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SYNTHESIS OF 3-HYDROXY-2,3-DIHYDRO-1*H*-ISOINDOLE-1-THIONE DERIVATIVES BY THE REACTION OF 2,*N*-DILITHIOBENZAMIDES WITH CARBOXYLIC ESTERS

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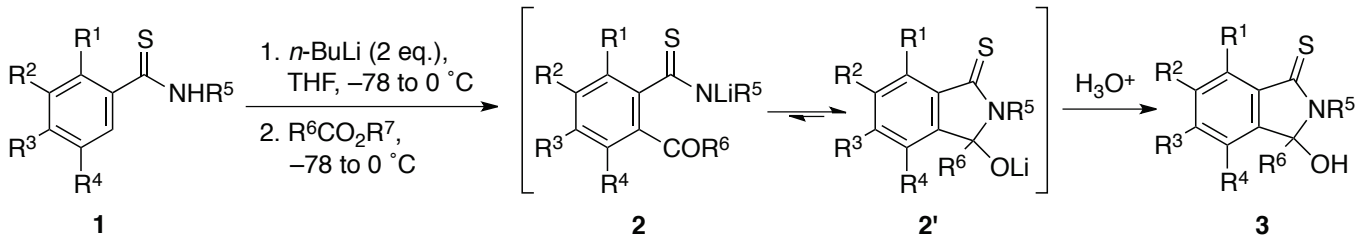
Abstract – An efficient one-pot method for the preparation of 2,3-disubstituted 3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thiones from secondary benzothioamides and carboxylic esters has been developed. Thus, the reaction of the starting thioamides with two equivalents of butyllithium generates the corresponding 2,*N*-dilithiobenzothioamides, which are then allowed to react with carboxylic esters to give the desired products. The similar preparation of 4- and 5-aza-analogues from 2(or 3)-bromopyridine-3(or 4)-carbothioamides, respectively, is also described.

Chlorthalidone is a famous diuretic having the 3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one structure. The thioxo analogue of chlorthalidone has recently attract respectable attention and some HQSAR investigations have been reported.[1] However, literature survey revealed that there are only a few reports on the preparation of 3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thione derivatives.[2] In the course of our study on exploring the versatility of 2,*N*-dilithiobenzothioamides as intermediates for the preparation of fused heterocycles,[3] we became interested in developing a general method for the preparation of 3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thione derivatives. Detailed here are the results of our study, which offer a facile method for the preparation of this class of heterocycles. We have found that the 2,*N*-dilithio compounds, generated from secondary benzothioamides (**1**), can be acylated at the 2-position on treatment with carboxylic esters to give rise to 2,3-disubstituted 3-hydroxy-2,3-dihydro-1*H*-isoindole-

1-thiones (**3**). In addition, we also present the applicability of the present method to the synthesis of 3-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,4-*b*(or *c*)]pyridine-1-thiones (**7**) from 2(or 3)-bromopyridine-3(or 4)-carbothioamides (**6**), respectively.

Our one-pot synthesis of **3** from **1** was conducted according to the procedure illustrated in Scheme 1. Thus, the starting materials (**1**) were treated with two equivalents of butyllithium in THF under the same conditions as described previously (–78 to 0 ˚C),[3] and the resulting 2,*N*-dilithiobenzothioamides were allowed to react with various carboxylic esters. The progress of the reaction of the dilithio compounds with carboxylic esters was very slow at –78 ˚C and it required gradual warming to 0 ˚C. It is thought that initially produced 2-acylated *N*-lithiothioamide intermediates (**2**) underwent tautomerization to form lithium alkoxides intermediates (**2'**). After aqueous workup, 2,3-disubstituted 3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thiones (**3**) were isolated by purification using column chromatography on silica gel. It is notable that addition of carboxylic esters to the solutions (or suspensions) of the dilithio compounds at 0 ˚C caused somewhat decreases of the yields of the products. Analyses by IR, ^{1}H NMR and ^{13}C NMR spectroscopies of the products indicated that the structure is 3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thione (**3**) not 2-acylbenzenecarbothioamide [protonated compounds of intermediates (**2**)]. The IR spectra do not show characteristic signals due to ν (C=O) and exhibit absorption bands at around 3300 cm^{-1} due to ν (O–H). The ^{13}C NMR spectra exhibit signals corresponding to C-3 of **3** at around δ 95 and do not show signals corresponding to the carbonyl carbons of protonated compounds of intermediates (**2**), probably at around δ 200. The ^{1}H NMR data are in good agreement with the structure (**3**).



Scheme 1

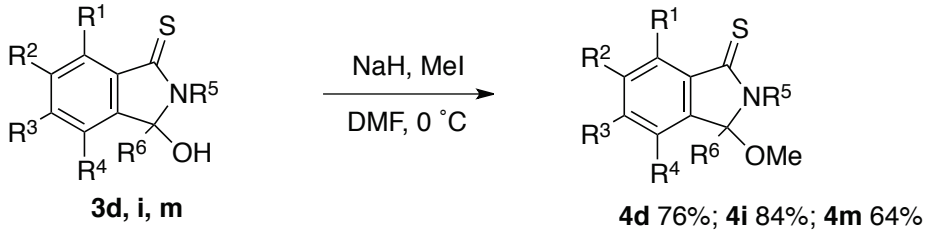
Relatively good yields were obtained by using benzoates as indicated in Table 1, Entries 1–7. Ethyl naphthalene-1-carboxylate also worked well to give a good yield of the corresponding product (**3h**) (Entry 8). The uses of hetarenecarboxylates, such as ethyl 2-chloropyridine-3-carboxylate and ethyl thiophene-2-carboxylate, provides the corresponding 3-hetaryl-3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thione derivative (**3i**) and (**3j**) in good yields (Entries 9 and 10, respectively). It is worth noting that the reaction of the dilithio compound from **1b** with ethyl cinnamate afforded the corresponding 3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thione derivative (**3k**) in a moderate yield (Entry 11). No products

