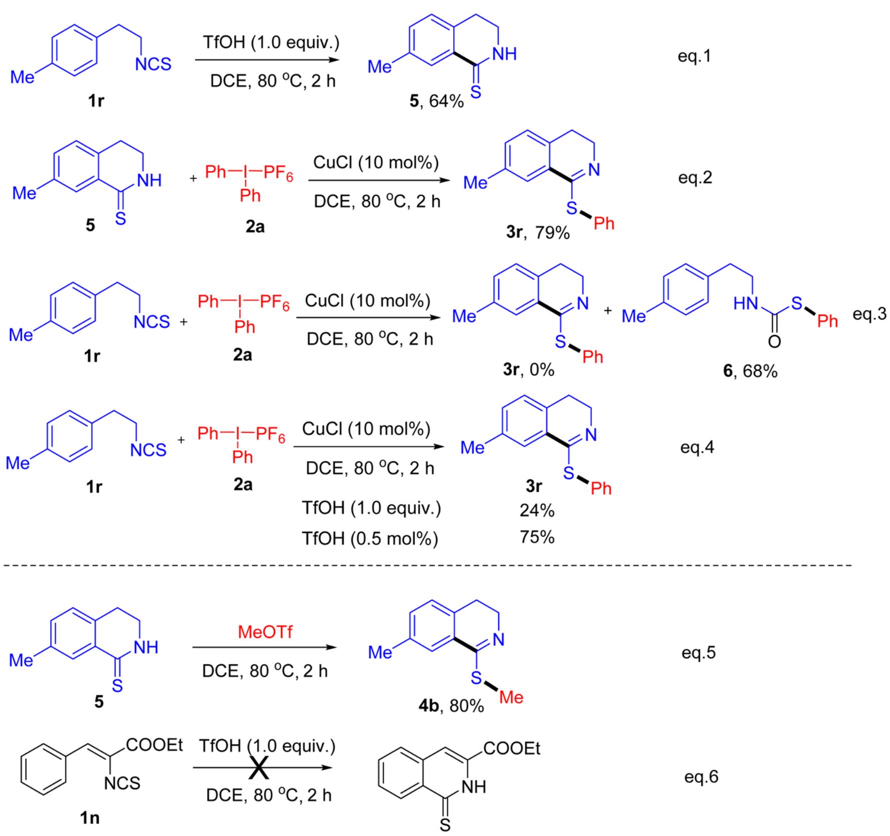


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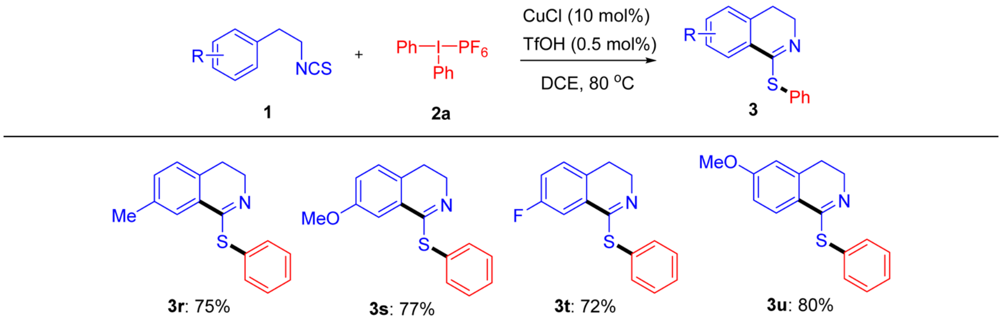
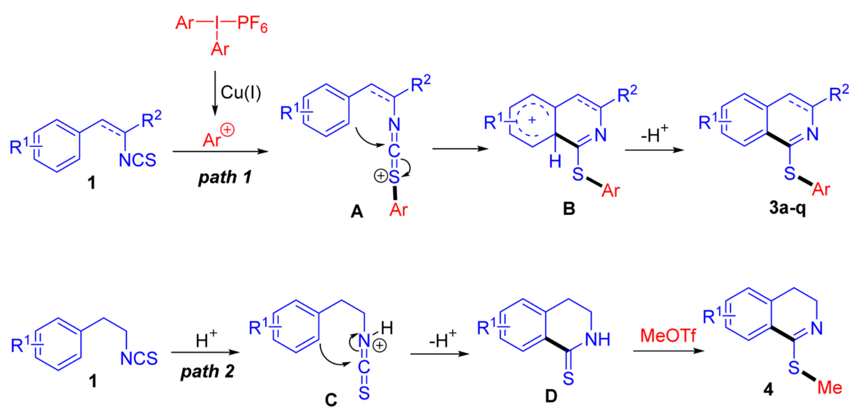
Table 4. Synthesis of Monosubstituted Derivatives 3[a,b]



[a]Reaction conditions: **1** (0.4 mmol), **2** (0.6 mmol), CuCl (0.04 mmol), TfOH (0.002 mmol), DCE (2 mL), 2 h, N_2. [b]Isolated yield.

