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SYNTHESIS OF BENZO[*c*]THIOPHEN-1(3*H*)-IMINE AND 2,3-DIHYDRO-1*H*-ISOINDOLE-1-THIONE DERIVATIVES THROUGH CYCLIZATIONS OF 2-(1-HYDROXYALKYL)BENZOTHIOAMIDES

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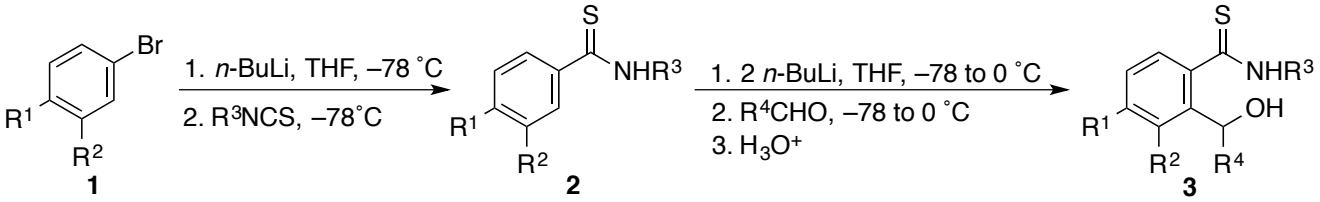
Abstract – The reaction of *N*-alkyl-2,*N*-dilithiobenzothioamides, generated by treating *N*-alkylbenzothioamides with two equivalents of butyllithium, with aldehydes gives the corresponding 2-(1-hydroxyalkyl)benzothioamides, which undergo cyclization on treatment with methanesulfonyl chloride in the presence of triethylamine to yield 3,*N*-disubstituted (*Z*)-benzo[*c*]thiophen-1(3*H*)-imines. 2,3-Disubstituted 2,3-dihydro-1*H*-isoindole-1-thiones are obtained by the reaction of the above hydroxy thioamides with two equivalents of sodium hydride followed by an equivalent of phenyl chloroformate.

Benzo[*c*]thiophen-1(3*H*)-imine derivatives have been previously synthesized due to their synthetic and medicinal importance.[1] In this paper we wish to report our results on a novel approach to the synthesis of 3,*N*-disubstituted (*Z*)-benzo[*c*]thiophen-1(3*H*)-imines (**4**) based on methanesulfonyl chloride-mediated cyclization of 2-(1-hydroxyalkyl)benzothioamides (**3**), derived from the reaction of *N*-alkyl-2,*N*-dilithiobenzothioamides with aldehydes. In addition, it is described that 2,3-disubstituted 2,3-dihydro-1*H*-isoindole-1-thiones (**5**) can be prepared by successive treatment of **3** with sodium hydride and phenyl chloroformate. The reaction of 2,3-dihydro-1*H*-isoindol-1-ones with phosphorous pentasulfide has been known as the commonly used method for the preparation of 2,3-dihydro-1*H*-isoindole-1-thiones,[2] though we have recently reported the synthesis of 2,3-dihydro-1*H*-isoindole-1-thione derivatives by cyclization of 1-(2-lithiophenyl)alkyl isothiocyanates.[3] 2,3-Dihydro-1*H*-isoindole-1-thione derivatives are also of biologically importance.[4]

The *N*-alkylbenzothioamides (**2**) used in this study were prepared by the reaction of aryllithiums, generated by the bromine/lithium exchange between bromobenzenes (**1**) and butyllithium, with alkyl

isothiocyanates in THF at –78 ˚C in generally good yields as compiled in Table 1, and were converted into 2-(1-hydroxyalkyl)benzothioamides (**3**), as illustrated in Scheme 1. Thus, treatment of compounds (**2**) with two equivalents of butyllithium in THF at –78 to 0 ˚C generated *N*-alkyl-2,*N*-dilithiobenzothioamides, which were allowed to react with aldehydes at –78 to 0 ˚C to afford, after aqueous workup, hydroxy thioamides (**3**) in relatively good yields as listed in Table 2, though the use of propanal caused a slight diminish of the yield (Entry 4), probably due to deprotonation of its α-hydrogen with the dilithio compound.