arising from conjugate addition to ethyl cinnamate were observed. *N*-Arylbenzothioamides (**1e**) and (**1f**) performed well to give the corresponding desired products (**3n**) and (**3o**) in relatively good yields (Entries 14 and 15). *N*-Ethylnaphthalene-1-carbothioamide (**1g**) also afforded the expected product, 2-ethyl-3-hydroxy-3-phenyl-2,3-dihydro-1*H*-benzo[*g*]isoindole-1-thione (**3p**), albeit in a rather decreased yield (Entry 16).

Table 1. Preparation of 3-hydroxy-1,3-dihydro-2*H*-isoindole-1-thiones (**3**)

Entry	**1**	R^1	R^2	R^3	R^4	R^5	R^6 in $R^6CO_2R^7$	**3**	Yield/%[a]
1	**1a**	H	H	H	H	Me	Ph[b]	**3a**	63
2	**1a**	H	H	H	H	Me	4-$MeOC_6H_4$[c]	**3b**	70
3	**1b**	H	H	H	H	Et	Ph[b]	**3c**	69
4	**1b**	H	H	H	H	Et	4-MeC_6H_4[c]	**3d**	73
5	**1b**	H	H	H	H	Et	4-ClC_6H_4[b]	**3e**	81
6	**1b**	H	H	H	H	Et	3-$MeOC_6H_4$[b]	**3f**	71
7	**1b**	H	H	H	H	Et	4-$MeOC_6H_4$[c]	**3g**	81
8	**1b**	H	H	H	H	Et	naphthalen-1-yl[b]	**3h**	74
9	**1b**	H	H	H	H	Et	2-chloropyridin-3-yl[b]	**3i**	82
10	**1b**	H	H	H	H	Et	thiophen-2-yl[b]	**3j**	70
11	**1b**	H	H	H	H	Et	(*E*)-PhCH=CH[b]	**3k**	55
12	**1c**	H	H	Cl	H	Et	Ph[b]	**3l**	65
13	**1d**	H	OMe	OMe	OMe	Et	Ph[b]	**3m**	50
14	**1e**	H	H	H	H	Ph	Ph[b]	**3n**	73
15	**1f**	H	H	H	H	4-$MeOC_6H_4$	Ph[b]	**3o**	72
16	**1g**	benzo		H	H	Et	Ph[b]	**3p**	32

[a] Yields of isolated products. [b] Ethyl ester. [c] Methyl ester.



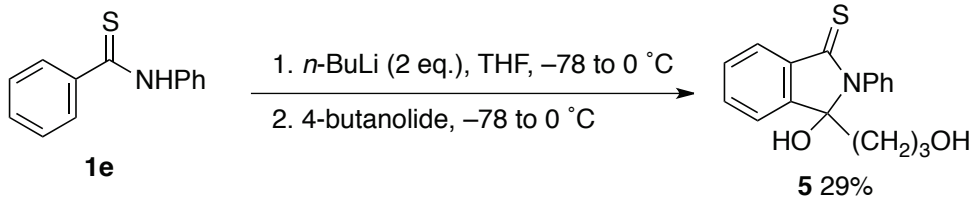
3d, i, m

4d 76%; **4i** 84%; **4m** 64%

Scheme 2

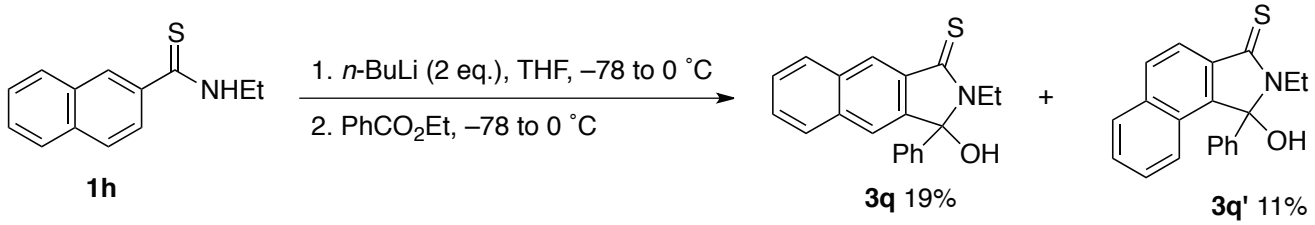
Behaviors of some of compounds (**3**) in methylation using sodium hydride/iodomethane in DMF were briefly examined. It was found that *O*-methylation occurred exclusively at 0 ˚C to afford 3-methoxy-2,3-dihydro-1*H*-isoindole-1-thiones (**4**) in fair-to-good yields, as shown in Scheme 2.

An aliphatic carboxylate carrying α-hydrogens, such as ethyl propionate, could not be successfully employed in the reaction with the dilithio compound from **1e**. It gave an intractable mixture of products. However, the reaction of the dilithio compound from **1e** with 4-butanolide provided 3-hydroxy-3-(3-hydroxypropyl)-2-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (**5**) in 29% yield, as shown in Scheme 3.