Scheme 3. Proposed Reaction Mechanism



the protocol, several vinyl isothiocyanates were synthesized and reacted with diaryliodonium salts **2**. The reaction proceeded smoothly, and isoquinolines **3n–q** were provided in moderate yields. The reason may be subject to the electron-withdrawing COOEt group, which makes the carbon atom of the NCS group more electron-deficient to facilitate the electrophilic cyclization. The structures of **3** were unambiguously confirmed by X-ray crystallographic analysis of compound **3a** (see Figure S1).

Considering that aryl carbocations generated from **2** could react with isothiocyanates **1**, we envisioned that methyl carbocation may proceed via a similar process to form 1-(methylthio)isoquinoline derivatives. To test the idea, methyl triflate (MeOTf) was chosen to react with isothiocyanates **1** under the above conditions without copper catalyst (Table 3). To our delight, 1-(methylthio)-3,4-dihydroisoquinolines **4a–f** were obtained in 51–86% yields. The reactions showed obvious electron effects, and higher yield was obtained with a highly electron-rich substrate (**4f**, 86%), whereas the electron-deficient 4-CF_3 substrate provided lower yield (**4e**, 51%). Notably, heterocyclic thiophene and indole substrates were also suitable for the reaction; the desired products **4g** and **4h** were obtained in 60% and 84% yields, respectively.

Interestingly, when vinyl isothiocyanate **1n** was used to react with MeOTf, 1-(methylthio)isoquinoline **4i** was not obtained, whereas 1-(phenylthio)isoquinoline **3n** was provided in 46% yield (Scheme 1). Furthermore, **4b** was produced in 72% yield when isothiocyanate **1r** was used, whereas **3r** was not formed. These phenomena suggested that the two reactions maybe proceed through different pathways.

In order to explain these phenomena, a series of control experiments were conducted (Scheme 2). Isothiocyanate **1r** could be cyclized smoothly to provide thioamide **5** in the presence of trifluoromethanesulfonic acid (TfOH) (eq 1). Then, the reaction of **5** with **2a** was performed under the standard conditions, and the dihydroisoquinoline **3r** was obtained in 79% yield (eq 2). However, when the reaction of **1r** with **2a** was directly performed under the standard conditions, no cyclized product **3r** was obtained, but thiocarbamate **6** was formed in 68% yield (eq 3). On the basis of the above results, we performed eqs 1 and 2 in one-pot in the presence of stoichiometric TfOH (eq 4), and **3r** was obtained, albeit in a low yield of 24%. Considering a trace amount of TfOH is sufficient to initiate the intramolecular electrophilic cyclization, 0.5 mol % TfOH was added in the reaction mixture; to our delight, the yield of **3r** increased to 75%. Thus, a cyclization/arylation process was proposed for the synthesis of monosubstituted product **3r**.

Otherwise, **4b** was generated in 80% yield from **5** under the standard conditions (eq 5). When vinyl isothiocyanate **1n** was used under the same conditions as eq 1, the thioamide was not obtained and only starting material **1n** was recovered (eq 6). These results indicated that the cyclization would occur prior to the methylation for the reactions of isothiocyanates with MeOTf, which was probably due to a trace amount of TfOH involving in MeOTf (MeOTf easily hydrolyzes to form TfOH). To verify this hypothesis, the reaction of **1r** with MeOTf was conducted with 10 mol % 2,6-di-*tert*-butylpyridine as a base, and it was completely prevented. These results confirmed that TfOH should play an important role in the cyclization process.

To further examine the generality of the reaction in Scheme 2, eq 4, other monosubstituted substrates (4-OMe, 4-F, 3-OMe) were investigated (Table 4); the results showed that the

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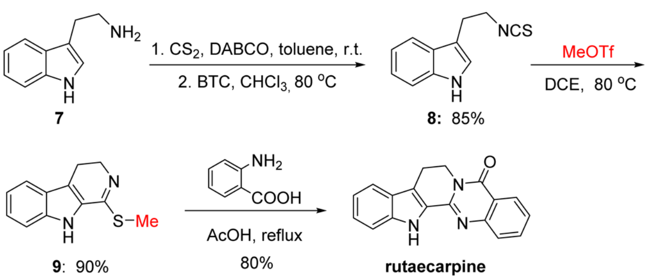
reactions could proceeded smoothly and the cyclized monosubstituted products **3s–u** were formed in good yields.

On the basis of the above results, a possible mechanism is proposed in Scheme 3. In path 1, when Ar_2IPF_6 reacts with isothiocyanate **1** in the absence of TfOH, the sulfonium intermediate **A** is formed initially through *S*-arylation of the generated aryl carbocation.[23a] Subsequently, the intermediate **A** undergoes intramolecular Friedel–Crafts-type cyclization, followed by deprotonation, to provide the desired 1-(arylthio)-isoquinolines **3a–q** (path 1). In path 2, when MeOTf reacts with **1**, the NCS group is initially protonated, followed by cyclization, to generate intermediate **D**. Finally, a methylation of **D** with MeOTf gives products **4**. The reaction mechanism for the synthesis of **3r–u** is similar to that of compounds **4**.

