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SYNTHESIS OF 4-ARYLISOQUINOLINE-1(2*H*)-THIONE DERIVATIVES BY SODIUM HYDRIDE-MEDIATED CYCLIZATIONS OF 2-(1-ARYLETHENYL)BENZOTHIOAMIDES

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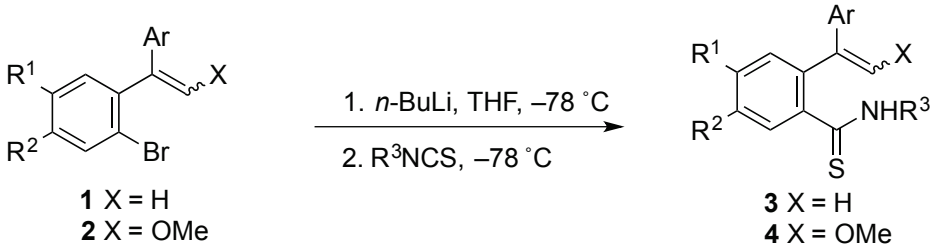
Abstract – A new and facile method for the general preparation of isoquinoline-1(2*H*)-thione derivatives has been developed. Thus, the sodium hydride-mediated cyclization of *N*-substituted 2-(1-arylethenyl)benzothioamides, which are derived from the reaction of 2-(1-arylethenyl)phenyllithiums with isothiocyanates, gives 2-substituted 4-aryl-3,4-dihydroisoquinoline-1(2*H*)-thiones. In addition, the use of *N*-substituted 2-(1-aryl-2-methoxyethenyl)benzothioamides from 2-(1-aryl-2-methoxyethenyl)phenyllithiums and isothiocyanates affording 2-substituted 4-arylisoquinoline-1(2*H*)-thiones is described.

Molecules including isoquinoline-1(2*H*)-thione structure have attracted much interest due to their pharmacological properties,[1] which include activity as protein phosphatase 1 inhibitors[1a] and antiproliferation.[1d] Moreover, some isoquinoline-1(2*H*)-thione derivatives have been utilized in biological investigations.[1c,2] These derivatives have ordinarily been prepared by sulfurization of the respective quinolin-1(2*H*)-one derivatives with phosphorus pentasulfide[3] or Lawesson's reagent.[4] Previously, 3,4-dihydroisoquinoline-1(2*H*)-thione derivatives were prepared by Couture *et al*. along with the corresponding isoquinoline-1(2*H*)-thione derivatives by photochemical reactions of benzothioamides bearing a vinylic substituent on the nitrogen atom.[5] Later, synthesis of 3,4-dihydroisoquinoline-1(2*H*)-thione derivatives by photochemical reactions of benzothioamides bearing an allylic substituent on the nitrogen atom was reported by Aoyama.[6] Recently, a synthesis of isoquinoline-1(2*H*)-thione derivatives by the palladium-nanoparticles-catalyzed oxidative annulation of benzothioamides with

alkynes has been reported by Sharma *et al*.[7] These methods are not, however, adequate for general preparation of isoquinoline-1(2*H*)-thione derivatives. In this paper, we present the results of our investigation focused on the general preparation of these heterocyclic derivatives. We previously reported syntheses of dihydrobenzo[*c*]thiophen-1(3*H*)-imine[8] and 3,4-dihydro-1*H*-2-benzothiopyran-1-imine derivatives[9] by acid or iodine-mediated cyclization reactions of *N*-substituted 2-(1-arylethenyl)benzothioamides (**3**) and (**4**), respectively. It has been found that base-mediated ring closures of these precursors (**3**) and (**4**) gave 2-substituted isoquinoline-1(2*H*)-thione derivatives (**5**) and (**6**), respectively.

Our procedure for constructing isoquinoline-1(2*H*)-thione structure commences with the treatment of 1-(1-arylethenyl)-2-bromobenzenes (**1**) and (**2**) with butyllithium in THF at –78 ˚C followed by addition of alkyl or aryl isothiocyanates affording the corresponding *N*-substituted 2-(1-arylethenyl)benzothioamides (**3**) and (**4**), respectively, as delineated in Scheme 1. The yields of the products are moderate to good as compiled in Tables 1 and 2. Although these transformations were carried out in diethyl ether at 0 ˚C in our previous studies,[8,9] the use of the present conditions allowed somewhat improved results in the yields of the products.