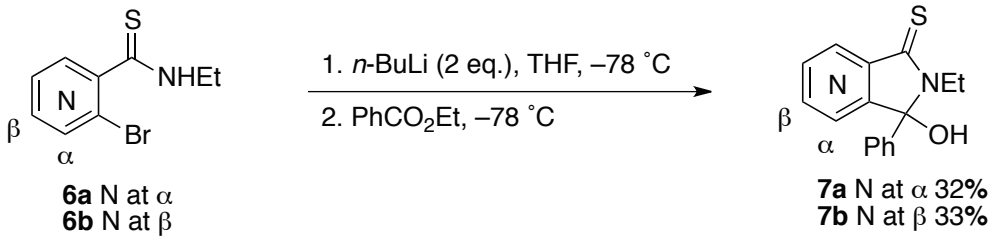
Scheme 3

Two regioisomers (**3q**) and (**3q'**) were produced by the successive treatment of *N*-ethylnaphthalene-2-carbothioamide (**1h**) with butyllithium and ethyl benzoate under the same conditions, as shown in Scheme 4.



Scheme 4

Subsequently, we attempted the preparation of 4- and 5-aza-analogues of compounds (**3**). *N*-Ethylpyridine-2-carbothioamide and *N*-ethylpyridine-3-carbothioamide were first exposed to the same conditions, which had been successfully used for the preparation of **3**. Unfortunately, however, the desired products could not be obtained at all. Gratifyingly, it was found that when 2-bromo-*N*-ethylpyridine-3-carbothioamide (**6a**) was successively treated with two equivalents of butyllithium and ethyl benzoate in THF at –78 ˚C, 2-ethyl-3-hydroxy-3-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]pyridine-1-thione (**7a**) was obtained albeit in rather lower 32% yield. 2-Ethyl-3-hydroxy-3-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-1-thione (**7b**) was also obtained in 33% yield by subjection of 3-bromo-*N*-ethylpyridine-4-carbothioamide (**6b**) to the same conditions. These results are shown in Scheme 5. In these cases, the benzoylation of the dilithio compounds proceeded at –78 ˚C.



Scheme 5

In conclusion, we have developed an efficient one-pot preparation of 3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thione derivatives of potential biological interest, which are hard to prepare by conventional methods, by the reaction of 2,*N*-dilithiobenzothioamides with carboxylic esters. We have also demonstrated that the method can be applied to the synthesis of 4- and 5-aza-analogues of 3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thione. The present method may find some value in that the starting materials are readily available and that the synthetic operations are very simple.

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. ^{1}H 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 and ESI, positive) or a JEOL JMS-T100GCV (EI, TOF; 70 eV) 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. *N*-Substituted benzothioamides (**1a-f**) and 3-bromo-*N*-ethylpyridine-4-carbothioamide (**6b**) were prepared by the reaction of the respective aryllithiums with isothiocyanate according to the procedure reported previously.[3] *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Compounds (**1g**) and (**1h**) were prepared from the respective bromonaphthalenes and EtNCS as described for the preparation of **1a-f**.

***N*-Ethylnaphthalene-1-carbothioamide (1g):** yield: 66%; a white solid; mp 111–113 °C (hexane/CH_2Cl_2); IR (KBr) 3162, 1532, 1398, 1243 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, *J* = 7.4 Hz, 3H), 3.88–3.93 (m, 2H), 7.42 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.47–7.52 (m, 4H), 7.82–7.84 (m, 2H), 8.09 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.2, 41.1, 124.2, 124.7, 125.0, 126.3, 126.9, 128.3, 128.9, 129.4, 133.6, 141.7, 200.0. Anal Calcd for $C_{13}H_{13}NS$: C, 72.52; H, 6.09; N, 6.51; S, 14.89. Found: C, 72.46; H, 5.97; N, 6.52; S, 15.03.

***N*-Ethylnaphthalene-2-carbothioamide (1h):** yield: 81%; a white solid; mp 97–100 °C (hexane/CH_2Cl_2); IR (KBr) 3338, 1530, 1392, 1213 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, *J* = 7.4 Hz, 3H), 3.84–3.89 (m, 2H), 7.48–7.54 (m, 2H), 7.76–7.85 (m, 5H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 41.7, 124.3, 125.7, 126.8, 127.4, 127.6, 128.2, 128.9, 132.4, 134.3, 138.9, 198.7. Anal Calcd for $C_{13}H_{13}NS$: C, 72.52; H, 6.09; N, 6.51; S, 14.89. Found: C, 72.48; H, 6.01; N, 6.49; S, 14.98.