Scheme 1

Table 1. Preparation of *N*-substituted benzothioamides (**2**)

Entry	**1**	R^1	R^2	R^3 in R^3NCS	**2**	Yield/%[a]
1	**1a**	H	H	Et	**2a**	75
2	**1a**	H	H	*n*-Bu	**2b**	84
3	**1b**	Cl	H	Et	**2c**	69
4	**1c**	MeO	H	Et	**2d**	91
5	**1d**	H	MeO	Et	**2e**	78

[a] Yields of isolated products.

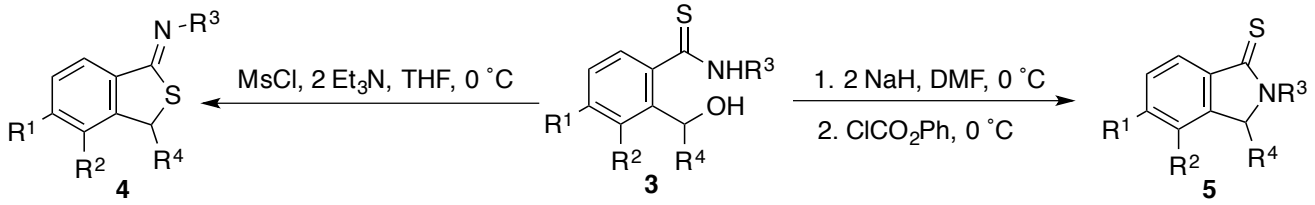
Table 2. Preparation of *N*-alkyl-2-[aryl(hydroxy)methyl]benzothioamides (**3**)

Entry	**2**	R^1	R^2	R^3	R^4 in R^4CHO	**3**	Yield/%[a]
1	**2a**	H	H	Et	Ph	**3a**	90
2	**2a**	H	H	Et	4-ClC_6H_4	**3b**	70
3	**2a**	H	H	Et	4-$MeOC_6H_4$	**3c**	88
4	**2a**	H	H	Et	Et	**3d**	58
5	**2b**	H	H	*n*-Bu	Ph	**3e**	70
6	**2b**	H	H	*n*-Bu	pyridin-3-yl	**3f**	73
7	**2c**	Cl	H	Et	Ph	**3g**	94
8	**2d**	MeO	H	Et	Ph	**3h**	70
9	**2e**	H	MeO	Et	Ph	**3i**	64

[a] Yields of isolated products.

The transformation **3** into 3,*N*-disubstituted (*Z*)-benzo[*c*]thiophen-1(3*H*)-imines (**4**) was conducted as shown in Scheme 2. Cyclization of **3** with methanesulfonyl chloride in the presence of triethylamine in THF proceeded rapidly and cleanly at 0 ˚C to give the desired products (**4**) as the sole stereoisomers. The benzo[*c*]thiophen-1(3*H*)-imine structures of these compounds were established unambiguously by direct

comparison of **4e** with a sample prepared in the previous work,[1g] in which geometry of the imino moiety was assumed to be *Z* on the basis of NOESY analyses. As can be seen from the results listed in Table 3, generally good yields of the products were obtained. However, the yield of product (**4g**) carrying an electron-withdrawing chloro substituent at the 5-position is somewhat lower than those of the others (Entry 7). This may be ascribed to the lower nucleophilicity of the thioamide moiety of **3g** owing to the chloro substituent.



Scheme 2

Table 3. Preparation of benzo[*c*]phiophen-1-imines (**4**) and 1*H*-isoindole-1-thiones (**5**)