The quinazolinone alkaloid rutaecarpine, isolated in 1915 from *Evodia rutaecarpa*, was used in Traditional Chinese Medicine for the treatment of inflammation-related disorders.[24] To further illustrate the potential utility of this new method, a concise total synthesis of rutaecarpine was explored (Scheme 4). Initially, isothiocyanate **8** was synthesized from commercially available tryptamine **7**. Under the above standard cyclization conditions, the methylthio-substituted 3,4-dihydro-*β*-carboline **9** was generated in 90% yield. Finally, annulation with 2-aminobenzoic acid afforded the natural alkaloid rutaecarpine.[24b] The facile synthetic route could provide a pathway for rutaecarpine analogues synthesis.

Scheme 4. Application in the Synthesis of Rutaecarpine



■ CONCLUSION

In summary, we have developed a new tandem reaction to synthesize 1-thio-substituted isoquinolines from isothiocyanates with diaryliodonium salts or methyl triflate under mild conditions. Control experiments suggest that two mechanistically different pathways might be involved. To the best of our knowledge, this is the first general method to construct 1-(arylthio)isoquinolines. In addition, the method was applied as a key step to the short synthesis of alkaloid rutaecarpine. Further studies to explore new synthetic methods using isothiocyanates are in progress.

■ EXPERIMENTAL SECTION

General Information. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere. DCE was distilled from CaH_2. Unless noted, all commercial reagents were used without further purification. Melting points were recorded on a microscopic melting apparatus and uncorrected. ^{1}H NMR spectra were recorded at 500 MHz, and ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$ or DMSO-d_6. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS). HRMS was obtained on a spectrometer with an ESI source. The X-ray single-crystal diffraction was performed on a CCD area detector. Silica gel (200–300 mesh) was used for column chromatography and silica GF254 for TLC.

Preparation of Starting Materials. Diaryliodonium salts[25] were prepared according to previously published procedures. The (2-isothiocyanatoethyl) benzenes[26] and ethyl (*Z*)-2-isothiocyanato-3-phenylacrylates[22a] were also synthesized according to previously published procedures.

General Procedure for the Synthesis of Compounds 3 (3a for Example). Under a N_2 atmosphere, a dry Schlenk tube was charged with a mixture of 4-(2-isothiocyanatoethyl)-1,2-dimethoxybenzene **1a** (90 mg, 0.40 mmol), diphenyliodonium salt **2a** (256 mg, 0.60 mmol), CuCl (4.0 mg, 0.04 mmol), and DCE (2.0 mL). The mixture was allowed to stir at 80 °C for 2 h. After completion, the mixture was cooled to room temperature, quenched with saturated $NaHCO_3$, and extracted with EtOAc (10 mL × 3). The organic layer was washed with saturated NaCl and dried over anhydrous $MgSO_4$. Evaporation of the solvent, followed by purification on silica gel (petroleum ether/ethyl acetate), provided product **3a**.

*6,7-Dimethoxy-1-(phenylthio)-3,4-dihydroisoquinoline (**3a**).* Isolated yield 108 mg (90%); white solid; mp 86–88 °C; R_f 0.20 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.68 (t, J = 7.4 Hz, 2H), 3.66 (t, J = 7.4 Hz, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 6.72 (s, 1H), 7.31 (s, 1H), 7.36–7.42 (m, 3H), 7.57 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 25.9, 48.6, 55.9, 56.1, 108.6, 110.1, 121.5, 128.5, 128.9, 129.8, 131.1, 134.8, 147.3, 151.1, 163.3; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{17}H_{17}NO_2S$, 300.1053, found 300.1054

*1-((4-Fluorophenyl)thio)-6,7-dimethoxy-3,4-dihydroisoquinoline (**3b**).* Isolated yield 122 mg (96%); white solid; mp 105–106 °C; R_f 0.24 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.65 (t, J = 7.4 Hz, 2H), 3.63 (t, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 6.70 (s, 1H), 7.09 (t, J = 8.6 Hz, 2H), 7.28 (s, 1H), 7.51–7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.0, 48.6, 56.0, 56.1, 108.3, 110.1, 116.2 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 121.5, 124.6, 131.1, 137.2 (d, $^1J_{C\text{-}F}$ = 248.3 Hz), 147.4, 151.2, 162.1, 163.1, 164.0; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{17}H_{16}FNO_2S$, 318.0959, found 318.0956.

*6,7-Dimethoxy-1-((4-methoxyphenyl)thio)-3,4-dihydroisoquinoline (**3c**).* Isolated yield 85 mg (64%); white solid; mp 138–140 °C; R_f 0.10 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.64 (t, J = 7.0 Hz, 2H), 3.62 (t, J = 7.0 Hz, 2H), 3.82 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 6.69 (s, 1H), 6.93 (d, J = 7.9 Hz, 2H), 7.31 (s, 1H), 7.47 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.1, 48.63, 55.27, 56.0, 56.2, 108.6, 110.2, 114.8, 120.0, 121.8, 131.1, 136.8, 147.5, 151.2, 160.2; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{18}H_{19}NO_3S$, 330.1164, found 330.1152.

*6,7-Dimethoxy-1-(p-tolylthio)-3,4-dihydroisoquinoline (**3d**).* Isolated yield 110 mg (88%); white solid; mp 129–131 °C; R_f 0.22 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.36 (s, 3H), 2.65 (t, J = 7.4 Hz, 2H), 3.64 (t, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.92 (s, 3H), 6.69 (s, 1H), 7.21 (d, J = 7.9 Hz, 2H), 7.30 (s, 1H), 7.43 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.3, 26.0, 48.6, 56.0, 56.1, 108.4, 110.0, 121.6, 125.9, 130.0, 131.1, 135.0, 138.8, 147.3, 151.0, 163.5; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{18}H_{19}NO_2S$, 314.1210, found 314.1212.