Typical Procedure for the Preparation of 3-Hydoroxy-2,3-dihydro-1*H*-isoindole-1-thiones (3). 3-Hydroxy-2-methyl-3-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (3a). To a stirred solution of **1a** (0.15 g, 1.0 mmol) in THF (8 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 2.0 mmol) dropwise. The temperature was gradually raised to 0 ˚C and stirring was continued for 1.5 h. The mixture was cooled again to –78 ˚C and ethyl benzoate (0.15 g, 1.0 mmol) was added dropwise. After the temperature was gradually raised to 0 ˚C, saturated aqueous NH_4Cl (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 (AcOEt/hexane 1:5) to afford **3a** (0.16 g, 63%); a yellow solid; mp 148–150 ˚C (hexane/CH_2Cl_2); IR (KBr) 3235, 1485, 1306, 1049 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98 (s, 3H), 4.18 (s, 1H), 7.26–7.30 (m, 3H), 7.32–7.35 (m, 3H), 7.46 (td, *J* = 7.4, 1.1 Hz, 1H), 7.50 (td, *J* = 7.4, 1.1 Hz, 1H), 7.90 (dd, *J* = 7.4, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.2, 96.9, 122.3, 124.9, 125.6, 128.78, 128.83, 129.8, 132.4, 136.1, 136.8, 146.0, 192.0. HR-MS (EI). Calcd for $C_{15}H_{13}NOS$ (M): 255.0718. Found: *m/z* 255.0720. Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.45; H, 5.16; N, 5.44.

3-Hydroxy-3-(4-methoxyphenyl)-2-methyl-2,3-dihydro-1*H*-isoindole-1-thione (3b): a yellow solid; mp 165–167 ˚C (hexane/CH_2Cl_2); IR (KBr) 3251, 1609, 1511, 1305, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98 (s, 3H), 3.78 (s, 3H), 4.14 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 7.4 Hz, 1H), 7.45 (td, *J* = 7.4, 1.1 Hz, 1H), 7.49 (td, *J* = 7.4, 1.1 Hz, 1H), 7.89 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.1, 55.3, 96.9, 114.0, 122.2, 124.9, 127.0, 128.6, 129.7, 132.4, 136.0, 146.1, 159.8, 191.7. HR-MS (EI). Calcd for $C_{16}H_{15}NO_2S$ (M): 285.0823. Found: *m/z* 285.0829. Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.34; H, 5.32; N, 4.88.

2-Ethyl-3-hydroxy-3-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (3c): a pale-yellow solid; mp 121–123 ˚C (hexane/CH_2Cl_2); IR (KBr) 3245, 1482, 1281, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, *J* = 7.4 Hz, 3H), 3.43–3.50 (m including s at 3.45, combined 2H), 3.85–3.92 (m, 1H), 7.23 (dd, *J* = 6.3, 2.8 Hz, 1H), 7.34 (s, 5H), 7.45–7.50 (m, 2H), 7.96 (dd, *J* = 6.3, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 38.5, 97.2, 122.1, 125.0, 125.9, 128.6, 128.9, 130.0, 132.4, 136.7, 137.1, 145.9, 191.7. HR-MS (DART). Calcd for $C_{16}H_{16}NOS$ (M+H): 270.0952. Found: *m/z* 270.0940. Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20. Found: C, 71.18; H, 5.80; N, 5.16.

2-Ethyl-3-hydroxy-3-(4-methylphenyl)-2,3-dihydro-1*H*-isoindole-1-thione (3d): a white solid; mp 139–141 ˚C (hexane/CH_2Cl_2); IR (KBr) 3307, 1481, 1280, 1058 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.4 Hz, 3H), 2.33 (s, 3H), 3.42 (s, 1H), 3.44–3.49 (m, 1H), 3.86–3.91 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.21–7.23 (m, 3H), 7.44–7.48 (m, 2H), 7.96 (dd, *J* = 7.4, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 21.1, 38.5, 97.3, 122.0, 125.0, 125.9, 129.3, 129.9, 132.3, 134.1, 136.7, 138.8, 146.0, 191.7. HR-MS (DART).

Calcd for $C_{17}H_{18}NOS$ (M+H): 284.1109. Found: *m/z* 284.1099. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 72.01; H, 6.06; N, 4.93.

3-(4-Chlorophenyl)-2-ethyl-3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thione (3e): a yellow solid; 132–134 °C (hexane/CH_2Cl_2); IR (neat) 3233, 1480, 1279, 1054 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (t, *J* = 7.4 Hz, 3H), 3.42–3.49 (m, 1H), 3.54 (br s, 1H), 3.82–3.90 (m, 1H), 7.20 (dd, *J* = 6.3, 2.3 Hz, 1H), 7.28 (d, *J* = 9.2 Hz, 2H), 7.31 (d, *J* = 9.2 Hz, 2H), 7.46–7.51 (m, 2H), 7.95 (dd, *J* = 6.3, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 38.5, 96.7, 122.0, 125.1, 127.5, 128.8, 130.2, 132.5, 134.9, 135.8, 136.6, 145.5, 191.8. HR-MS (DART). Calcd for $C_{16}H_{15}ClNOS$ (M+H): 304.0563. Found: *m/z* 304.0549. Anal. Calcd for $C_{16}H_{14}ClNOS$: C, 63.26; H, 4.65; N, 4.61. Found: C, 63.17; H, 4.74; N, 4.57.

2-Ethyl-3-hydroxy-3-(3-methoxyphenyl)-2,3-dihydro-1*H*-isoindole-1-thione (3f): a yellow amorphous powder; R_f 0.40 (Et_2O/hexane 1:2); IR (KBr) 3306, 1600, 1469, 1280, 1046 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.4 Hz, 3H), 3.40–3.50 (m, 1H), 3.57 (s, 1H), 3.77 (s, 3H), 3.85–3.92 (m, 1H), 6.82 (d, *J* = 7.4 Hz, 1H), 6.85 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.00 (s, 1H), 7.20–7.27 (m, 2H), 7.45–7.50 (m, 2H), 7.95 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 38.6, 55.3, 97.0, 111.9, 114.0, 118.3, 122.0, 125.0, 129.7, 129.9, 132.4, 136.6, 136.7, 145.8, 159.7, 191.7. HR-MS (EI). Calcd for $C_{17}H_{17}NO_2S$ (M): 299.0980. Found: *m/z* 299.0983. Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.20; H, 5.79; N, 4.73.