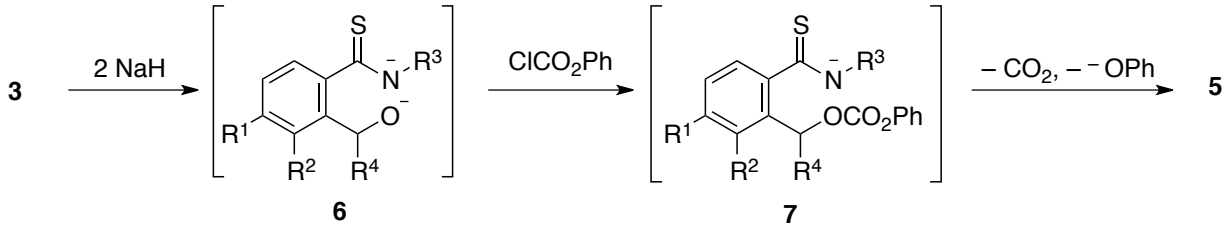
Entry	**3**	R^1	R^2	R^3	R^4	**4**	Yield/%[a]	**5**	Yield/%[a]
1	**3a**	H	H	Et	Ph	**4a**	77	**5a**	61
2	**3b**	H	H	Et	4-ClC_6H_4	**4b**	85	**5b**	51
3	**3c**	H	H	Et	4-$MeOC_6H_4$	**4c**	71	**5c**	50
4	**3d**	H	H	Et	Et	**4d**	73	**5d**	37
5	**3e**	H	H	*n*-Bu	Ph	**4e**	70	**5e**	41
6	**3f**	H	H	*n*-Bu	pyridin-3-yl	**4f**	83	**5f**	38
7	**3g**	Cl	H	Et	Ph	**4g**	67	**5g**	47
8	**3h**	MeO	H	Et	Ph	**4h**	79	**5h**	48
9	**3i**	H	MeO	Et	Ph	**4i**	78	**5i**	b

[a] Yields of isolated products. [b] An inseparable mixture of **4i** and **5i** (*ca*. 1:1) was obtained judging from its ^{1}H NMR spectrum.

We conceived that the reaction of a chloroformate with the *N*,*O*-dianion intermediates derived from **3** would result in the formation of 2,3-disubstituted 2,3-dihydro-1*H*-isoindole-1-thiones (**5**). In fact, addition of phenyl chloroformate to the dianion intermediates, generated by the treatment of **3** with two equivalents of sodium hydride in DMF at 0 ˚C, provided the desired products (**5**). Although consumption of the starting materials completed within 1.5 h, generally only moderate yields were obtained, as compiled in Table 3 as well. The product (**5d**) from the precursor derived from propanal (**3d**) was, however, obtained in only a lower yield (Entry 4). In the case of using *N*-butyl-thioamide precursors (**3e**) and (**3f**), the yields of the desired products (**5e)** and (**5f**), respectively, were also somewhat lower (Entries 5 and 6) than those using *N*-ethyl-thioamides, probably due to a bulkier butyl substituent. It should be noted that the use of methyl chloroformate or dimethyl carbonate in place of phenyl chloroformate gave poorer results. In these cases, rather complicated mixtures of products were obtained. We also should note

that the reaction of **3i** with phenyl chloroformate under the same conditions gave an inseparable mixture of **4i** and **5i** (Entry 9).

A probable mechanism for the formation of **5** from **3** is shown in Scheme 3. Thus, the *N*,*O*-dianion intermediate (**6**), generated by treating **3** with two equivalents of sodium hydride, is *O*-phenoxycarbonylated with phenyl chloroformate to give the carbonate intermediate (**7**). The amide anion of **7** attacks on the benzyl carbon to provide **5** with losses of carbon dioxide and phenoxide.



Scheme 3

In conclusion, we have demonstrated that benzo[*c*]thiophen-1(3*H*)-imine and 2,3-dihydro-1*H*-isoindole-1-thione derivatives, can be prepared in reasonable yields *via* the same precursors, which are derived from readily available starting materials by simple manipulations. These heterocyclic compounds are hard to prepare by previous methods and may be of biological interest.

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 JEOL JMS-T100GCV (EI, TOF; 70 eV) or a Thermo Scientific Exactive (ESI) 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. Butyllithium was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of *N*-Substituted Thiobenzamides (2). *N*-Ethylbenzothioamide (2a).[5] To a stirred solution of C_6H_5Br (0.31 g, 2.0 mmol) in THF (4 mL) at –78 °C was added *n*-BuLi (1.6 M in hexane; 2.0 mmol) dropwise. After 15 min, EtNCS (0.17 g, 2.0 mmol) was added and the mixture was gradually warmed to 0 °C. Stirring was continued for 2 h at the same

temperature before addition of saturated aqueous NH_4Cl (10 mL) and the resulting 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 **2a** (0.25 g, 75%); a yellow liquid; R_f 0.43 (Et_2O/hexane 1:1). The ^1H NMR data for this compound was identical to those reported previously.[6]

