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SYNTHESIS OF 3-BROMOQUINOLINE-2(1*H*)-THIONES AND 2-(ALKYLSULFANYL)-3-BROMOQUINOLINES BASED ON THE REACTION OF 2-(2,2-DIBROMOETHENYL)PHENYL ISOTHIOCYANATES WITH BUTYLLITHIUM

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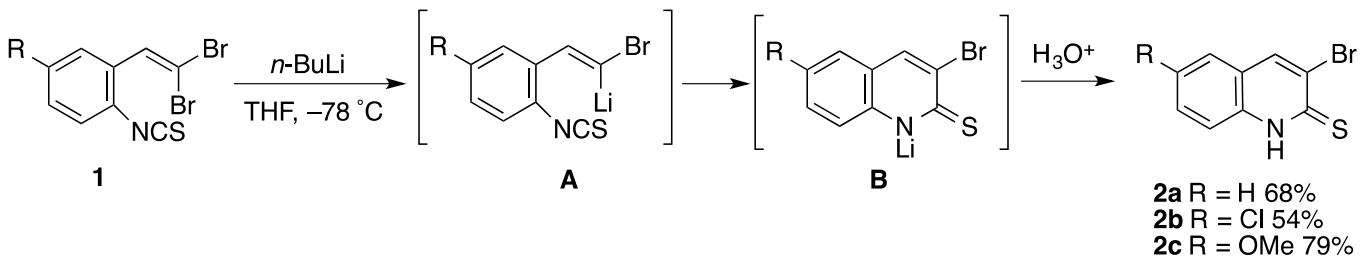
Abstract – The synthesis of 3-bromoquinoline-2(1*H*)-thiones and 2-(alkylsulfanyl)-3-bromoquinolines from readily available starting materials was accomplished. Thus, 2-(2,2-dibromoethenyl)phenyl isothiocyanates were treated with butyllithium to afford, after aqueous workup, 3-bromoquinoline-2(1*H*)-thiones. When haloalkanes were added prior to workup, 2-(alkylsulfanyl)-3-bromoquinolines were obtained. An elaboration of one of these compounds to a thieno[2,3-*b*]quinoline derivative and one-pot preparation of 3-substituted quinoline-2(1*H*)-thiones were also achieved.

INTRODUCTION

3-Bromoquinoline-2(1*H*)-thiones and related derivatives have been of interest due to their use as the precursors for the preparation of biologically important compounds[1] and fluorescent sensors.[2] Recently, the use of quinoline-2(1*H*)-thione as a ligand of a metal complex has been reported.[3] Although a few methods for the general synthesis of quinoline-2(1*H*)-thione derivatives had appeared previously in the literature,[4] no methods for the general preparation of 3-bromo derivatives have been recorded so far. The preparation of 3-bromoquinoline-2(1*H*)-thione has been achieved by Nowak *et al*. and it was converted into 3-bromo-2-(methylsulfanyl)quinoline on treatment with iodomethane.[5] However, these suffer from the drawback in the lack of generality. In the present paper, we wish to report an efficient method for the preparation of 3-bromoquinoline-2(1*H*)-thiones (**2**) and 2-(alkylsulfanyl)-3-bromoquinolines (**3**), which is based on the reaction of readily available 2-(2,2-dibromoethenyl)phenyl isothiocyanates (**1**) with butyllithium. We also describe some elaborations of these 3-bromoquinoline derivatives.