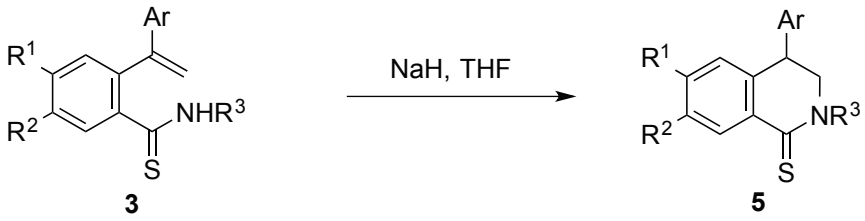


1 X = H
2 X = OMe

3 X = H
4 X = OMe

Scheme 1

When compounds (**3**) were treated with sodium hydride in THF, the desired 2-substituted 4-aryl-3,4-dihydroisoquinoline-1(2*H*)-thiones (**5**) were obtained as shown in Scheme 2. The thioamide structure of the products confirmed by their ^{13}C NMR spectra. They exhibit signals due to the thiocarbonyl carbon at δ 190.5–193.9. The yields of the products are moderate to good, as listed in Table 1 as well. While intramolecular cyclization by the attack of the amide anions generated from *N*-alkyl derivatives (**3a**), (**3b**), (**3f**), and (**3h**) on the β-position of the styrene moiety proceeded well even at room temperature to give the corresponding 2-alkyl derivatives (**5a**), (**5b**), (**5f**), and (**5h**) (Entries 1, 2, 6 and 8, respectively), that of *N*-aryl derivatives (**3c**), (**3d**), (**3e**), (**3g**), (**3i**), and (**3j**), affording the corresponding 2-aryl derivatives (**5c**), (**5d**), (**5e**), (**5g**), (**5i**), and (**5j**), required heating at reflux temperature (Entries 3, 4, 5, 7, 9 and 10, respectively). This difference of the reactivities may be ascribed to the poorer reactivity of *N*-arylamide anions compared to *N*-alkylamide anions.



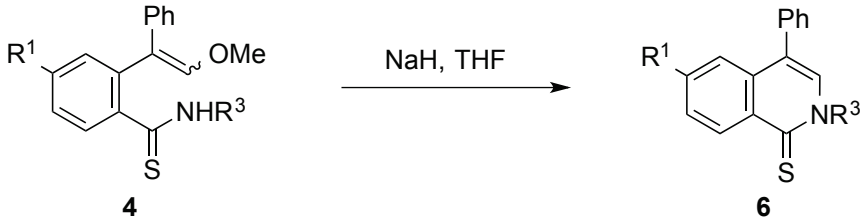
Scheme 2

Table 1. Preparation of 2,4-disubstituted 3,4-dihydroisoquinoline-1(2*H*)-thiones (**5**) *via* **3**

Entry	**1**	R^1	R^2	Ar	R^3 in R^3NCS	**3**	Yield/%[a]	**5**	Temp	Yield/%[a]
1	**1a**	H	H	Ph	Et	**3a**	81	**5a**	rt	71
2	**1a**	H	H	Ph	*c*-Hex	**3b**	81	**5b**	rt	85
3	**1a**	H	H	Ph	Ph	**3c**	82	**5c**	reflux	78
4	**1a**	H	H	Ph	4-ClC_6H_4	**3d**	61	**5d**	reflux	53
5	**1a**	H	H	Ph	4-$MeOC_6H_4$	**3e**	78	**5e**	reflux	74
6	**1b**	H	H	4-ClC_6H_4	*c*-Hex	**3f**	71	**5f**	rt	75
7	**1b**	H	H	4-ClC_6H_4	Ph	**3g**	85	**5g**	reflux	60
8	**1c**	H	H	4-$MeOC_6H_4$	Et	**3h**	82	**5h**	rt	47
9	**1d**	Cl	H	Ph	Ph	**3i**	73	**5i**	reflux	53
10	**1e**	OMe	OMe	Ph	Ph	**3j**	50	**5j**	reflux	58

[a] Yields of isolated products.

Subsequently, the possibility of introduction of an alkyl group at the 4-position of the products was investigated. To the reaction mixtures after treating **3** with sodium hydride were added alkyl halides, such as methyl iodide and allyl bromide. Unfortunately, however, no more than trace amounts of 4-alkylated products were formed. It is thought that the benzyl anion intermediates resulting from the addition of the amide anions to the β-position of the styrene moiety were protonated quickly with contaminated water (or maybe 2-H of THF) before addition of alkyl halides.



Scheme 3

Similar treatment of *N*-substituted 2-(2-methoxy-1-phenylethenyl)benzothioamides (**4**) with sodium hydride as described for the preparation of **5** from **3** gave the corresponding 2-substituted 4-phenylisoquinoline-1(2*H*)-thiones (**6**), as depicted in Scheme 3. The results are summarized in Table 2. The thioamide structure of the products was also confirmed by their ^{13}C NMR spectra. They exhibit

signals due to the thiocarbonyl carbon at δ 182.7–185.0. It seems that elimination of methoxide from the benzyl anion intermediates, generated by the addition of the amide anions to the β-position of the styrene moiety, immediately occurred to provide **6**.

Table 2. Preparation of 2,4-disubstituted isoquinoline-1(2*H*)-thiones (**6**) *via* **4**

Entry	**2**	R^1	R^2	Ar	R^3 in R^3NCS	**4**	Yield/%[a]	Temp	**6**	Yield/%[a]
1	**2a**	H	H	Ph	*c*-Hex	**4a**	56	rt	**6a**	90
2	**2a**	H	H	Ph	Ph	**4b**	74	reflux	**6b**	86
3	**2a**	H	H	Ph	*m*-Tol	**4c**	80	reflux	**6c**	90
4	**2a**	H	H	Ph	4-BrC_6H_4	**4d**	59	reflux	**6d**	89
5	**2a**	H	H	Ph	2-$MeOC_6H_4$	**4e**	54	reflux	**6e**	80
6	**2b**	OMe	H	Ph	*m*-Tol	**4f**	65	reflux	**6f**	70

[a] Yields of isolated products.