***N*-Butylbenzothioamide (2b):**[7] yield: 84%; a yellow liquid; R_f 0.28 (Et_2O/hexane 1:3). The ^1H NMR data for this compound was identical to those reported previously.[8]

4-Chloro-*N*-ethylbenzothioamide (2c):[9] yield: 69%; a yellow solid; mp 47–48 ˚C (hexane); IR (KBr) 3242, 1529, 1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t, *J* = 7.4 Hz, 3H), 3.83–3.88 (m, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.47 (br, 1H), 7.69 (d, *J* = 8.6 Hz, 2H).

***N*-Ethyl-4-methoxybenzothioamide (2d):**[10] yield: 91%; yellow needles; mp 75–77 ˚C (hexane/CH_2Cl_2); IR (KBr) 3328, 1605, 1535, 1258 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (t, *J* = 7.4 Hz, 3H), 3.84 (s, 3H), 3.86 (q, *J* = 7.4 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.43 (br, 1H), 7.76 (d, *J* = 8.6 Hz, 2H).

***N*-Ethyl-3-methoxybenzothioamide (2e):** yield: 78%; a yellow solid; mp 70–72 ˚C (hexane/CH_2Cl_2); IR (KBr) 3306, 1530, 1258 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (t, *J* = 7.4 Hz, 3H), 3.83 (q, *J* = 7.4 Hz, 2H), 3.84 (s, 3H), 6.99 (ddd, *J* = 8.0, 1.7, 1.1 Hz, 1H), 7.22 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 1.7, 1.1 Hz, 1H), 7.57 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 41.6, 55.4, 112.5, 117.0, 118.0, 129.4, 143.3, 159.4, 198.7. HR-MS (EI). Calcd for $C_{10}H_{13}NOS$ (M): 195.0718. Found: *m/z* 195.0722.

Typical Procedure for the Preparation of *N*-Substituted 2-(1-Hydroxyalkyl)benzothioamides (3). *N*-Ethyl-2-[hydroxy(phenyl)methyl]benzothioamide (3a). To a stirred solution of **2a** (0.42 g, 2.5 mmol) in THF (6 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 5.1 mmol) dropwise and the mixture was gradually warmed to 0 ˚C. After 1.5 h stirring at the same temperature, it was cooled to –78 ˚C and treated with PhCHO (0.27 g, 2.5 mmol), then temperature was gradually raised to 0 ˚C. The mixture worked up as described for the preparation of **2a**. The residue was purified by column chromatography on SiO_2 to give **3a** (0.62 g, 90%); a yellow oil; R_f 0.26 (AcOEt/hexane 1:1); IR (neat) 3347, 3245, 1531, 1244 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.4 Hz, 3H), 3.52 (br s, 1H), 3.59–3.72 (m, 2H), 6.12 (s, 1H), 7.26–7.36 (m, 9H), 7.53 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.8, 41.3, 73.0, 126.6, 127.27, 127.30, 127.9, 128.2, 128.8, 129.6, 139.5, 142.5, 143.3, 199.8. HR-MS (ESI, negative). Calcd for $C_{16}H_{16}NOS$ (M–H): 270.0953. Found: *m/z* 270.0965.

2-[(4-Chlorophenyl)(hydroxy)methyl]-*N*-ethylbenzothioamide (3b): a white solid; mp 126–128 ˚C (hexane/CH_2Cl_2); IR (KBr) 3403, 3241, 1541, 1247 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, *J* = 7.4 Hz, 3H), 3.65–3.74 (m, 3H), 6.11 (s, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.28–7.35 (m, 7H), 7.51 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.9, 41.3, 72.4, 127.0, 128.0, 128.1, 128.2, 129.0, 129.7, 132.9, 139.6, 141.0, 143.2, 199.7.

Anal. Calcd for $C_{16}H_{16}ClNOS$: C, 62.84; H, 5.27; N, 4.58. Found: C, 62.73; H, 5.29; N, 4.54.