2-Ethyl-3-hydroxy-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-isoindole-1-thione (3g): a yellow amorphous powder; R_f 0.44 (Et_2O/hexane 1:2); IR (KBr) 3280, 1513, 1252, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, *J* = 6.9 Hz, 3H), 3.41–3.52 (m including s at 3.47, 2H), 3.78 (s, 3H), 3.82–3.89 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 7.21–7.26 (m, 3H), 7.44–7.50 (m, 2H), 7.95 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 38.4, 55.3, 97.2, 113.9, 120.0, 124.9, 127.3, 128.9, 129.9, 132.4, 136.6, 146.0, 159.9, 191.4. HR-MS (ESI). Calcd for $C_{17}H_{18}NO_2S$ (M+H): 300.1058. Found: *m/z* 300.1051. Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.06; H, 5.94; N, 4.59.

2-Ethyl-3-hydroxy-3-(naphthalen-1-yl)-2,3-dihydro-1*H*-isoindole-1-thione (3h): a yellow solid; mp 137–141 °C (hexane/CH_2Cl_2); IR (KBr) 3255, 1480, 1279, 1073 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.4 Hz, 3H), 3.41 (br s, 1H), 3.48–3.55 (m, 1H), 3.72–3.79 (m, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 7.13 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.56 (dd, *J* = 8.6, 7.4 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 7.4 Hz, 1H), 8.52 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 38.8, 96.3, 121.8, 123.1, 125.0, 125.4, 125.6, 126.9, 127.3, 129.1, 129.5, 130.2, 130.8, 130.9, 132.7, 134.0, 137.0, 146.4, 192.3. HR-MS (DART). Calcd for $C_{20}H_{18}NOS$ (M+H): 320.1109. Found: *m/z* 320.1094. Anal. Calcd for $C_{20}H_{17}NOS$: C, 75.20; H, 5.36; N, 4.39. Found: C, 74.90; H, 5.44; N, 4.35.

3-(2-Chloropyridin-3-yl)-2-ethyl-3-hydroxy-2,3-dihydro-1*H*-isoindole-1-thione (3i): a yellow solid; mp 182–184 °C (hexane/CH_2Cl_2); IR (KBr) 3139, 1577, 1410, 1283, 1047 cm^{-1}; ^1H NMR (DMSO-d_6) δ

1.02 (t, *J* = 7.4 Hz, 3H), 3.43–3.50 (m, 1H), 3.64–3.71 (m, 1H), 7.15 (br s, 1H), 7.54–7.56 (m, 2H), 7.64 (dd, *J* = 7.4, 4.5 Hz, 1H), 7.85–7.90 (m, 2H), 8.45 (dd, *J* = 4.5, 2.9 Hz, 1H), 8.70 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 12.0, 30.4, 93.9, 121.7, 123.5, 123.9, 129.8, 131.9, 132.3, 138.4, 139.7, 144.0, 147.7, 150.1, 192.5. HR-MS (DART). Calcd for $C_{15}H_{14}ClN_2OS$ (M+H): 305.0515. Found: *m/z* 305.1500. Anal. Calcd for $C_{15}H_{13}ClN_2OS$: C, 59.11; H, 4.30; N, 9.19. Found: C, 58.87; H, 4.34; N, 9.01.

2-Ethyl-3-hydroxy-3-(thiophen-2-yl)-2,3-dihydro-1*H*-isoindole-1-thione (3j): a light gray solid; mp 141–143 °C (hexane/CH_2Cl_2); IR (KBr) 3247, 1481, 1420, 1278, 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, *J* = 7.4 Hz, 3H), 3.57–3.64 (m, 1H), 3.78 (br s, 1H), 3.88–3.95 (m, 1H), 6.84 (dd, *J* = 4.0, 1.1 Hz, 1H), 6.94 (dd, *J* = 4.6, 4.0 Hz, 1H), 7.31 (dd, *J* = 4.6, 1.1 Hz, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.48 (td, *J* = 7.4, 1.1 Hz, 1H), 7.53 (td, *J* = 7.4, 1.1 Hz, 1H), 7.91 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 38.4, 95.7, 122.2, 124.9, 125.8, 126.5, 127.2, 130.3, 132.4, 136.1, 141.0, 145.0, 191.2. HR-MS (ESI). Calcd for $C_{14}H_{14}NOS_2$ (M+H): 276.0517. Found: *m/z* 276.0512. Anal. Calcd for $C_{14}H_{13}NOS_2$: C, 61.06; H, 4.76; N, 5.09. Found: C, 60.83; H, 4.82; N, 5.05.