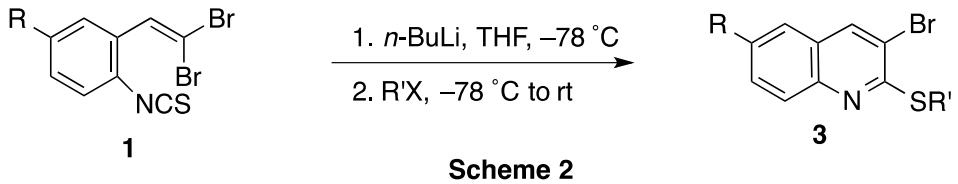
RESULTS AND DISCUSSION

The synthesis of 3-bromoquinoline-2(1*H*)-thiones (**2**) from 2-(2,2-dibromoethenyl)phenyl isothiocyanates (**1**), prepared by an easy five-step sequence from commercially available 2-nitrobenzaldehydes, was carried out as shown in Scheme 1. Reaction of **1** with butyllithium in THF at –78 ˚C gave, after aqueous workup and the subsequent recrystallization of the crude products, the corresponding products (**2**) in moderate to fair yields. The vinyllithium intermediates (**A**) was formed by the bromine/lithium exchange between **1** and butyllithium, and cyclized by the attack of the vinyl anion on the isothiocyanato carbon to produce the corresponding 1-lithioquinoline-2(1*H*)-thione intermediates (**B**). This reaction sequence proceeded rapidly and the products (**2**) were obtained by quenching of **B** at –78 ˚C. The corresponding 2-(butylsulfanyl)-3-bromoquinolines were not obtained. This indicates that the reaction of **B** with 1-bromobutane, generated by the bromine/lithium exchange, did not occur at –78 ˚C.



Scheme 1

The preparation of 2-(alkylsulfanyl)-3-bromoquinolines (**3**) is outlined in Scheme 2, and the yields are compiled in Table 1. After the treatment of **1** with butyllithium as described above, haloalkanes were added to the resulting solutions of lithium compounds (**B**), and the temperature was warmed to rt. After workup followed by separation by column chromatography on silica gel, the desired products (**3**) were isolated. As can be seen from Table 1, the yields of the products derived from **1a** were moderate-to-fair



Scheme 2

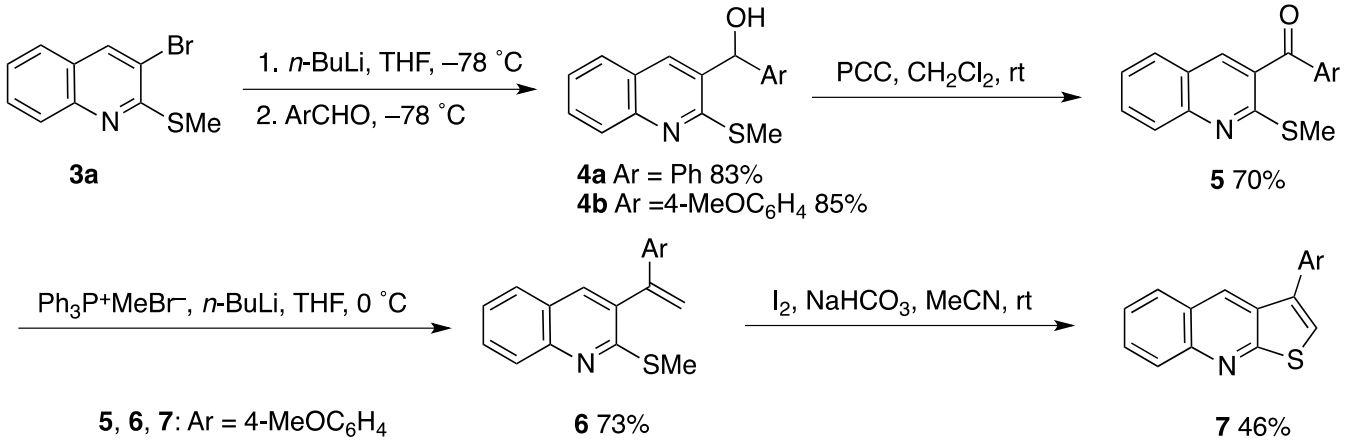
(Entries 1–5). While those derived from **1b** were low-to-moderate (Entries 6 and 7), those derived from **1c** were relatively good (Entries 8 and 9). Phenacyl bromide (Entry 5) and *tert*-butyl 2-bromoacetate (Entry 7) could be used in this reaction. An inactivated halide, such as *n*-butyl bromide, proved to be usable in the present reaction, though a considerably extended time at room temperature was required and the yields of the product (**3c**) was slightly lower than those from **1a** (Entry 3).