The foregoing results have indicated that sodium hydride-mediated cyclizations of *N*-substituted 2-(1-arylethenyl)benzothioamides and *N*-substituted 2-(1-aryl-2-methoxyethenyl)benzothioamides, which are easily accessible by the reactions of 2-(1-arylethenyl)phenyllithiums[10] and 2-(1-aryl-2-methoxyethenyl)phenyllithiums with isothiocyanates, provides reliable routes to 3,4-dihydroisoquinoline-1(2*H*)-thione and isoquinoline-1(2*H*)-thione derivatives, respectively. The procedures described here should be of use in synthesizing these classes of heterocycles because of the ready availability of the starting materials and the simplicity of the experimental operations.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a PerkinElmer Spectrum 65 FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a Thermo Scientific Exactive spectrometer (DART or ESI, positive). Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 1-(1-Arylethenyl)-2-bromobenzenes (**1a**),[11] (**1b**),[8a] (**1c**),[12] (**1d**),[10a] (**1e**),[13] and 1-bromo-2-(2-methoxy-1-phenylethenyl)benzenes (**2**)[14] were prepared according to the appropriate reported procedures. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of *N*-Substituted 2-(1-Arylethenyl)benzothioamides (3) and (4). *N*-Ethyl-2-(1-phenylethenyl)benzothioamide (3a).[8a] To a stirred solution of **1a** (0.30 g, 1.2 mmol)

in THF (4 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 1.2 mmol) dropwise. After 5 min, EtNCS (0.10 g, 1.2 mmol) was added dropwise and stirring was continued for an additional 20 min. Water (20 mL) was added and the mixture was extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 (Et_2O/hexane 1:15) to afford **3a** (0.26 g, 81%); a yellow solid; mp 68–69 ˚C (hexane) (lit.,[8a] 69–70 ˚C). The spectral (IR and ^{1}H NMR) data for this compound were identical to those reported previously.[8a]

***N*-Cyclohexyl-2-(1-phenylethenyl)benzothioamide (3b):**[8a] a yellow solid; mp 120–121 ˚C (hexane/CH_2Cl_2) (lit.,[8a] 117–120 ˚C). The spectral (IR and ^{1}H NMR) data for this compound were identical to those reported previously.[8a]

***N*-Phenyl-2-(1-phenylethenyl)benzothioamide (3c):**[8a] a yellow solid; mp 157–159 ˚C (hexane/CH_2Cl_2) (lit.,[8a] 154–159 ˚C). The spectral (IR, ^{1}H and ^{13}C NMR) data for this compound were identical to those reported previously.[8a]

***N*-(4-Chlorophenyl)-2-(1-phenylethenyl)benzothioamide (3d):** a yellow solid; mp 102–104 ˚C (hexane/CH_2Cl_2); IR (KBr) 3243, 1592, 1489, 1357 cm^{-1}; ^{1}H NMR δ 5.47 (s, 1H), 5.79 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.21–7.29 (m, 7H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.87 (d, *J* = 7.4 Hz, 1H), 8.67 (br s, 1H); ^{13}C NMR δ 116.2, 124.1, 126.8, 128.4, 128.45, 128.51, 128.8, 130.4, 130.5, 131.0, 131.7, 136.9, 137.1, 139.0, 142.6, 148.9, 198.7. HR-MS (DART). Calcd for $C_{21}H_{17}ClNS$ (M+H): 350.0770. Found: *m/z* 350.0759.

***N*-(4-Methoxyphenyl)-2-(1-phenylethenyl)benzothioamide (3e):** a yellow solid; mp 116–118 ˚C (hexane/CH_2Cl_2); IR (KBr) 3231, 1599, 1508, 1373 cm^{-1}; ^{1}H NMR δ 3.77 (s, 3H), 5.47 (s, 1H), 5.80 (s, 1H), 6.79 (d, *J* = 9.2 Hz, 2H), 7.09 (d, *J* = 9.2 Hz, 2H), 7.25–7.30 (m, 5H), 7.36 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.43 (td, *J* = 7.4, 1.7 Hz, 1H), 7.47 (td, *J* = 7.4, 1.7 Hz, 1H), 7.89 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.64 (br s, 1H); ^{13}C NMR δ 55.4, 113.8, 114.1, 116.1, 124.9, 126.9, 128.3, 128.5, 130.1, 130.4, 131.0, 131.7, 136.9, 139.2, 142.7, 148.8, 158.0, 198.3. HR-MS (DART). Calcd for $C_{22}H_{20}NOS$ (M+H): 346.1265. Found: *m/z* 346.1255.

2-[1-(4-Chlorophenyl)ethenyl]-*N*-cyclohexylbenzothioamide (3f):[8a] a yellow solid; mp 98–100 ˚C (hexane/CH_2Cl_2) (lit.,[8a] 98–100 ˚C). The spectral (IR, ^{1}H NMR) data for this compound were identical to those reported previously.[8a]

2-[1-(4-Chlorophenyl)ethenyl]-*N*-phenylbenzothioamide (3g):[8a] a yellow solid; mp 129–131 ˚C (hexane/CH_2Cl_2) (lit.,[8a] 128–130 ˚C). The spectral (IR, ^{1}H NMR) data for this compound were identical to those reported previously.[8a]

***N*-Ethyl-2-[1-(4-methoxyphenyl)ethenyl]benzothioamide (3h):** a yellow oil; R_f 0.26 (Et_2O/hexane 1:3); IR (neat) 3378, 1607, 1538, 1180 cm^{-1}; ^{1}H NMR δ 1.03 (t, *J* = 7.4 Hz, 3H), 3.39–3.44 (m, 2H), 3.78 (s,

3H), 5.29 (br s, 1H), 5.30 (s, 1H), 5.69 (s, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.28 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.38 (td, *J* = 7.4, 1.7 Hz, 1H), 7.41 (td, *J* = 7.4, 1.7 Hz, 1H), 7.81 (d, *J* = 7.4, 1.7 Hz, 1H); ^{13}C NMR δ 12.5, 41.4, 55.2, 113.7, 114.0, 127.9, 128.1, 129.7, 130.1, 130.7, 131.9, 137.2, 141.7, 148.0, 159.6, 199.2. HR-MS (DART). Calcd for $C_{18}H_{20}NOS$ (M+H): 298.1265. Found: *m*/*z* 298.1259.