***N*-Ethyl-2-[(hydroxy)(4-methoxyphenyl)methyl]benzothioamide (3c):** a pale-yellow solid; mp 105–107 °C (hexane/CH_2Cl_2); IR (KBr) 3214, 1609, 1508, 1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, *J* = 7.4 Hz, 3H), 3.55 (br, 1H), 3.58–3.72 (m, 2H), 3.79 (s, 3H), 6.05 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.25–7.33 (m, 4H), 7.68 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 41.2, 55.3, 72.4, 113.6, 127.3, 127.76, 127.79, 128.4, 129.5, 134.7, 139.6, 143.1, 158.0, 199.8. Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.75; H, 6.35; N, 4.65. Found: C, 67.74; H, 6.50; N, 4.56.

***N*-Ethyl-2-(1-hydroxypropyl)benzothioamide (3d):** a yellow oil; R_f 0.27 (AcOEt/hexane 1:2); IR (neat) 3217, 1532, 1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.34 (t, *J* = 7.4 Hz, 3H), 1.78–1.95 (m, 2H), 3.08 (br s, 1H), 3.80–3.85 (m, 2H), 4.71 (t, *J* = 7.4 Hz, 1H), 7.27 (td, *J* = 7.4, 1.7 Hz, 1H), 7.36–7.38 (m, 2H), 7.41 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.11 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 10.8, 13.0, 28.9, 41.3, 72.3, 126.5, 127.5, 127.7, 129.7, 139.0, 143.3, 200.0. HR-MS (EI). Calcd for $C_{12}H_{17}NOS$ (M): 223.1031. Found: *m/z* 223.1018.

***N*-Butyl-2-[hydroxy(phenyl)methyl]benzothioamide (3e):** a yellow oil; R_f 0.24 (AcOEt/hexane 2:3); IR (neat) 3222, 1531, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.30–1.39 (m, 2H), 1.52–1.57 (m, 2H), 3.57 (d, *J* = 4.0 Hz, 1H), 3.60–3.68 (m, 2H), 6.11 (d, *J* = 4.0 Hz, 1H), 7.26–7.33 (m, 9H), 7.61 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.2, 29.8, 46.2, 72.9, 126.5, 127.2, 127.3, 127.9, 128.2, 128.8, 129.6, 139.6, 142.5, 143.4, 199.9. HR-MS (EI). Calcd for $C_{18}H_{21}NOS$ (M): 299.1344. Found: *m/z* 299.1348.

***N*-Butyl-2-[hydroxy(pyridin-3-yl)methyl]benzothioamide (3f):** a yellow solid; mp 142–144 °C (hexane/THF); IR (KBr) 3216, 1547, 1220 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.87 (t, *J* = 7.4 Hz, 3H), 1.26–1.31 (m, 2H), 1.51–1.54 (m, 2H), 3.55–3.59 (m, 2H), 5.94 (d, *J* = 4.6 Hz, 1H), 6.23 (d, *J* = 4.6 Hz, 1H), 7.07 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.25–7.29 (m, 2H), 7.36 (td, *J* = 7.4, 1.1 Hz, 1H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.64 (dt, *J* = 8.0, 1.7 Hz, 1H), 8.38 (dd, *J* = 5.2, 1.7 Hz, 1H), 8.47 (d, *J* = 1.7 Hz, 1H), 10.25 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.7, 19.7, 29.0, 45.1, 68.0, 123.1, 126.2, 126.78, 126.83, 128.4, 134.0, 139.7, 140.2, 142.4, 147.9, 148.1, 197.9. Anal. Calcd for $C_{17}H_{20}N_2OS$: C, 67.97; H, 6.71; N, 9.32; S, 10.67. Found: C, 67.77; H, 6.75; N, 9.13; S, 10.49.

4-Chloro-*N*-ethyl-2-[hydroxy(phenyl)methyl]benzothioamide (3g): a yellow oil; R_f 0.31 (Et_2O/hexane 1:4); IR (neat) 3218, 1532, 1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (t, *J* = 7.4 Hz, 3H), 3.54–3.69 (m, 3H), 6.07 (s, 1H), 7.25–7.35 (m, 8H), 7.55 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 41.3, 72.4, 126.6, 127.7, 128.0, 128.4, 128.57, 128.65, 128.66, 135.4, 141.3, 141.7, 198.4. HR-MS (ESI, positive). Calcd for $C_{16}H_{17}ClNOS$ (M+H): 306.0719. Found: *m/z* 306.0713.