Table 1. Preparation of 3-bromo-2-sulfanylquinolines (**3**)

Entry	**1**	R'X	Time at rt	**3**	Yield/%[a]
1	**1a** (R = H)	MeI	5 min	**3a**	62
2	**1a**	EtI	30 min	**3b**	57
3	**1a**	*n*-BuBr	overnight	**3c**	51
4	**1a**	BnBr	5 min	**3d**	54
5	**1a**	$PhCOCH_2Br$	5 min	**3e**	64
6	**1b** (R = Cl)	EtI	30 min	**3f**	35
7	**1b**	*t*-$BuOCOCH_2Br$	5 min	**3g**	43
8	**1c** (R = OMe)	MeI	5 min	**3h**	75
9	**1c**	BnBr	5 min	**3i**	70

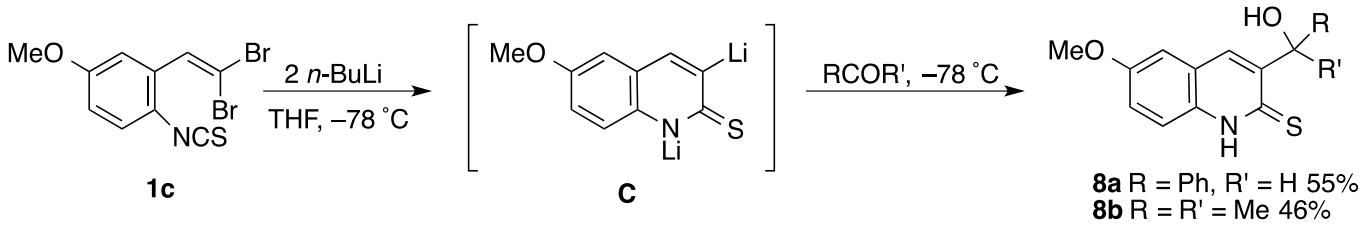
[a] Yields of isolated products.

We then tried to introduce a carbon substituent at the 3-position of the quinoline ring of **3**. Accordingly, the bromine/lithium exchange between **3a** and butyllithium generated the corresponding lithium compound, which was treated with aromatic aldehydes to provide aryl[2-(methylsulfanyl)quinolin-3-yl]methanols (**4**) in good yields, as illustrated in Scheme 3. Compound (**4b**) was oxidized with pyridinium chlorochromate (PCC) to give (4-methoxyphenyl)[2-(methylsulfanyl)quinolin-3-yl]methanone (**5**). A synthesis of aryl[2-(methylsulfanyl)quinolin-3-yl]methanones by reaction of α-aroylketene-*N*,*S*-acetals with Vilsmeier reagents and their utilization for the preparation of benzothiopyrano-fused quinoline derivatives have been reported by Mahata *et al.*[6] Compound (**5**) was then converted into 3-[1-(4-methoxyphenyl)ethenyl]-2-(methylsulfanyl)quinoline (**6**), of which treatment with iodine in the presence of sodium hydrogencarbonate[7] to afford 3-(4-methoxyphenyl)thieno[2,3-*b*]quinoline (**7**). Recently, some compounds with the thieno[2,3-*b*]quinoline structure have been reported to exhibit useful pharmacological activities,[8] and several synthetic methods for the preparation of thieno[2,3-*b*]quinoline derivatives have been developed.[9,10]