4-Chloro-*N*-phenyl-2-(1-phenylethenyl)benzothioamide (3i): a yellow solid; mp 130–132 °C (hexane/CH_2Cl_2); IR (KBr) 3270, 1584, 1523, 1157 cm^{-1}; ^{1}H NMR δ 5.49 (s, 1H), 5.82 (s, 1H), 7.20–7.30 (m, 10H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.42 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 8.67 (br s, 1H); ^{13}C NMR δ 116.8, 122.9, 126.8, 126.9, 128.4, 128.58, 128.61, 128.7, 130.6 (2 overlapped Cs), 132.0, 136.0, 138.40, 138.44, 141.2, 147.8, 197.0. HR-MS (DART). Calcd for $C_{21}H_{17}ClNS$ (M+H): 350.0770. Found: *m*/*z* 350.0762.

4,5-Dimethoxy-2-(1-phenylethenyl)-*N*-phenylbenzothioamide (3j): a yellow solid; mp 164 °C (decomp) (hexane/CH_2Cl_2); IR (KBr) 3298, 1594, 1505, 1117 cm^{-1}; ^{1}H NMR δ 3.94 (s, 3H), 3.98 (s, 3H), 5.48 (s, 1H), 5.81 (s, 1H), 6.81 (s, 1H), 7.17–7.27 (m, 10H), 7.56 (s, 1H), 8.81 (br s, 1H); ^{13}C NMR δ 56.1, 56.2, 113.3, 114.0, 115.7, 123.0, 126.7 (2 overlapped Cs), 128.45, 128.52, 128.6, 129.7, 135.3, 138.8, 139.0, 148.6, 148.9, 150.4, 197.8. HR-MS (DART). Calcd for $C_{23}H_{22}NO_2S$ (M+H): 376.1371. Found: *m*/*z* 376.1358.

2-(2-Methoxy-1-phenylethenyl)benzothioamides (4). For physical and spectral data for these compounds, see ref. 9.

General Procedure for the Preparation of 2,4-Disubstituted 3,4-Dihydroisoquinoline-1(2*H*)-thiones (5). To a stirred suspension of NaH (60% in mineral oil; 40 mg, 1.0 mmol) in THF (6 mL) at 0 °C was added a solution of **3** (1.0 mmol) in THF (2 mL) dropwise. After evolution of H_2 gas has ceased, stirring was continued at the temperature indicated in Table 1 until the spot of the starting material disappeared by TLC analyses (AcOEt/hexane 1:10). Saturated aqueous NH_4Cl and H_2O (20 mL each) were added to the cooled reaction mixture and the resulting mixture was extracted with AcOEt (3 × 15 mL). The combined extracts were washed with H_2O (3 × 15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by recrystallization or column chromatography on SiO_2 to afford **5**.

2-Ethyl-4-phenyl-3,4-dihydroisoquinoline-1(2*H*)-thione (5a): a yellow solid; mp 92–94 °C (hexane/CH_2Cl_2); IR (KBr) 1506, 1353 cm^{-1}; ^{1}H NMR δ 0.94 (t, *J* = 6.9 Hz, 3H), 3.71 (dd, *J* = 12.6, 5.7 Hz, 1H), 3.80–3.88 (m, 2H), 4.17 (t, *J* = 5.7 Hz, 1H), 4.23–4.30 (m, 1H), 6.87 (dd, *J* = 6.9, 2.3 Hz, 1H), 7.00 (d, *J* = 7.4 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.27–7.30 (m, 2H), 8.61 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 10.4, 43.4, 50.7, 55.2, 126.7, 127.3, 127.4, 128.2, 128.8, 131.6, 132.5, 134.3, 135.1, 139.8, 190.6. HR-MS (DART). Calcd for $C_{17}H_{18}NS$ (M+H): 268.1160. Found: *m*/*z* 268.1153. Anal. Calcd for $C_{17}H_{17}NS$: C, 76.36; H, 6.41; N, 5.24; S, 11.99. Found: C, 76.36; H, 6.19; N, 5.17; S, 12.15.