*6,7-Dimethoxy-1-(o-tolylthio)-3,4-dihydroisoquinoline (**3e**).* Isolated yield 101 mg (81%); white solid; mp 94–96 °C; R_f 0.23 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.43 (s, 3H), 2.65 (t, J = 7.4 Hz, 2H), 3.62 (t, J = 7.2 Hz, 2H), 3.92 (s, 6H), 6.70 (s, 1H), 7.20–7.23 (m, 1H), 7.30–7.32 (m, 3H), 7.55 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.9, 26.0, 48.6, 55.9, 56.1, 108.6, 110.1, 121.7, 126.5, 128.9, 129.4, 130.6, 131.1, 136.2, 142.6, 147.4, 151.0, 162.5; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{18}H_{19}NO_2S$, 314.1210, found 314.1211.

*6,7-Dimethoxy-1-(m-tolylthio)-3,4-dihydroisoquinoline (**3f**).* Isolated yield 90 mg (72%); white solid; mp 93–95 °C; R_f 0.24 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.36 (s, 3H), 2.66 (t, J = 7.4 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 6.70 (s, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.26–7.30 (m, 2H), 7.35–7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.3, 26.0, 48.6, 56.0, 56.1, 108.6, 110.1, 121.6, 128.8, 129.3, 129.5, 131.1, 132.0, 135.4, 138.7, 147.4, 151.1, 163.4; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{18}H_{19}NO_2S$, 314.1210, found 314.1214.

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J. Org. Chem. 2017, 82, 1428–1436

5-(Phenylthio)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (**3g**). Isolated yield 59 mg (52%); white solid; mp 154−156 °C; R_f 0.39 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.63 (t, *J* = 7.3 Hz, 2H), 3.60 (t, *J* = 7.3 Hz, 2H), 6.00 (s, 2H), 6.68 (s, 1H), 7.31 (s, 1H), 7.34−7.41 (m, 3H), 7.55 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 26.7, 48.4, 80.7, 84.1, 101.4, 105.9, 107.8, 122.9, 128.6, 129.0, 133.0, 135.0, 146.4, 149.5, 163.2; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{16}H_{13}NO_2S$, 284.0745, found 284.0752.

5-(p-Tolylthio)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (**3h**). Isolated yield 60 mg (50%); white solid; mp 161−163 °C; R_f 0.40 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.36 (s, 3H), 2.61 (t, *J* = 7.3 Hz, 2H), 3.59 (t, *J* = 7.3 Hz, 2H), 5.99 (s, 2H), 6.67 (s, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.31 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 26.7, 48.5, 101.4, 105.9, 107.8, 130.0, 125.8, 129.9, 130.0, 135.2, 138.8, 146.3, 149.3, 163.3; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{17}H_{15}NO_2S$, 298.0902, found 298.0912.

5-((4-Methoxyphenyl)thio)-7,8-dihydro-[1,3]dioxolo[4,5-g]-isoquinoline (**3i**). Isolated yield 91 mg (73%); white solid; mp 153−155 °C; R_f 0.28 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.61 (t, *J* = 7.3 Hz, 2H), 3.58 (t, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 5.99 (s, 2H), 6.67 (s, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 7.31 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 26.8, 48.5, 55.3, 101.4, 105.8, 107.8, 114.8, 119.8, 123.0, 133.0, 137.0, 146.4, 149.3, 160.2, 163.6; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{17}H_{15}NO_3S$, 314.0851, found 314.0862.

5-((4-Fluorophenyl)thio)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (**3j**). Isolated yield 82 mg (68%); white solid; mp 156−158 °C; R_f 0.62 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.62 (t, *J* = 7.3 Hz, 2H), 3.58 (t, *J* = 7.3 Hz, 2H), 6.00 (s, 2H), 6.68 (s, 1H), 7.09 (t, *J* = 8.9 Hz, 2H), 7.28 (s, 1H), 7.50−7.52 (m, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 26.7, 48.5, 101.4, 105.7, 107.9, 116.2 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 122.8, 124.6, 133.0, 137.2, 137.3, 146.4, 149.5, 162.9, 163.1 (d, $^1J_{C\text{-}F}$ = 248.3 Hz); HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{16}H_{12}FNO_2S$, 302.0651, found 302.0659.

5-((2-Fluorophenyl)thio)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (**3k**). Isolated yield 89 mg (74%); white solid; mp 159−161 °C; R_f 0.52 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.64 (t, *J* = 7.3 Hz, 2H), 3.61 (t, *J* = 7.3 Hz, 2H), 6.02 (s, 2H), 6.70 (s, 1H), 7.15−7.22 (m, 2H), 7.40−7.44 (m, 1H), 7.58 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 26.6, 48.5, 101.4, 105.9, 107.8, 116.0 (d, $^2J_{C\text{-}F}$ = 22.7 Hz), 117.0 (d, $^2J_{C\text{-}F}$ = 18.1 Hz), 122.7, 124.5, 131.3, 133.0, 137.2, 146.4, 149.5, 161.3, 162.7 (d, $^1J_{C\text{-}F}$ = 253.0 Hz); HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{16}H_{12}FNO_2S$, 302.0651, found 302.0661.