Scheme 3

Subsequently, one-pot preparation of 3-substituted quinoline-2(1*H*)-thiones from **1** was carried out as depicted in Scheme 4. Thus, 2-(2,2-dibromoethenyl)-4-methoxyphenyl isothiocyanates (**1c**) was treated with two equivalents of butyllithium in THF at –78 ˚C to generate the dilithium intermediate (**C**), which was allowed to react with carbonyl compounds, such as benzaldehyde and acetone, to result in the formation of 3-(1-hydroxyalkyl)quinoline-2(1*H*)-thiones (**8**), after aqueous workup, in moderate yields. Unfortunately, however, when compound (**1a**) and (**1c**) were used in the present one-pot reaction, only low yields of the corresponding products were obtained as inseparable mixtures with structure undefined byproducts.



Scheme 4

In conclusion, we have developed a simple procedure for the preparation of 3-bromoquinoline-2(1*H*)-thiones and 2-(alkylsulfanyl)-3-bromoquinolines from easily available 2-(2,2-bromoethenyl)phenyl isothiocyanates through the bromine/lithium exchange. We have also shown that these compounds could be converted into the corresponding derivatives carrying a carbon substituent at the 3-position through the further bromine/lithium exchange. Transformation of one of these derivatives into a new thieno[2,3-*b*]quinoline derivative of potentially biological importance has also been accomplished.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum 65 FTIR spectrophotometer. ^{1}H NMR 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) or a JEOL JMS-T100GCV (EI, TOF; 70eV) spectrometer. 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-(2,2-Dibromoethenyl)-2-isocyano-5-methoxybenzene, 1-(2,2-dibromoethenyl)-2-isothiocyanatobenzene were prepared according to the reported procedures.[9] *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

1-(2,2-Dibromoethenyl)-2-isothiocyanato-5-methoxybenzene (1b). This compound was prepared by the reaction of 1-(2,2-dibromoethenyl)-2-isocyano-5-methoxybenzene[9] with S_8 in the presence of a catalytic amount of Se under conditions reported previously.[11,12] Yield: 87%; a white solid; mp 45–47 ˚C (hexane/CH_2Cl_2); IR (neat) 2080, 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.86 (dd, *J* = 8.0, 2.9 Hz, 1H), 7.17 (d, *J* = 2.9 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H). Anal. Calcd for $C_{10}H_7Br_2NOS$: C, 34.41; H, 2.02; N, 4.01. Found: C, 34.27; H, 2.07; N, 3.96.

Typical Procedure for the Preparation of 3-Bromoquinoline-2(1*H*)-thiones (2). 3-Bromo-5-methoxyquinoline-2(1*H*)-thione (2c). To a stirred solution of **1c** (0.21 g, 0.60 mmol) in THF (4 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane, 0.60 mmol) dropwise. After 5 min, saturated aqueous water (15 mL) was added. The mixture was warmed to rt and extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was purified by recrystallization from hexane/THF to give **2c** (0.13 g, 79%); a yellow solid; mp 215–217 ˚C; IR (KBr) 3436, 1235, 1115 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.80 (s, 3H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.32 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.57 (d, *J* = 9.2 Hz, 1H), 8.54 (s, 1H), 14.10 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.61, 107.24, 117.58, 122.11, 123.49, 127.36, 134.20, 137.49, 155.89, 176.50. HR-MS (EI). Calcd for $C_{10}H_8BrNOS$ (M): 268.9510. Found: *m/z* 268.9512. Anal. Calcd for $C_{10}H_8BrNOS$: C, 44.46; H, 2.99; N, 5.19. Found: C, 44.44; H, 3.04; N, 5.18.