2-Ethyl-3-hydroxy-3-((*E*)-2-phenylethenyl)-2,3-dihydro-1*H*-isoindole-1-thione (3k): a white solid; mp 152–154 °C (hexane/CH_2Cl_2); IR (KBr) 3238, 1650, 1481, 1274, 1131 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, *J* = 6.9 Hz, 3H), 3.33 (s, 1H), 3.70–3.77 (m, 1H), 3.85–3.92 (m, 1H), 5.95 (d, *J* = 16.0 Hz, 1H), 7.16 (d, *J* = 16.0 Hz, 1H), 7.27–7.42 (m, 6H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.93 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 38.1, 95.8, 122.2, 124.5, 125.0, 126.9, 128.5, 128.7, 130.2, 132.2, 132.9, 135.5, 136.9, 143.8, 191.1. HR-MS (DART). Calcd for $C_{18}H_{18}NOS$ (M+H): 296.1109. Found: *m/z* 296.1095. Anal. Calcd for $C_{18}H_{17}NOS$: C, 73.19; H, 5.80; N, 4.74. Found: C, 73.20; H, 5.86; N, 4.75.

5-Chloro-2-ethyl-3-hydroxy-3-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (3l): a yellow solid; mp 154–156 °C (hexane/CH_2Cl_2); IR (KBr) 3243, 1462, 1314, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, *J* = 7.4 Hz, 3H), 3.48–3.54 (m, 1H), 3.66 (s, 1H), 3.83–3.89 (m, 1H), 7.20 (d, *J* = 1.1 Hz, 1H), 7.33–7.36 (m, 5H), 7.39 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 38.8, 96.8, 122.6, 125.9, 126.1, 128.8, 129.1, 130.3, 134.9, 136.4, 138.8, 147.4, 190.5. HR-MS (DART). Calcd for $C_{16}H_{15}ClNOS$ (M+H): 304.0563. Found: *m/z* 304.0551. Anal. Calcd for $C_{16}H_{14}ClNOS$: C, 63.26; H, 4.65; N, 4.61. Found: C, 63.20; H, 4.69; N, 4.57.

2-Ethyl-3-hydroxy-4,5,6-trimethoxy-3-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (3m): a yellow solid; mp 144–154 °C (hexane/CH_2Cl_2); IR (KBr) 3283, 1610, 1485, 1341, 1109 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (t, *J* = 6.9 Hz, 3H), 3.36 (s, 3H), 3.45–3.50 (m, 1H), 3.61 (s, 1H), 3.80–3.87 (m including s at 3.84, 4H), 3.97 (s, 3H), 7.32–7.37 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 12.7, 38.5, 56.5, 60.5, 61.0, 96.4, 103.4, 126.0, 128.4, 128.7, 130.8, 132.6, 137.4, 145.8, 147.7, 155.8, 191.0. HR-MS (DART). Calcd for $C_{19}H_{22}NO_4S$ (M+H): 360.1269. Found: *m/z* 360.1255.

3-Hydroxy-2,3-diphenyl-2,3-dihydro-1*H*-isoindole-1-thione (3n): a pale-yellow solid; mp 176–178 °C (hexane/CH_2Cl_2); IR (KBr) 3237, 1407, 1306, 1042 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.08 (d, J = 7.4 Hz, 2H), 7.19 (d, J = 7.4 Hz, 2H), 7.25–7.32 (m, 7H), 7.61 (t, J = 7.4 Hz, 1H), 7.66 (t, J = 7.4 Hz, 1H), 7.96 (br s, 1H), 8.00 (d, J = 7.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 98.5, 122.7, 124.8, 125.9, 127.9, 128.3, 128.36, 128.44, 129.0, 129.7, 133.0, 136.4, 137.1, 138.3, 146.6, 193.1. HR-MS (DART). Calcd for $C_{20}H_{16}NOS$ (M+H): 318.0952. Found: *m/z* 318.0939. Anal. Calcd for $C_{20}H_{15}NOS$: C, 75.68; H, 4.76; N, 4.41. Found: C, 75.39; H, 4.77; N, 4.51.

3-Hydroxy-2-(3-methoxyphenyl)-3-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (3o): a pale-yellow solid; mp 168–171 °C (hexane/CH_2Cl_2); IR (KBr) 3295, 1599, 1452, 1299, 1043 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59 (s, 3H), 4.15 (br, 1H), 6.60 (dd, J = 2.3, 1.7 Hz, 1H), 6.69 (dd, J = 8.0, 1.7 Hz, 1H), 6.83 (dd, J = 8.0, 2.3 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.26 (s, 5H), 7.30 (d, J = 7.4 Hz, 1H), 7.49 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 8.07 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.1, 98.5, 114.3, 114.5, 121.2, 122.5, 125.7, 126.2, 128.2, 128.7, 129.3, 130.1, 132.8, 136.9, 137.4, 137.7, 145.6, 159.6, 194.2. HR-MS (DART). Calcd for $C_{21}H_{18}NO_2S$ (M+H): 348.1058. Found: *m/z* 348.1044. Anal. Calcd for $C_{21}H_{17}NO_2S$: C, 72.60; H, 4.93; N, 4.03. Found: C, 72.59; H, 4.88; N, 3.99.

2-Ethyl-3-hydroxy-3-phenyl-2,3-dihydro-1*H*-benzo[*g*]isoindole-1-thione (3p): a yellow solid; mp 123–125 °C (hexane/CH_2Cl_2); IR (KBr) 3304, 1452, 1221, 1063 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (t, J = 7.4 Hz, 3H), 3.49–3.55 (m, 2H), 3.88–3.95 (m, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.29–7.35 (m, 5H), 7.54 (ddd, J = 7.4, 6.9, 1.1 Hz, 1H), 7.68 (ddd, J = 7.4, 6.9, 1.1 Hz, 1H), 7.81 (t, J = 7.4 Hz, 2H), 10.29 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.6, 38.2, 96.0, 118.8, 124.9, 126.0 (2 overlapped Cs), 126.7, 128.5, 128.6, 128.7, 128.8, 129.6, 133.8, 134.6, 136.8, 147.0, 192.6. HR-MS (DART). Calcd for $C_{20}H_{18}NOS$ (M+H): 320.1109. Found: *m/z* 320.1094. Anal Calcd for $C_{20}H_{17}NOS$: C, 75.20; H, 5.36; N, 4.39; S, 10.04. Found: C, 75.08; H, 5.63; N, 4.31; S, 9.92.