5-((3-Fluorophenyl)thio)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (**3l**). Isolated yield 72 mg (60%); white solid; mp 125−127 °C; R_f 0.58 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.64 (t, *J* = 7.4 Hz, 2H), 3.62 (t, *J* = 7.4 Hz, 2H), 6.00 (s, 2H), 6.68 (s, 1H), 7.05 (t, *J* = 8.1 Hz, 1H), 7.28−7.35 (m, 4H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 26.6, 48.5, 101.4, 105.9, 107.9, 115.6 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 121.6 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 122.8, 130.0, 131.8, 133.1, 146.5, 149.6, 162.4, 162.5 (d, $^1J_{C\text{-}F}$ = 247.3 Hz); HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{16}H_{12}FNO_2S$, 302.0651, found 302.0648.

5-((2,4-Dimethylphenyl)thio)-7,8-dihydro-[1,3]dioxolo[4,5-g]-isoquinoline (**3m**). Isolated yield 102 mg (82%); white solid; mp 118−120 °C; R_f 0.40 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.36 (s, 3H), 2.40 (s, 3H), 2.62 (t, *J* = 7.3 Hz, 2H), 3.59 (t, *J* = 7.3 Hz, 2H), 6.02 (s, 2H), 6.70 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.15 (s, 1H), 7.38 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 20.8, 21.3, 48.5, 101.3, 105.9, 107.8, 123.0, 125.1, 127.4, 131.5, 132.9, 136.4, 139.6, 142.6, 146.3, 149.3, 162.5; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{18}H_{17}NO_2S$, 312.1058, found 312.1062.

Ethyl 1-(Phenylthio)isoquinoline-3-carboxylate (**3n**). Isolated yield 63 mg (51%); white solid; mp 63−65 °C; R_f 0.68 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 1.33 (t, *J* = 7.2 Hz, 3H), 2.40 (q, *J* = 7.1 Hz, 2H), 7.38−7.44 (m, 3H), 7.69−7.78 (m, 4H), 7.93 (d, *J* = 8.0 Hz, 1H), 8.29 (s, 1H), 8.38 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 14.1, 29.6, 61.3, 121.5, 124.9, 128.1, 128.5, 128.8, 129.4, 129.9, 131.0, 134.6, 135.5, 141.0, 159.6, 165.5; HRMS (ESI-TOF, [M + H]$^+$): Calcd for $C_{18}H_{15}NO_2S$, 310.0902, found 310.0914.

Ethyl 7-Methyl-1-(phenylthio)isoquinoline-3-carboxylate (**3o**). Isolated yield 75 mg (58%); white solid; mp 84−86 °C; R_f 0.56 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 1.32 (t, *J* = 7.3 Hz, 3H), 2.60 (s, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 7.38−7.44 (m, 3H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.82 (d, *J* = 7.9 Hz, 1H), 8.14 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 14.1, 22.2, 61.2, 121.4, 124.0, 127.2, 128.4, 128.5, 128.8, 130.0, 133.1, 133.6, 134.6, 140.1, 140.3, 158.5, 165.6; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{19}H_{17}NO_2S$, 324.1058, found 324.1049.

Ethyl 7-Methoxy-1-(phenylthio)isoquinoline-3-carboxylate (**3p**). Isolated yield 82 mg (60%); white solid; mp 112−114 °C; R_f 0.50 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 1.33 (t, *J* = 7.0 Hz, 3H), 2.60 (s, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 7.35−7.42 (m, 4H), 7.56 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 9.2 Hz, 1H), 8.27 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 14.1, 55.6, 61.2, 121.6, 123.7, 128.2, 128.8, 129.9, 130.3, 130.8, 134.0, 139.4, 157.1, 160.3, 165.6; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{19}H_{17}NO_3S$, 340.1007, found 340.1012.

Ethyl 1-((4-Methoxyphenyl)thio)-7-methylisoquinoline-3-carboxylate (**3q**). Isolated yield 89 mg (63%); white solid; mp 89−91 °C; R_f 0.55 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 1.32 (t, *J* = 7.3 Hz, 3H), 2.60 (s, 3H), 3.84 (s, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 7.9 Hz, 1H), 8.13 (s, 1H), 8.22 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 14.0, 22.1, 55.3, 61.1, 114.5, 120.1, 121.0, 123.8, 128.0, 128.5, 133.0, 133.5, 136.9, 139.9, 140.3, 159.4, 160.2, 165.7; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{20}H_{19}NO_3S$, 354.1158, found, 354.1171.

General Procedure for the Synthesis of Compounds 4 (4a for Example). A dry Schlenk tube was charged with a mixture of (2-isothiocyanatoethyl) benzene **1c** (66 mg, 0.40 mmol), methyltriflate (99 mg, 0.60 mmol), and DCE (2.0 mL). The mixture was allowed to stir at 80 °C for 2 h under a N_2 atomsphere. After that, the mixture was cooled to room temperature, quenched with saturated $NaHCO_3$, and extracted with EtOAc (10 mL × 3). The organic layer was washed with saturated NaCl and dried over anhydrous $MgSO_4$. Evaporation of the solvent, followed by purification on silica gel (petroleum ether/ethyl acetate), provided the product **4a**.