3-Bromoquinoline-2(1*H*)-thione (2a):[5] a yellow solid; mp 179–181 ˚C (hexane/THF) (lit.[5] mp 231–233 ˚C). The IR and ^1H NMR of this product were identical to those reported previously.[5]

3-Bromo-5-chloroquinoline-2(1*H*)-thione (2b): a yellow solid; mp 217–220 ˚C (hexane/THF); IR (KBr) 3440, 1621, 1289, 1128 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.67 (d, *J* = 9.2 Hz, 1H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.96 (s, 1H), 8.64 (s, 1H), 14.27 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 118.08, 123.55, 126.26, 128.42, 128.55, 131.84, 136.83, 137.75, 179.23. HR-MS (EI). Calcd for $C_9H_5BrClNS$ (M): 272.9015. Found: *m/z* 272.9024. Anal. Calcd for $C_9H_5BrClNS$: C, 39.37; H, 1.84; N, 5.10. Found: C, 39.16; H, 1.96; N, 5.01.

Typical Procedure for the Preparation of 3-Bromo-2-sulfanylquinolines (3). 3-Bromo-5-methoxy-2-(methylsulfanyl)quinoline (3h). Compound (**1c**) (0.24 g, 0.70 mmol) in THF (4 mL) was treated with *n*-BuLi (1.6 M in hexane, 0.70 mmol) as described for the preparation of **2c**. Then, MeI (99 mg, 0.70 mmol) was added and the mixture was warmed to rt. After the same workup as described for the preparation of **2c**, the residue was purified by preparative TLC on SiO_2 (hexane/CH_2Cl_2 1:1) to afford **3h** (0.15 g, 75%); a white solid; mp 100–102 ˚C (hexane/CH_2Cl_2); IR (KBr) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (s, 3H), 3.90 (s, 3H), 6.92 (d, *J* = 3.1 Hz, 1H), 7.30 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.84 (d, *J* = 9.1 Hz, 1H),

8.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.54, 55.53, 104.41, 117.46, 122.11, 127.51, 129.37, 136.45, 142.83, 155.92, 157.19. HR-MS (ESI). Calcd for $C_{11}H_{11}BrNOS$ (M+H): 283.9744. Found: *m/z* 283.9739. Anal. Calcd for $C_{11}H_{10}BrNOS$: C, 46.49; H, 3.55; N, 4.93. Found: C, 46.44; H, 3.55; N, 5.01.

3-Bromo-2-(methylsulfanyl)quinoline (3a):[5] colorless needles; mp 49–50 ˚C (hexane/CH_2Cl_2) (lit.,[5] mp 28–29 ˚C). The spectral (IR and ^{1}H NMR) data were identical to those reported previously.[5]

3-Bromo-2-(ethylsulfanyl)quinoline (3b): a pale-yellow oil; R_f 0.39 (hexane); IR (neat) 1614 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.46 (t, *J* = 7.6 Hz, 3H), 3.32 (q, *J* = 7.6 Hz, 2H), 7.43 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.01, 25.67, 117.01, 125.74, 126.65, 126.67, 127.95, 129.75, 137.49, 146.65, 158.71. HR-MS (EI). Calcd for $C_{11}H_{10}BrNS$ (M): 266.9717. Found: *m/z* 266.9730. Anal. Calcd for $C_{11}H_{10}BrNS$: C, 49.27; H, 3.76; N, 5.22. Found: C, 49.26; H, 4.04; N, 5.16.

3-Bromo-2-(butylsulfanyl)quinoline (3c): a pale-yellow oil; R_f 0.45 ($CHCl_3$/hexane 1:5); IR (neat) 1614 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, *J* = 7.4 Hz, 3H), 1.54 (sext, *J* = 7.4 Hz, 2H), 1.78 (quint, *J* = 7.4 Hz, 2H), 3.33 (t, *J* = 7.4 Hz, 2H), 7.43 (dd, *J* = 8.0, 6.9 Hz, 1H), 7.64–7.66 (m, 2H), 7.91 (d, *J* = 8.6 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.78, 22.22, 30.94 (2 overlapped Cs), 117.08, 125.71, 126.65 (2 overlapped Cs), 127.92, 129.75, 137.47, 146.56, 158.80. HR-MS (DART). Calcd for $C_{13}H_{15}BrNS$ (M+H): 296.0108. Found: *m/z* 296.0099. Anal. Calcd for $C_{13}H_{14}BrNS$: C, 52.71; H, 4.76; N, 4.73. Found: C, 52.61; H, 4.93; N, 4.63.