2-Cyclohexyl-4-phenyl-3,4-dihydroisoquinoline-1(2*H*)-thione (5b): a yellow solid; mp 156–158 °C (hexane); IR (KBr) 1480, 1357 cm^{-1}; ^1H NMR δ 0.85–0.93 (m, 1H), 0.99–1.07 (m, 1H), 1.25–1.49 (m, 2H), 1.62–1.66 (m, 4H), 1.79–1.83 (m, 1H), 1.88–1.92 (m, 1H), 3.72 (dd, *J* = 13.2, 6.3 Hz, 1H), 3.75 (dd, *J* = 13.2, 4.6 Hz, 1H), 4.18 (dd, *J* = 6.3, 4.6 Hz, 1H), 5.65–5.71 (m, 1H), 6.94 (dd, *J* = 7.4, 2.3 Hz, 1H), 7.06 (dd, *J* = 8.6, 1.7 Hz, 2H), 7.26–7.44 (m, 5H), 8.68 (dd, *J* = 7.4, 2.3 Hz, 1H); ^{13}C NMR δ 25.2, 25.40, 25.43, 28.1, 29.2, 43.5, 49.6, 60.3, 126.5, 127.3, 127.4, 128.3, 128.7, 131.5, 133.1, 135.1, 135.2, 139.6, 190.7. HR-MS (DART). Calcd for $C_{21}H_{24}NS$ (M+H): 322.1629. Found: *m/z* 322.1613. Anal. Calcd for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.40; H, 7.19; N, 4.26.

2,4-Diphenyl-3,4-dihydroisoquinoline-1(2*H*)-thione (5c): a yellow amorphous powder; R_f 0.29 (AcOEt/hexane 1:10); IR (KBr) 1477, 1331 cm^{-1}; ^1H NMR δ 4.06 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.31 (dd, *J* = 13.2, 4.7 Hz, 1H), 4.40 (dd, *J* = 5.2, 4.7 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 6.9 Hz, 2H), 7.27–7.37 (m, 7H), 7.42 (td, *J* = 7.4, 1.1 Hz, 1H), 7.47 (td, *J* = 7.4, 1.1 Hz, 1H), 8.73 (dd, *J* = 7.4, 1.1 Hz, 1H); ^{13}C NMR δ 43.9, 59.2, 126.2, 127.1, 127.5, 127.6, 127.7, 128.2, 128.9, 129.6, 132.2, 132.8, 134.5, 135.1, 139.9, 147.3, 193.5. HR-MS (DART). Calcd for $C_{21}H_{18}NS$ (M+H): 316.1160. Found: *m/z* 316.1155.

2-(4-Chlorophenyl)-4-phenyl-3,4-dihydroisoquinoline-1(2*H*)-thione (5d): a yellow amorphous powder; R_f 0.27 (CH_2Cl_2/hexane 1:2); IR (KBr) 1488, 1317 cm^{-1}; ^1H NMR δ 4.02 (dd, *J* = 12.6, 4.7 Hz, 1H), 4.31 (dd, *J* = 12.6, 4.0 Hz, 1H), 4.40 (dd, *J* = 4.7, 4.0 Hz, 1H), 6.83 (d, *J* = 6.8 Hz, 2H), 7.09–7.13 (m, 3H), 7.30–7.38 (m, 5H), 7.42 (td, *J* = 7.4, 1.1 Hz, 1H), 7.48 (td, *J* = 7.4, 1.7 Hz, 1H), 8.70 (dd, *J* = 7.4, 1.7 Hz, 1H); ^{13}C NMR δ 43.9, 59.3, 127.2, 127.6, 127.71, 127.72, 128.1, 128.9, 129.8, 132.4, 132.8, 133.4, 134.4, 135.0, 139.7, 145.7, 193.9. HR-MS (DART). Calcd for $C_{21}H_{17}ClNS$ (M+H): 350.0770. Found: *m/z* 350.0758.

2-(4-Methoxyphenyl)-4-phenyl-3,4-dihydroisoquinoline-1(2*H*)-thione (5e): a yellowish orange solid; mp 179–181 °C (hexane/CH_2Cl_2); IR (KBr) 1609, 1508, 1319 cm^{-1}; ^1H NMR δ 3.77 (s, 3H), 4.05 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.30 (dd, *J* = 13.2, 4.6 Hz, 1H), 4.38 (dd, *J* = 5.2, 4.6 Hz, 1H), 6.85 (br s, 4H), 7.08 (d, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 6.9 Hz, 2H), 7.28–7.36 (m, 3H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 8.73 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 43.9, 55.3, 59.5, 114.7, 127.1 (2 overlapped Cs), 127.5, 127.6, 128.2, 128.9, 132.1, 132.9, 134.6, 135.1, 139.9, 140.3, 158.6, 193.7. HR-MS (DART). Calcd for $C_{22}H_{20}NOS$ (M+H): 346.1265. Found: *m/z* 346.1254. Anal. Calcd for $C_{22}H_{19}NOS$: C, 76.49; H, 5.54; N, 4.05; S, 9.28. Found: C, 76.34; H, 5.32; N, 3.99; S, 9.15.

4-(4-Chlorophenyl)-2-cyclohexyl-3,4-dihydroisoquinoline-1(2*H*)-thione (5f): a yellow solid; 164–165 °C (MeOH); IR (KBr) 1483, 1316 cm^{-1}; ^1H NMR δ 0.83–0.91 (m, 1H), 1.01–1.06 (m, 1H), 1.24–1.49 (m, 4H), 1.65–1.69 (m, 2H), 1.80–1.90 (m, 2H), 3.70 (dd, *J* = 13.2, 5.7 Hz, 1H), 3.74 (dd, *J* = 13.2, 4.6 Hz,

1H), 4.17 (dd, *J* = 5.7, 4.6 Hz, 1H), 5.64–5.71 (m, 1H); 6.94 (dd, *J* = 8.6, 3.4 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.36–7.40 (m, 2H), 8.67 (dd, *J* = 9.2, 3.4 Hz, 1H); ^{13}C NMR δ 25.1, 25.4 (2 overlapped Cs), 28.2, 29.2, 42.9, 49.4, 60.2, 126.4, 127.6, 128.9, 129.6, 131.7, 133.2, 133.3, 134.5, 135.0, 138.2, 190.7. HR-MS (DART). Calcd for $C_{21}H_{23}ClNS$ (M+H): 356.1239. Found: *m/z* 356.1230. Anal. Calcd for $C_{21}H_{22}ClNS$: C, 70.87; H, 6.23; N, 3.94. Found: C, 70.53; H, 6.28; N, 3.88.