1-(Methylthio)-3,4-dihydroisoquinoline (**4a**).[22b] Isolated yield 46 mg (64%); colorless oil; R_f 0.48 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.44 (s, 3H), 2.74 (t, *J* = 7.3 Hz, 2H), 3.76 (t, *J* = 7.3 Hz, 2H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 12.2, 26.5, 48.2, 124.7, 126.9, 127.3, 129.3, 130.8, 136.8, 164.0; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{10}H_{11}NS$, 178.0685, found 178.0689.

7-Methyl-1-(methylthio)-3,4-dihydroisoquinoline (**4b**). Isolated yield 55 mg (72%); colorless oil; R_f 0.43 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.36 (s, 3H), 2.44 (s, 3H), 2.68 (t, *J* = 7.3 Hz, 2H), 3.74 (t, *J* = 7.3 Hz, 2H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.47 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 12.2, 21.2, 26.2, 48.5, 125.3, 127.2, 129.2, 131.5, 133.8, 136.5, 164.1; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{11}H_{14}NS$, 192.0841, found 192.0837.

7-Methoxy-1-(methylthio)-3,4-dihydroisoquinoline (**4c**). Isolated yield 62 mg (75%); colorless oil; R_f 0.40 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.44 (s, 3H), 2.66 (t, *J* = 7.3 Hz, 2H), 3.73 (t, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 6.92 (q, *J* = 3.7 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.21 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 12.4, 25.7, 48.7, 55.5, 110.0, 116.7, 128.2, 129.0, 130, 158.5, 164.0; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{11}H_{13}NOS$, 208.0791, found 208.0795.

7-Fluoro-1-(methylthio)-3,4-dihydroisoquinoline (**4d**). Isolated yield 44 mg (56%); white solid; mp 49−51 °C; R_f 0.50 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.44

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J. Org. Chem. 2017, 82, 1428−1436

(s, 3H), 2.70 (t, J = 7.0 Hz, 2H), 3.75 (t, J = 7.3 Hz, 2H), 7.07 (td, J = 7.9, 2.4 Hz, 1H), 7.16 (t, J = 7.0 Hz, 1H), 7.37 (dd, J = 9.2, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.4, 25.8, 48.4, 111.9 (d, $^2J_{C\text{-}F}$ = 23.3 Hz), 117.6 (d, $^2J_{C\text{-}F}$ = 20.9 Hz), 128.7 (d, $^3J_{C\text{-}F}$ = 7.0 Hz), 130.4 (d, $^3J_{C\text{-}F}$ = 7.0 Hz), 132.4 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 161.5 (d, $^1J_{C\text{-}F}$ = 245.3 Hz), 163.1; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{10}H_{10}FNS$, 196.0591, found 196.0594.

*1-(Methylthio)-7-(trifluoromethyl)-3,4-dihydroisoquinoline **(4e)**.* Isolated yield 50 mg (51%); white solid; mp 46−48 °C; R_f 0.46 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): 2.45 (s, 3H), 2.79 (t, J = 7.0 Hz, 2H), 3.78 (t, J = 7.3 Hz, 2H), 7.32 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.3, 26.5, 47.8, 121.7, 123.8 (d, ^1J = 272.1 Hz), 127.3, 127.9, 129.2 (d, ^2J = 32.7 Hz), 129.5, 140.7, 162.9; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{11}H_{11}F_3NS$, 246.0559, found 246.0557

*6,7-Dimethoxy-1-(methylthio)-3,4-dihydroisoquinoline **(4f)**.*[22b] Isolated yield 82 mg (86%); white solid; mp 92−94 °C; R_f 0.37 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz):[22b] δ 2.43 (s, 3H), 2.65 (t, J = 7.3 Hz, 2H), 3.71 (t, J = 7.0 Hz, 2H), 3.90 (s, 6H), 6.68 (s, 1H), 7.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.3, 26.2, 48.3, 55.9, 56.1, 108.1, 110.0, 122.1, 130.4, 147.5, 151.0, 163.4; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{12}H_{16}NO_2S$, 238.0896, found 238.0894.

*4-(Methylthio)-6,7-dihydrothieno[3,2-c]pyridine **(4g)**.*[27] Isolated yield 44 mg (60%); colorless oil; R_f 0.65 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.44 (s, 3H), 2.86 (t, J = 7.9 Hz, 2H), 3.85 (t, J = 7.9 Hz, 2H), 7.07 (d, J = 5.5 Hz, 1H), 7.15 (d, J = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.8, 22.8, 49.0, 122.2, 123.3, 131.1, 141.9, 160.2; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_8H_9NS_2$, 184.0249, found 184.0252.

*9-Methyl-1-(methylthio)-4,9-dihydro-3H-pyrido[3,4-b]indole **(4h)**.* Isolated yield 78 mg (84%); white solid; mp 55−58 °C; R_f 0.60 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.54 (s, 3H), 2.85 (t, J = 7.6 Hz, 2H), 3.87 (t, J = 7.6 Hz, 2H), 4.04 (s, 3H), 7.14−7.18 (m, 1H), 7.34 (d, J = 3.7 Hz, 2H), 7.61 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.2, 20.0, 32.5, 49.6, 110.2, 117.4, 119.9, 120.0, 124.2, 124.3, 130.0, 138.5, 156.4; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{13}H_{14}N_2S$, 231.0950, found 231.0956.