2-Ethyl-3-hydroxy-3-phenyl-2,3-dihydro-1*H*-benzo[*e*]isoindole-1-thione (3q): a yellow solid; mp 117–120 °C (hexane/CH_2Cl_2); IR (KBr) 3247, 1477, 1204, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.4 Hz, 3H), 3.51–3.58 (m, 2H), 3.92–3.99 (m, 1H), 7.32–7.39 (m, 5H), 7.49–7.53 (m, 2H), 7.61 (s, 1H), 7.74 (dd, J = 9.2, 4.0 Hz, 1H), 7.95 (dd, J = 9.2, 4.0 Hz, 1H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 38.9, 97.0, 121.7, 125.7, 126.1, 127.1, 128.0, 128.5, 128.6, 128.9, 129.8, 133.8, 134.7, 135.2, 138.0, 142.1, 191.2. HR-MS (DART). Calcd for $C_{20}H_{18}NOS$ (M+H): 320.1109. Found: *m/z* 320.1094. Anal Calcd for $C_{20}H_{17}NOS$: C, 75.20; H, 5.36; N, 4.39; S, 10.04. Found: C, 74.98; H, 5.33; N, 4.31; S, 9.72.

2-Ethyl-3-hydroxy-3-phenyl-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-thione (3q'): a yellow solid; mp 150–152 °C (hexane/CH_2Cl_2); IR (KBr) 3252, 1456, 1196, 1047 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7.4 Hz, 3H), 3.58 (s, 1H), 3.60–3.65 (m, 1H), 3.86–3.90 (m, 1H), 7.30–7.31 (m, 3H), 7.39–7.42 (m, 3H), 7.51

(ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.9, 38.2, 97.2, 120.9, 124.6, 125.9, 126.1, 127.5, 127.6, 128.7, 128.89, 128.94, 131.0, 134.4, 135.8, 137.1, 141.7, 191.7. HR-MS (DART). Calcd for $C_{20}H_{18}NOS$ (M+H): 320.1109. Found: *m/z* 320.1095. Anal Calcd for $C_{20}H_{17}NOS$: C, 75.20; H, 5.36; N, 4.39; S, 10.04. Found: C, 75.16; H, 5.38; N, 4.28; S, 9.77.

Typical Procedure for the Preparation of 3-Methoxy-2,3-dihydro-1*H*-isoindole-1-thiones (4). 2-Ethyl-3-methoxy-3-(4-methylphenyl)-2,3-dihydro-1*H*-isoindole-1-thione (4d). To a stirred suspension of NaH (60% in mineral oil; 11 mg, 0.28 mmol) in DMF (2 mL) at 0 ˚C was added dropwise a solution of **3d** (79 mg, 0.28 mmol) in DMF (1 mL). After evolution of H_2 gas had ceased, MeI (40 mg, 0.28 mmol) was added and stirring was continued for 15 min at the same temperature. The mixture was worked up as described for the preparation of **3a** and the crude product was purified by column chromatography on SiO_2 to give **4d** (67 mg, 76%); a yellow viscous oil; R_f 0.43 (AcOEt/hexane 1:20); IR (neat) 1407, 1073 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J* = 7.4 Hz, 3H), 2.32 (s, 3H), 2.99 (s, 3H), 3.57–3.61 (m, 1H), 3.78–3.82 (m, 1H), 7.10–7.13 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.47–7.51 (m, 2H), 8.08 (dd, *J* = 6.9, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.9, 21.1, 38.4, 51.2, 101.6, 122.3, 125.0, 126.0, 129.1, 129.8, 132.0, 134.4, 138.1, 138.6, 142.5, 193.2. HR-MS (DART). Calcd for $C_{18}H_{20}NOS$ (M+H): 298.1265. Found: *m/z* 298.1251.

3-(2-Chloropyridin-3-yl)-2-ethyl-3-methoxy-2,3-dihydro-1*H*-isoindole-1-thione (4i): a yellow gum; R_f 0.28 (AcOEt/hexane 1:3); IR (neat) 1398, 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.4 Hz, 3H), 3.56–3.70 (m, 2H), 2.88 (s, 3H), 6.96 (d, *J* = 6.9 Hz, 1H), 7.39 (dd, *J* = 8.0, 4.6 Hz, 1H), 7.45–7.51 (m, 2H), 8.03 (d, *J* = 7.4 Hz, 1H), 8.39 (dd, *J* = 4.6, 1.7 Hz, 1H), 8.63 (dd, *J* = 8.0, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.5, 38.2, 50.2, 98.0, 121.6, 122.4, 124.9, 130.4, 131.5, 132.1, 139.1, 139.4, 140.0, 149.2, 149.8, 195.2. HR-MS (DART). Calcd for $C_{16}H_{16}ClN_2OS$ (M+H): 319.0672. Found: *m/z* 319.0657.