***N*-Ethyl-2-[hydroxy(phenyl)methyl]-4-methoxybenzothioamide (3h):** a yellow oil; R_f 0.24

(Et_2O/hexane 1:2); IR (neat) 3345, 3219, 1605, 1532, 1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (t, *J* = 7.4 Hz, 3H), 3.55–3.70 (m, 2H), 3.74 (s, 3H), 3.83 (d, *J* = 4.6 Hz, 1H), 6.08 (d, *J* = 4.6 Hz, 1H), 6.77 (s, 1H), 6.79 (dd, *J* = 6.9, 2.8 Hz, 1H), 7.24–7.36 (m, 6H), 7.72 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.9, 41.4, 55.3, 72.9, 112.8, 114.5, 126.5, 127.3, 128.2, 129.3, 135.9, 141.5, 142.1, 160.4, 199.3. HR-MS (ESI, positive). Calcd for $C_{17}H_{20}NO_2S$ (M+H): 302.1214. Found: *m*/*z* 302.1210.

***N*-Ethyl-2-[hydroxy(phenyl)methyl]-3-methoxybenzothioamide (3i):** a yellow solid; mp 38–40 °C (pentane); IR (KBr) 3545, 3211, 1528, 1248 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.4 Hz, 3H), 3.41–3.50 (m, 1H), 3.53–3.61 (m, 1H), 3.72 (s, 3H), 4.20 (d, *J* = 5.7 Hz, 1H), 6.18 (d, *J* = 5.7 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.25–7.30 (m, 5H), 7.38 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 41.1, 55.9, 69.9, 112.1, 120.3, 125.7, 126.5, 127.3, 127.8, 129.0, 143.8, 144.7, 157.5, 199.5. HR-MS (ESI, positive). Calcd for $C_{17}H_{20}NO_2S$ (M+H): 302.1214. Found: *m*/*z* 302.1208.

Typical Procedure for the Preparation of *N*-alkylbenzo[*c*]thiophen-1(3*H*)-imines (4). (*Z*)-*N*-Ethyl-3-phenylbenzo[*c*]thiophen-1(3*H*)-imine (4a). To a stirred solution of **3a** (0.31 g, 1.1 mmol) in THF (3 mL) containing Et_3N (0.23 g, 2.3 mmol) at 0 °C was added MsCl (0.13 g, 1.1 mmol) dropwise. After 15 min, saturated $NaHCO_3$ (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 (AcOEt/hexane 1:3) to give **4a** (0.22 g, 77%); a pale-yellow solid; mp 81–83 °C (hexane/CH_2Cl_2); IR (KBr) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, *J* = 7.4 Hz, 3H), 3.46–3.57 (m, 2H), 5.85 (s, 1H), 7.12 (dd, *J* = 8.6, 3.4 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 2H), 7.27–7.33 (m, 3H), 7.37–7.39 (m, 2H), 7.96 (dd, *J* = 9.2, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.4, 52.0, 55.7, 122.9, 125.9, 127.86, 127.94, 128.2, 128.8, 130.8, 137.6, 141.0, 147.7, 165.4. HR-MS (EI). Calcd for $C_{16}H_{15}NS$ (M): 253.0925. Found: *m*/*z* 253.0926.

3-(4-Chlorophenyl)-(*Z*)-*N*-ethylbenzo[*c*]thiophen-1(3*H*)-imine (4b): a yellow oil; R_f 0.62 (AcOEt/hexane 1:6); IR (neat) 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, *J* = 7.4 Hz, 3H), 3.46–3.57 (m, 2H), 5.82 (s, 1H), 7.09 (dd, *J* = 8.6, 3.4 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.38–7.40 (m, 2H), 7.96 (dd, *J* = 9.2, 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.3, 52.0, 54.9, 123.1, 125.8, 128.1, 129.0, 129.6, 131.0, 133.8, 137.5, 139.7, 147.2, 164.9. HR-MS (EI). Calcd for $C_{16}H_{14}ClNS$ (M): 287.0535. Found: *m*/*z* 287.0536. Anal. Calcd for $C_{16}H_{14}ClNS$: C, 66.77; H, 4.90; N, 4.87. Found: C, 66.16; H, 4.99; N, 4.92.