4-(4-Chlorophenyl)-2-phenyl-3,4-dihydroisoquinoline-1(2*H*)-thione (5g): a yellow solid; mp 72–74 °C (hexane/CH_2Cl_2); IR (KBr) 1495, 1335 cm^{-1}; ^{1}H NMR δ 4.03 (dd, *J* = 13.2, 4.6 Hz, 1H), 4.32 (dd, *J* = 13.2, 4.6 Hz, 1H), 4.37 (t, *J* = 4.6 Hz, 1H), 6.95 (d, *J* = 6.9 Hz, 1H), 7.06–7.12 (m, 3H), 7.29–7.34 (m, 4H), 7.38 (dd, *J* = 8.0, 7.4 Hz, 2H), 7.44 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H), 7.46 (td, *J* = 7.4, 1.7 Hz, 1H), 8.73 (dd, *J* = 7.4, 1.7 Hz, 1H); ^{13}C NMR δ 43.4, 59.0, 126.1 (2 overlapped Cs), 127.0, 127.9, 129.1, 129.5, 129.7, 132.3, 133.0, 133.4, 134.4, 134.5, 138.5, 147.2, 193.5. HR-MS (DART). Calcd for $C_{21}H_{17}ClNS$ (M+H): 350.0770. Found: *m/z* 350.0760. Anal. Calcd for $C_{21}H_{16}ClNS$: C, 72.09; H, 4.61; N, 4.00. Found: C, 71.86; H, 4.71; N, 3.93.

2-Ethyl-4-(4-methoxyphenyl)-3,4-dihydroisoquinoline-1(2*H*)-thione (5h): a yellow solid; mp 115–116 °C (hexane/CH_2Cl_2); IR (KBr) 1611, 1501, 1351 cm^{-1}; ^{1}H NMR δ 1.04 (t, *J* = 7.4 Hz, 3H), 3.73–3.79 (m including s at 3.78, 4H), 3.90 (dd, *J* = 13.2, 5.1 Hz, 1H), 3.92 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.21 (t, *J* = 5.1 Hz, 1H), 4.32–4.39 (m, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.35–7.38 (m, 2H), 8.67 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 10.5, 42.6, 50.7, 55.2, 55.3, 114.1, 126.6, 127.3, 129.2, 131.6, 131.7, 132.5, 134.2, 135.4, 158.8, 190.5. HR-MS (DART). Calcd for $C_{18}H_{20}NOS$ (M+H): 298.1265. Found: *m/z* 298.1260. Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71; S, 10.78. Found: C, 72.68; H, 6.51; N, 4.70; S, 10.86.

6-Chloro-2,4-diphenyl-3,4-dihydroisoquinoline-1(2*H*)-thione (5i): a yellow solid; mp 182–184 °C (hexane/CH_2Cl_2); IR (KBr) 1492, 1272 cm^{-1}; ^{1}H NMR δ 4.06 (dd, *J* = 12.6, 5.2 Hz, 1H), 4.29 (dd, *J* = 12.6, 4.6 Hz, 1H), 4.37 (dd, *J* = 5.2, 4.6 Hz, 1H), 6.94 (br s, 2H), 7.06 (s, 1H), 7.14 (d, *J* = 6.9 Hz, 2H), 7.28–7.39 (m, 7H), 8.68 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR δ 43.8, 59.0, 126.0, 126.9, 127.81, 127.84, 127.9, 128.1, 129.0, 129.6, 132.9, 134.5, 136.7, 138.6, 139.0, 147.0, 192.3. HR-MS (DART). Calcd for $C_{21}H_{17}ClNS$ (M+H): 350.0770. Found: *m/z* 350.0764. Anal. Calcd for $C_{21}H_{16}ClNS$: C, 72.09; H, 4.61; N, 4.00. Found: C, 71.82; H, 4.55; N, 3.96.

6,7-Dimethoxy-2,4-diphenyl-3,4-dihydroisoquinoline-1(2*H*)-thione (5j): a yellow solid; mp 187–189 °C (hexane/CH_2Cl_2); IR (KBr) 1516, 1294 cm^{-1}; ^{1}H NMR δ 3.85 (s, 3H), 4.00 (dd, *J* = 12.6, 4.6 Hz, 1H), 4.01 (s, 3H), 4.29 (t, *J* = 4.6 Hz, 1H), 4.33 (dd, *J* = 12.6, 4.6 Hz, 1H), 6.53 (s, 1H), 6.92 (br s, 2H), 7.15 (d, *J* = 6.9 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.31–7.37 (m, 5H), 8.32 (s, 1H); ^{13}C NMR δ 43.7, 56.1, 56.2, 59.4, 109.0, 115.2, 126.3, 127.5, 127.6, 127.8, 128.1, 128.8, 128.9, 129.5, 140.2, 147.5, 148.1, 152.6,

192.8. HR-MS (ESI). Calcd for $C_{23}H_{22}NO_2S$ (M+H): 376.1371. Found: *m/z* 376.1353. Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N, 3.73; S, 8.54. Found: C, 73.38; H, 5.58; N, 3.68; S, 8.15.