Procedure for the Synthesis of Compound 5. Under a N_2 atmosphere, a dry Schlenk tube was charged with a mixture of 1-(2-isothiocyanatoethyl)-4-methylbenzene **1r** (71 mg, 0.40 mmol), TfOH (90 mg, 0.60 mmol), and DCE (2.0 mL). The mixture was allowed to stir at 80 °C for 2 h. After completion, the mixture was cooled to room temperature, neutralized with saturated $NaHCO_3$, and extracted with EtOAc (10 mL × 3). The organic layer was washed with saturated NaCl and dried over anhydrous $MgSO_4$. Evaporation of the solvent, followed by purification on silica gel (petroleum ether/ethyl acetate), provided the product **5** as an oily yellow solid.

*7-Methyl-3,4-dihydroisoquinoline-1(2H)-thione **(5)**.*[28] Isolated yield 45 mg (64%); oily yellow solid; R_f 0.40 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.38 (s, 3H), 2.96 (t, J = 6.8 Hz, 2H), 3.50−3.54 (m, 2H), 7.05 (d, J = 7.9 Hz, 1H), 7.24 (s, 1H), 8.33 (s, 1H), 8.43 (br s, 1H).

General Procedure for the Synthesis of Compounds 3r−u (3r for Example). Under a N_2 atmosphere, a dry Schlenk tube was charged with a mixture of **1r** (71 mg, 0.40 mmol), diphenyliodonium salt **2a** (256 mg, 0.60 mmol), CuCl (4 mg, 0.04 mmol), TfOH (0.18 μL, 0.002 mmol), and DCE (2.0 mL). The mixture was allowed to stir at 80 °C for 2 h. After completion, the mixture was cooled to room temperature, quenched with saturated $NaHCO_3$, and extracted with EtOAc (10 mL × 3). The organic layer was washed with saturated NaCl and dried over anhydrous $MgSO_4$. Evaporation of the solvent, followed by purification on silica gel (petroleum ether/ethyl acetate), provided the product **3r** as a colorless oil (76 mg, 75%).

*7-Methyl-1-(phenylthio)-3,4-dihydroisoquinoline **(3r)**.* Isolated yield 76 mg (75%); colorless oil, R_f 0.62 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.37 (s, 3H), 2.62 (t, J = 7.2 Hz, 2H), 3.50 (t, J = 7.3 Hz, 2H), 7.20 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.41 (m, 3H), 7.51 (m, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 21.2, 25.7, 48.4, 115.7, 122.8, 125.0, 125.1, 127.8, 128.1, 128.5, 129.2, 129.4, 129.6, 129.8, 132.3, 132.5, 134.6, 135.7, 136.8, 162.5; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{16}H_{16}NS$, 254.0998, found 254.0997.

*7-Methoxy-1-(phenylthio)-3,4-dihydroisoquinoline **(3s)**.* Isolated yield 83 mg (77%); white solid; mp 75−77 °C; R_f 0.47 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.65 (t, J = 7.3 Hz, 2H), 3.65 (t, J = 7.0 Hz, 2H), 3.84 (s, 3H), 6.94 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 7.34 (s, 1H), 7.39 (q, J = 8.1 Hz, 3H), 7.56 (d, J = 6.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 25.5, 48.9, 55.5, 110.3, 117.0, 128.3, 128.6, 129.0, 129.5, 135.1, 158.4, 163.6. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{16}H_{16}NOS$, 270.0947, found 270.0947.

*7-Fluoro-1-(phenylthio)-3,4-dihydroisoquinoline **(3t)**.* Isolated yield 74 mg (72%); white solid; mp 89−91 °C; R_f 0.58 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.70 (t, J = 7.0 Hz, 2H), 3.68 (t, J = 7.3 Hz, 2H), 7.11 (td, J = 8.3, 2.3 Hz, 1H), 7.20 (t, J = 6.7 Hz, 1H), 7.37−7.45 (m, 3H), 7.53 (dd, J = 9.0, 2.2 Hz, 1H), 7.58 (d, J = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 25.6, 48.7, 112.2 (d, ^2J = 23.3 Hz), 117.8 (d, ^2J = 21.2 Hz), 128.9, 129.1, 130.0, 133.0, 134.7, 135.2, 161.5 (d, ^1J = 242.7 Hz), 162.8. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{15}H_{13}FNS$, 258.0747, found 258.0746.

*6-Methoxy-1-(phenylthio)-3,4-dihydroisoquinoline **(3u)**.* Isolated yield 86 mg (80%); white solid; mp 102−104 °C; R_f 0.53 (petroleum ether/ethyl acetate = 10:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.72 (t, J = 7.3 Hz, 2H), 3.66 (t, J = 7.3 Hz, 2H), 3.86 (s, 3H), 6.74 (s, 1H), 6.82 (dd, J = 8.5, 2.2 Hz, 1H), 7.36−7.42 (m, 3H), 7.58 (d, J = 7.3 Hz, 2H), 7.76 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.9, 48.4, 55.4, 111.8, 111.9, 122.4, 127.0, 128.9, 135.0, 139.7, 161.5, 163.3. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{16}H_{16}NOS$, 270.0947, found 270.0948.