3-Bromo-2-[(phenylmethyl)sulfanyl]quinoline (3d): a white solid; mp 72–74 ˚C (hexane/CH_2Cl_2); IR (KBr) 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.57 (s, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.45 (dd, *J* = 8.0, 6.9 Hz, 1H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.64–7.69 (m, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.71, 116.50, 125.91, 126.69, 126.85, 127.14, 127.87, 128.45, 129.35, 129.90, 137.65, 137.69, 146.46, 158.16. HR-MS (DART). Calcd for $C_{16}H_{13}BrNS$ (M+H): 329.9952. Found: *m/z* 329.9944. Anal. Calcd for $C_{16}H_{12}BrNS$: C, 58.19; H, 3.66; N, 4.24; S, 9.71. Found: C, 57.99; H, 3.66; N, 4.13; S, 9.51.

2-[(3-Bromoquinolin-2-yl)sulfanyl]-1-phenylethanone (3e): a yellow solid; mp 121–123 ˚C (hexane/CH_2Cl_2); IR (KBr) 1685, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.71 (s, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.52–7.55 (m, 3H), 7.61–7.65 (m, 2H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.55, 116.15, 126.05, 126.64, 126.90, 127.52, 128.51, 128.65, 129.87, 133.29, 136.81, 137.89, 146.25, 156.99, 194.53. HR-MS (EI). Calcd for $C_{17}H_{12}BrNOS$ (M): 356.9823. Found: *m/z* 356.9820. Anal. Calcd for $C_{17}H_{12}BrNOS$: C, 57.00; H, 3.38; N, 3.91. Found: C, 57.22; H, 3.47; N, 3.86.

3-Bromo-6-chloro-2-(ethylsulfanyl)quinoline (3f): a white solid; mp 86–88 ˚C (hexane/CH_2Cl_2); IR (KBr) 1609 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (t, *J* = 7.6 Hz, 3H), 3.30 (q, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 8.4

Hz, 1H), 7.61 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.93, 25.75, 118.21, 125.29, 127.12, 129.51, 130.58, 131.29, 136.44, 145.02, 159.41. HR-MS (EI). Calcd for $C_{11}H_9BrClNS$ (M): 300.9328. Found: *m/z* 300.9338. Anal. Calcd for $C_{11}H_9BrClNS$: C, 43.66; H, 3.00; N, 4.63. Found: C, 43.55; H, 3.08; N, 4.58.

1,1-Dimethylethyl 2-[(3-Bromo-6-chloroquinolin-2-yl)sulfanyl]acetate (3g): a white solid; mp 136–138 ˚C (hexane/CH_2Cl_2); IR (KBr) 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 3.93 (s, 2H), 7.56 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.62 (d, *J* = 2.3 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.03, 35.25, 81.86, 117.51, 125.37, 127.38, 129.39, 130.77, 131.65, 136.72, 144.76, 158.08, 168.10. HR-MS (EI). Calcd for $C_{15}H_{15}BrClNO_2S$ (M): 386.9695. Found: *m/z* 386.9712. Anal. Calcd for $C_{15}H_{15}BrClNO_2S$: C, 46.35; H, 3.89; N, 3.60. Found: C, 46.44; H, 3.92; N, 3.56.