2-Ethyl-3,4,5,6-tetramethoxy-3-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (4m): a yellow gum; R_f 0.39 (AcOEt/hexane 1:7); IR (neat) 1609, 1347, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, *J* = 7.4 Hz, 3H), 3.07 (s, 3H), 3.33 (s, 3H), 3.52–3.56 (m, 1H), 3.72–3.76 (m, 1H), 3.86 (s, 3H), 3.99 (s, 3H), 7.31–7.36 (m, 5H), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.9, 38.4, 51.4, 56.4, 60.1, 60.9, 101.0, 103.4, 126.2, 126.9, 128.2, 128.6, 133.8, 137.4, 145.8, 148.0, 156.0, 192.3. HR-MS (DART). Calcd for $C_{20}H_{24}NO_4S$ (M+H): 374.1426. Found: *m/z* 374.1410.

3-Hydroxy-3-(3-hydroxypropyl)-2-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (5): a yellow solid; mp 163–165 ˚C (hexane/THF); IR (KBr) 3391, 3251, 1378, 1110 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.86–0.90 (m, 1H), 1.21–1.23 (m, 1H), 1.70–1.76 (m, 1H), 1.99–2.08 (m, 1H), 2.49 (t, *J* = 1.7 Hz, 1H), 3.19 (t, *J* = 6.3 Hz, 2H), 4.35 (br, 1H), 7.41 (d, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.72 (td, *J* = 7.4, 1.1 Hz, 1H), 7.92 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 26.3,

33.1, 60.2, 98.9, 122.2, 124.6, 128.2, 128.9, 129.0, 129.5, 132.5, 136.8, 137.0, 144.3, 192.7. HR-MS (DART). Calcd for $C_{17}H_{18}NO_2S$ (M+H): 300.1047. Found: *m/z* 300.1058. Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 67.97; H, 5.77; N, 4.63.

2-Bromo-*N*-ethylpyridine-3-carothioamide (6a). 2-Bromo-3-lithiopyridine was generated by treating 2-bromopyridine (0.47 g, 3.0 mmol) with LDA (6.0 mmol), generated from *i*-Pr_2NH (0.61 g, 6.0 mmol) and *n*-BuLi (1.6 M in hexane; 6.0 mmol) by the standard method, in THF (10 mL) at –78 ˚C as described previously,[4] and allowed to react with EtNCS (0.25 g, 3.0 mmol). After 15 min, the mixture was worked up as described for the preparation of **3a**. The residue was purified by column chromatography on SiO_2 (Et_2O/hexane 1:4) to give **6a** (0.40 g, 54%); a white solid; mp 97–100 ˚C (hexane/CH_2Cl_2); IR (KBr) 3212, 1387, 1051 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t, *J* = 7.4 Hz, 3H), 3.83–3.88 (m, 2H), 7.29 (dd, *J* = 7.4, 4.6 Hz, 1H), 7.80 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.82 (br s, 1H), 8.29 (dd, *J* = 4.6, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 41.4, 122.8, 136.5, 138.1, 141.1, 150.0, 195.6. HR-MS (DART). Calcd for $C_8H_{10}BrN_2S$ (M+H): 244.9748. Found: *m/z* 244.9739.

Typical Procedure for the Preparation of 3-Hydroxypyrrolopyridine-1-thiones (7). 2-Ethyl-3-hydroxy-3-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]pyridine-1-thione (7a). To a stirred solution of **6a** (0.14 g, 0.59 mmol) in THF (10 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 1.2 mmol) dropwise. After 3 min, $PhCO_2Et$ (88 mg, 0.59 mmol) was added and stirring was continued for an additional 10 min. The mixture was worked up as described for the preparation of **3a**, and the residue was purified by column chromatography on SiO_2 (AcOEt/hexane 1:2) to give **7a** (89 mg, 56%); a yellow solid; mp 130–132 ˚C (hexane/CH_2Cl_2); IR (KBr) 3110, 1604, 1409, 1062 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.4 Hz, 3H), 3.56–3.60 (m, 1H), 4.07–4.11 (m, 1H), 6.21 (s, 1H), 7.24 (dd, *J* = 7.4, 4.6 Hz, 1H), 7.36–7.41 (m, 5H), 8.18–8.21 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.8, 39.0, 96.4, 124.8, 126.1, 128.8, 129.2, 131.0, 133.6, 136.3, 151.3, 163.6, 189.3. HR-MS (DART). Calcd for $C_{15}H_{15}N_2OS$ (M+H): 271.0905. Found: *m/z* 271.0892. Anal Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.37; H, 5.13; N, 10.34; S, 12.24.

2-Ethyl-3-hydroxy-3-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-1-thione (7b): a yellow solid; mp 171–173 ˚C (hexane/CH_2Cl_2); IR (KBr) 3091, 1609, 1464, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, *J* = 7.4 Hz, 3H), 3.47–3.54 (m, 1H), 3.92–3.99 (m, 1H), 7.18 (br s, 1H), 7.34–7.37 (m, 5H), 7.68 (d, *J* = 4.6 Hz, 1H), 8.11 (s, 1H), 8.14 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 38.8, 97.6, 118.7, 125.8, 128.9, 129.3, 136.4, 141.1, 143.1, 143.8, 149.4, 188.3. HR-MS (DART). Calcd for $C_{15}H_{15}N_2OS$ (M+H): 271.0905. Found: *m/z* 271.0894. Anal Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.55; H, 5.13; N, 10.38; S, 11.92.

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