General Procedure for the Preparation of 2,4-Disubstituted isoquinoline-1(2*H*)-thiones (6). To a stirred suspension of NaH (60% in mineral oil; 40 mg, 1.0 mmol) in THF (6 mL) at 0 ˚C was added a solution of **4** (1.0 mmol) in THF (2 mL) dropwise. After evolution of H_2 gas has ceased, stirring was continued at the temperature indicated in Table 2 until disappearance of the spot of the starting material by TLC analyses (AcOEt/hexane 1:5) had been confirmed. The resulting mixture was worked up as described for the preparation of **3** and the crude product was purified by recrystallization or column chromatography on SiO_2 to afford **6**.

2-Cyclohexyl-4-phenylisoquinoline-1(2*H*)-thione (6a): a yellow solid; mp 178–180 ˚C (hexane); IR (KBr) 1622, 1484, 1293 cm^{-1}; ^1H NMR δ 1.21–1.26 (m, 1H), 1.55–1.66 (m, 5H), 1.78–1.82 (m, 1H), 1.90–1.94 (m, 2H), 2.15–2.18 (m, 2H), 6.35 (br s, 1H), 7.40–7.45 (m, 3H), 7.47–7.57 (m, 2H), 7.56–7.62 (m, 3H), 9.31 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 25.5, 25.8, 32.1, 62.1, 124.9, 125.6, 128.2 (2 overlapped Cs), 128.8, 129.9 (2 overlapped Cs), 131.4, 132.1, 133.88 133.92, 136.1, 182.7. HR-MS (DART). Calcd for $C_{21}H_{22}NS$ (M+H): 320.1473. Found: *m/z* 320.1458. Anal. Calcd for $C_{21}H_{21}NS$: C, 78.95; H, 6.63; N, 4.38; S, 10.04. Found: C, 78.65; H, 6.55; N, 4.29; S, 9.72.

2,4-Diphenylisoquinoline-1(2*H*)-thione (6b): a yellow solid; mp 163–164 ˚C (hexane/CH_2Cl_2); IR (KBr) 1618, 1479, 1323 cm^{-1}; ^1H NMR δ 7.40–7.49 (m, 9H), 7.54 (t, *J* = 7.4 Hz, 2H), 7.60–7.66 (m, 1H), 7.68 (d, *J* = 7.4 Hz, 2H), 9.26 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR δ 124.8, 125.3, 127.0, 128.2, 128.67, 128.72, 128.8, 129.6, 129.8, 132.0, 132.5, 132.6, 133.1, 134.2, 135.2, 146.3, 185.0. HR-MS (DART). Calcd for $C_{21}H_{16}NS$ (M+H): 314.1003. Found: *m/z* 314.0990. Anal. Calcd for $C_{21}H_{15}NS$: C, 80.48; H, 4.82; N, 4.47; S, 10.23. Found: C, 80.44; H, 4.77; N, 4.44; S, 10.37.

2-(3-Methylphenyl)-4-phenylisoquinoline-1(2*H*)-thione (6c): a yellow amorphous powder; R_f 0.31 (AcOEt/hexane 1:15); IR (KBr) 1606, 1479, 1319 cm^{-1}; ^1H NMR δ 2.42 (s, 3H), 7.22 (s, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.40 (s, 1H), 7.41–7.49 (m, 6H), 7.61–7.69 (m, 3H), 9.26 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 21.4, 124.0, 124.8, 125.3, 127.4, 128.2, 128.6, 128.7, 129.4, 129.5, 129.8, 132.0, 132.6 (2 overlapped Cs), 133.1, 134.2, 135.3, 139.8, 146.2, 184.8. HR-MS (DART). Calcd for $C_{22}H_{18}NS$ (M+H): 328.1160. Found: *m/z* 316.1153.

2-(4-Bromophenyl)-4-phenylisoquinoline-1(2*H*)-thione (6d): a yellow solid; mp 178–180 ˚C (hexane/CH_2Cl_2); IR (KBr) 1626, 1497, 1324 cm^{-1}; ^1H NMR δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.35 (s, 1H), 7.44–7.50 (m, 5H), 7.62–7.69 (m, 5H), 9.22 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR δ 122.8, 125.2, 125.4, 128.3, 128.79, 128.83, 128.9, 129.8, 131.97, 132.03, 132.88, 132.93, 133.1, 134.1, 135.1, 145.1, 185.0. HR-MS (DART). Calcd for $C_{21}H_{15}BrNS$ (M+H): 392.0108. Found: *m/z* 392.0092. Anal. Calcd for $C_{21}H_{14}BrNS$: C, 64.29; H, 3.60; N, 3.57; S, 8.17. Found: C, 64.12; H, 3.61; N, 3.52; S, 8.33.