3-Bromo-5-methoxy-2-[(phenylmethyl)sulfanyl]quinoline (3i): a colorless crystals; mp 99–101 ˚C (hexane/CH_2Cl_2); IR (KBr) 1621 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 4.54 (s, 2H), 6.92 (d, *J* = 2.3 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.32 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.87 (d, *J* = 9.2 Hz, 1H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.65, 55.57, 104.51, 117.07, 122.24, 127.10, 127.80, 128.41, 129.33, 129.36, 136.36, 137.83, 142.71, 155.10, 157.37. HR-MS (EI). Calcd for $C_{17}H_{14}BrNOS$ (M): 358.9979. Found: *m/z* 358.9972. Anal. Calcd for $C_{17}H_{14}BrNOS$: C, 56.68; H, 3.92; N, 3.89. Found: C, 56.53; H, 3.93; N, 3.80.

Typical Procedure for the Preparation of Aryl(2-sulfanylquinolin-3-yl)methanols (4). [(2-Methylsulfanyl)quinolin-3-yl](phenyl)methanol (4a). To a stirred solution of **3a** (0.24 g, 0.96 mmol) in THF at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 0.96 mmol) dropwise. After 5 min, PhCHO was added dropwise at the same temperature and stirring was continued for an additional 15 min. The mixture was then worked up as described for the preparation of **2c** to give a residual solid, which was recrystallized from hexane/CH_2Cl_2 to give **4a** (0.22 g, 83%); colorless needles; mp 117–119 ˚C; IR (KBr) 3255, 1614 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.58 (d, *J* = 3.8 Hz, 1H), 2.67 (s, 3H), 6.15 (d, *J* = 3.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.41–7.43 (m, 3H), 7.63 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.30, 72.06, 125.31, 125.67, 127.40, 127.63, 127.87, 128.14, 128.56, 129.47, 132.55, 134.90, 141.39, 147.36, 157.88. HR-MS (EI). Calcd for $C_{17}H_{15}NOS$ (M): 281.0874. Found: *m/z* 281.0880. Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.27; H, 5.27; N, 4.91.

(4-Methoxyphenyl)[(2-methylsulfanyl)quinolin-3-yl]methanol (4b): a colorless gum; R_f 0.29 (CH_2Cl_2); IR (neat) 3392, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.54 (d, *J* = 3.8 Hz, 1H), 2.65 (s, 3H), 3.78 (s, 3H), 6.07 (d, *J* = 3.8 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.4 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.29,

55.22, 71.65, 113.92, 125.27, 125.69, 127.61, 127.84, 128.85, 129.36, 132.10, 133.55, 135.06, 147.30, 157.83, 159.41. HR-MS (EI). Calcd for $C_{18}H_{17}NO_2S$ (M): 311.0980. Found: *m/z* 311.0989. Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.16; H, 5.50; N, 4.40.

(4-Methoxyphenyl)[(2-methylsulfanyl)quinolin-3-yl]methanone (5). A mixture of **4b** (0.31 g, 1.0 mmol) and PCC (0.43 g, 2.0 mmol) in CH_2Cl_2 (12 mL) containing Celite® 545 (2.0 g) was stirred at rt for 1 h. The resulting mixture was filtered off under reduced pressure and the filtrate was concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **5** (0.22 g, 70%); a yellow viscous oil; R_f 0.43 (CH_2Cl_2/hexane 3:2); IR (neat) 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (s, 3H), 3.89 (s, 3H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.72–7.75 (m, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 8.00 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H). HR-MS (EI). Calcd for $C_{18}H_{15}NO_2S$ (M): 309.0823. Found: *m/z* 309.0826.

3-[1-(4-Methoxyphenyl)ethenyl]-2-(methylsulfanyl)quinoline (6). To a stirred suspension of $Ph_3P^+MeBr^-$ (0.37 g, 1.0 mmol) in THF (2 mL) at 0 ˚C was added *n*-BuLi (1.6 M in hexane; 1.0 mmol) dropwise. After 15 min, a solution of **5** in THF (2 mL) was added dropwise and stirring was continued for 30 min at the same temperature before addition of water (15 mL). The resulting mixture was extracted with AcOEt (3 × 10 mL) and the combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **6** (0.16 g, 73%); a yellow viscous oil; R_f 0.26 (AcOEt/hexane 1:30); IR (neat) 1606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.80 (s, 3H), 5.32 (s, 1H), 5.82 (s, 1H), 6.84 (d, *J* = 9.2 Hz, 2H), 7.27 (d, *J* = 9.2 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.66 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.82 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H). HR-MS (EI). Calcd for $C_{19}H_{17}NOS$ (M): 307.1031. Found: *m/z* 307.1044.