Procedure for the Synthesis of Compound 6. Under a N_2 atmosphere, a dry Schlenk tube was charged with a mixture of 1-(2-isothiocyanatoethyl)-4-methylbenzene **1r** (71 mg, 0.40 mmol), diphenyliodonium salt **2a** (256 mg, 0.60 mmol), CuCl (4 mg, 0.04 mmol), and DCE (2.0 mL). The mixture was allowed to stir at 80 °C for 2 h. After completion, the mixture was cooled to room temperature, quenched with saturated $NaHCO_3$, and extracted with EtOAc (10 mL × 3). The organic layer was washed with saturated NaCl and dried over anhydrous $MgSO_4$. Evaporation of the solvent, followed by purification on silica gel (petroleum ether/ethyl acetate), provided the product **6** as a white solid (62 mg, 68%).

*S-Phenyl 4-Methylphenethylcarbamothioate **(6)**.* Isolated yield 62 mg (68%); White solid; mp 71−73 °C; R_f 0.45 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.33 (s, 3H), 2.74 (s, 2H), 3.49 (d, J = 6.9 Hz, 2H), 5.29 (brs, 1H), 6.98 (d, J = 6.4 Hz, 2H), 7.08 (d, J = 6.8 Hz, 2H), 7.38 (m, 3H), 7.49 (d, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.0, 35.0, 42.5, 128.5, 129.4 129.5, 129.6, 135.1, 135.5, 136.1, 166.1; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{16}H_{17}NOS$, 272.1109, found 272.1112.

Procedure for the Synthesis of Rutaecarpine. A round-bottom flask was charged with a mixture of 2-(1*H*-indol-3-yl)ethan-1-amine **7** (0.80 g, 5.0 mmol), DABCO (4.40 g, 20.0 mmol), and toluene (25 mL). To the stirred mixture was added CS_2 (1.52 g, 20.0 mmol) dropwise, and the mixture was stirred for overnight at room temperature. Then, the dithiocarbamate salt was filtered and washed with toluene. To a round-bottom flask was added the dithiocarbamate salt and $CHCl_3$ (15 mL). The mixture was cooled to 0 °C, and BTC (0.50 g, dissolved in $CHCl_3$) was added dropwise. The mixture was stirred for 1 h at 0 °C and refluxed for 2 h at 80 °C. After completion, the mixture was evaporated under reduced pressure and purified by silica gel column chromatography (petroleum ether/ethyl acetate) to obtain the 3-(2-isothiocyanatoethyl)-1*H*-indole **8**.

*3-(2-Isothiocyanatoethyl)-1H-indole **(8)**.*[29] Isolated yield 858 mg (85%); white solid; mp 45−47 °C (lit. mp 46−47 °C); R_f 0.58 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.16 (t, J = 6.8 Hz, 2H), 3.76 (t, J = 6.7 Hz, 2H), 7.09 (s,

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J. Org. Chem. 2017, 82, 1428−1436

1H), 7.15 (t, J = 7.3 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 8.04 (br s, 1H).

A Schlenk tube was charged with **8** (122 mg, 0.60 mmol), methyltriflate (148 mg, 0.90 mmol), and DCE (3 mL). The mixture was stirred for 2 h at 80 °C under N_2. After completion, the mixture was cooled to room temperature, quenched with saturated $NaHCO_3$, and extracted with EtOAc (10 mL × 3). The organic layer was washed with saturated NaCl and dried over anhydrous $MgSO_4$. Evaporation of the solvent, followed by purification on silica gel (petroleum ether/ethyl acetate), provided the product **9** as a white solid.

*1-(Methylthio)-4,9-dihydro-3H-pyrido[3,4-b]indole (**9**).* Isolated yield 117 mg (90%); white solid; mp 136−138 °C; R_f 0.36 (petroleum ether/ethyl acetate = 4:1 v/v). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.53 (s, 3H), 2.90 (t, J = 8.2 Hz, 2H), 3.95 (t, J = 8.0 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 8.29 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.4, 19.7, 49.8, 112.0, 116.2, 120.1, 120.5, 124.7, 125.5, 128, 136.4, 156.2; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{12}H_{12}N_2S$, 217.0799, found 217.0792.

A round-bottom flask was charged with a mixture of anthranilic acid (69 mg, 0.5 mmol), **9** (108 mg, 0.5 mmol), and acetic acid (5 mL). The mixture was refluxed under stirring for 12 h. After cooling and evaporation of the solvent, the crude product was recrystallized from EtOH to furnish the rutaecarpine as a white solid.

Rutaecarpine.[30] Isolated yield 115 mg (80%); white solid; mp 259−261 °C (lit. 259−260 °C); R_f 0.56 (petroleum ether/ethyl acetate = 2:1 v/v). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.18 (t, J = 6.8 Hz, 2H), 4.45 (t, J = 6.8 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.46−7.50 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.81 (t, J = 7.0 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 11.88 (s, 1H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02605.

^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

X-ray data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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