2-(2-Methoxyphenyl)-4-phenylisoquinoline-1(2*H*)-thione (6e): a yellow solid; mp 157–159 ˚C (hexane/CH_2Cl_2); IR (KBr) 1600, 1484, 1319 cm^{-1}; ^1H NMR δ 3.82 (s, 3H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.33 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.43–7.46 (m, 6H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.65–7.70 (m, 2H), 9.26 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR δ 55.9, 112.7, 121.2, 124.7, 125.2, 128.1, 128.27, 128.30, 128.7, 129.9, 130.3, 132.1, 132.5, 133.0, 133.1, 134.2, 134.7, 135.5, 153.8, 184.9. HR-MS (DART). Calcd for $C_{22}H_{18}NOS$ (M+H): 344.1109. Found: *m/z* 344.1105. Anal. Calcd for $C_{22}H_{17}NOS$: C, 76.94; H, 4.99; N, 4.08; S, 9.33. Found: C, 76.58; H, 5.01; N, 3.99; S, 9.20.

6-Methoxy-2-(3-methylphenyl)-4-phenylisoquinoline-1(2*H*)-thione (6f): a yellow solid; mp 196–199 ˚C (hexane/CH_2Cl_2); IR (KBr) 1608, 1496, 1328 cm^{-1}; ^1H NMR δ 2.42 (s, 3H), 3.82 (s, 3H), 7.01 (d, *J* = 2.3 Hz, 1H), 7.19–7.27 (m, 4H), 7.37 (s, 1H), 7.40–7.49 (m, 6H), 9.20 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR δ 21.4, 55.5, 105.9, 118.1, 124.1, 124.2, 127.5, 128.2, 128.8, 128.9, 129.3, 129.5, 129.7, 133.2, 134.2, 135.5, 135.6, 139.7, 146.2, 163.3, 183.6. HR-MS (ESI). Calcd for $C_{23}H_{20}NOS$ (M+H): 358.1265. Found: *m/z* 358.1255. Anal. Calcd for $C_{23}H_{19}NOS$: C, 77.28; H, 5.36; N, 3.92. Found: C, 77.06; H, 5.35; N, 3.95.

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REFERENCES AND NOTES

1. (a) A. Popov, A. Juhem, J.-C. Florent, and C.-H. Nguyen, *PCT Int. Appl.*, 2011, WO 2011107709 (*Chem. Abstr.*, 2011, **155**, 431696); (b) R. Narayanan, J. T. Dalton, and E. Levin, *U.S. Pat. Appl. Publ.*, 2013, US 20130150403 (*Chem. Abstr.*, 2013, **159**, 105334); (c) T. Lavergne, R. Lamichhane, D. A. Malyshev, Z. Li, L. Li, E. Sperling, J. R. Williamson, D. P. Millar, and F. E. Romesberg, *ACS Chem. Biol.*, 2016, **11**, 1347; (d) B. Clement, U. Girreser, T. N. Steinhauer, C. Meier, D. Marko, G. Aichinger, I. Kaltefleiter, L. Stenzel, D. Heber, M. Weide, U. Wolschendorf, I. Zebothsen, and D. Zur Nieden, *ChemMedChem*, 2016, **11**, 2155; (e) J. T. Dalton, R. Narayanam, and M. Yepuru, *U.S. Pat. Appl. Publ.*, 2017, US 20170014401 (*Chem. Abstr.*, 2017, **166**, 174990); (f) S. Arimori, *PCT Int. Appl.*, 2017, WO 2017110863 (*Chem. Abstr.*, 2017, **167**, 100881).
2. Z. Li, T. Lavergne, D. A. Malyshev, J. Zimmermann, R. Adhikary, K. Dhami, P. Ordoukhanian, Z. Sun, J. Xing, and F. E. Romemsberg, *Chem. Eur. J.*, 2013, **19**, 14205.
3. R. Fujita, N. Watanabe, and H. Tomisawa, *Heterocycles*, 2001, **55**, 435.
4. A. G. Waterson, J. P. Kennedy, J. D. Patrone, N. F. Pelz, M. D. Feldkamp, A. O. Frank, B. Vagamudi, E. M. Souza-Fagundes, O. W. Rossanese, W. J. Chazin, and S. W. Fesik, *ACS Med. Chem. Lett.*, 2015, **6**, 140.

5. A. Couture, R. Dubies, and A. Lablache-Combier, *Tetrahedron*, 1984, **40**, 1835.
6. H. Aoyama, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1851.
7. N. Sharma, R. Saha, N. Parveen, and G. Sekar, *Adv. Synth. Catal.*, 2017, **359**, 1947.
8. (a) K. Kobayashi, S. Fujita, M. Hase, O. Morikawa, and H. Konishi, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 763; (b) K. Kobayashi, S. Fujita, and H. Konishi, *Heterocycles*, 2008, **75**, 2555.
9. K. Kobayashi, D. Nakai, K. Hayashi, and H. Konishi, *Heterocycles*, 2008, **75**, 3025.
10. Our recent reports on the utilization of 2-(1-arylethenyl)phenyllithiums in heterocycle synthesis: (a) K. Kobayashi, T. Ueyama, and M. Horiuchi, *Heterocycles*, 2017, **94**, 2065; (b) K. Kobayashi and T. Ueyama, *Heterocycles*, 2018, **96**, 1570.
11. M. E. Jason, *Tetrahedron Lett.*, 1982, **23**, 1635.
12. K. Kobayashi, T. Kozuki, S. Fukamachi, and H. Konishi, *Heterocycles*, 2010, **81**, 163.
13. S. Fukamachi, M. Tanmatsu, H. Konishi, and K. Kobayashi, *Heterocycles*, 2009, **78**, 2077.
14. K. Kobayashi, K. Hayashi, K. Miyamoto, O. Morikawa, and H. Konishi, *Synthesis*, 2006, 2934.