3-(4-Methoxyphenyl)thieno[2,3-*b*]quinoline (7). A mixture of **6** (0.14 g, 0.45 mmol) and I_2 (0.33 g, 1.4 mmol) in MeCN (9 mL) containing $NaHCO_3$ (0.11 g, 1.4 mmol) was stirred at rt for 1 h. 10% Aqueous $Na_2S_2O_3$ (15 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **7** (62 mg, 46%); a white solid; mp 148–150 ˚C (hexane/CH_2Cl_2); IR (KBr) 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91 (s, 3H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.48 (s, 1H), 7.55 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.67 (ddd, *J* = 8.6, 6.9, 1.1 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.41, 114.46, 123.74, 125.45, 127.80, 128.29, 128.49, 129.46, 129.54 (2 overlapped Cs), 129.77, 130.59, 134.79, 146.62, 159.52, 163.78. HR-MS (EI). Calcd for $C_{18}H_{13}NOS$ (M): 291.0718. Found: *m/z* 291.0729. Anal. Calcd for $C_{18}H_{13}NOS$: C, 74.20; H, 4.50; N, 4.81. Found: C, 73.33; H, 4.68; N, 4.68.

Typical Procedure for the Preparation of 3-(1-Hydroxyalky)-5-methoxyquinoline-2(1*H*)-thiones (8).

3-[Hydroxy(phenyl)methyl]-5-methoxyquinoline-2(1*H*)-thione (8a). To a stirred solution of **1c** (0.24 g,

0.70 mmol) in THF (4 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane, 1.4 mmol) dropwise. After 5 min, PhCHO (74 mg, 0.70 mmol) was added and the mixture was stirred at the same temperature for an additional 5 min before the same workup as described for the preparation of **2c**. The residual solid was purified by recrystallization from hexane/THF to give **8a** (0.12 g, 55%); a yellow solid; mp 203–205 ˚C; IR (KBr) 3300, 3151, 1236, 1164 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.83 (s, 3H), 3.95 (br, 1H), 6.38 (s, 1H), 6.90 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 9.2, 2.3 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.39 (s, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.50–7.54 (m, 3H), 12.76 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.66, 73.33, 107.74, 117.19, 122.50, 124.00, 127.25, 127.77, 128.48, 133.39, 134.16, 140.43, 142.48, 156.81, 177.14. HR-MS (ESI). Calcd for $C_{17}H_{16}NO_2S$ (M+H): 298.0901. Found: *m/z* 298.0893. Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.65; H, 5.19; N, 4.60.

3-[1-Hydroxy-1-methylethyl]-5-methoxyquinoline-2(1*H*)-thione (8b): a yellow solid; mp 202–204 ˚C (hexane/THF); IR (KBr) 3306, 3133, 1241, 1118 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.70 (s, 6H), 3.81 (s, 3H), 6.46 (br s, 1H), 7.28 (dd, J = 9.2, 1.7 Hz, 1H), 7.37 (d, J = 1.7 Hz, 1H), 7.64 (d, J = 9.2 Hz, 1H), 8.19 (s, 1H), 13.77 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.65, 55.54, 72.30, 108.02, 117.34, 121.62, 123.64, 131.74, 133.47, 145.37, 155.93, 176.19. HR-MS (EI). Calcd for $C_{13}H_{15}NO_2S$ (M): 249.0823. Found: *m/z* 249.0829. Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.36; H, 6.20; N, 5.56.

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