(*Z*)-*N*-Ethyl-3-(4-methoxyphenyl)benzo[*c*]thiophen-1(3*H*)-imine (4c): a white solid; mp 70–72 °C (hexane/CH_2Cl_2); IR (KBr) 1642, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, *J* = 7.4 Hz, 3H), 3.46–3.57 (m, 2H), 3.79 (s, 3H), 5.83 (s, 1H), 6.84 (d, *J* = 9.2 Hz, 2H), 7.11–7.12 (m, 1H), 7.15 (d, *J* = 9.2 Hz, 2H), 7.36–7.39 (m, 2H), 7.94–7.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.4, 52.0, 55.28, 55.30, 114.2, 122.9, 125.8,

127.8, 129.4, 130.8, 132.9, 137.6, 148.0, 159.3, 165.6. HR-MS (EI). Calcd for $C_{17}H_{17}NOS$ (M): 283.1031. Found: *m/z* 283.1025. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 71.86; H, 5.99; N, 4.83.

(*Z*)-3,*N*-Diethylbenzo[*c*]thiophen-1(3*H*)-imine (4d): a colorless oil; R_f 0.47 (AcOEt/hexane 1:10); IR (neat) 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, *J* = 7.4 Hz, 3H), 1.39 (t, *J* = 7.4 Hz, 3H), 1.76–1.85 (m, 1H), 2.20–2.28 (m, 1H), 3.47–3.57 (m, 2H), 4.76 (dd, *J* = 9.2, 3.4 Hz, 1H), 7.34–7.38 (m, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.6, 15.3, 30.2, 51.8, 54.0, 122.9, 124.3, 127.7, 130.5, 137.8, 147.6, 165.7. HR-MS (EI). Calcd for $C_{12}H_{15}NS$ (M): 205.0925. Found: *m/z* 205.0916. Anal. Calcd for $C_{12}H_{15}NS$: C, 70.20; H, 7.36; N, 6.82. Found: C, 70.00; H, 7.47; N, 6.68.

(*Z*)-*N*-Butyl-3-phenylbenzo[*c*]thiophen-1(3*H*)-imine (4e):[1g] a yellow oil; R_f 0.66 (AcOEt/hexane 1:6). The spectral (IR, ^1H and ^{13}C NMR) data were identical to those reported previously.[1g]

(*Z*)-*N*-Butyl-3-(pyridin-3-yl)benzo[*c*]thiophen-1(3*H*)-imine (4f): an orange oil; R_f 0.36 (AcOEt/hexane 1:2); IR (neat) 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.45–1.52 (m, 2H), 1.76–1.82 (m, 2H), 3.44–3.53 (m, 2H), 5.85 (s, 1H), 7.09 (dd, *J* = 4.6, 4.0 Hz, 1H), 7.23 (dd, *J* = 7.4, 2.8 Hz, 1H), 7.40–7.42 (m, 2H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.98–8.00 (m, 1H), 8.51 (d, *J* = 4.6 Hz, 1H), 8.56 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.7, 32.5, 52.7, 57.6, 123.3, 124.0, 125.7, 128.2, 131.1, 135.8, 137.1, 137.6, 146.7, 149.3, 149.3, 164.5. HR-MS (EI). Calcd for $C_{17}H_{18}N_2S$ (M): 282.1191. Found: *m/z* 282.1184.

5-Chloro-(*Z*)-*N*-ethyl-3-phenylbenzo[*c*]thiophen-1(3*H*)-imine (4g): a yellow oil; R_f 0.38 (AcOEt/hexane 1:10); IR (neat) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t, *J* = 7.4 Hz, 3H), 3.44–3.55 (m, 2H), 5.80 (s, 1H), 7.10 (d, *J* = 1.1 Hz, 1H), 7.23–7.25 (m, 2H), 7.29–7.37 (m, 4H), 7.89 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.3, 52.0, 55.2, 123.8, 125.9, 128.22, 128.24, 128.5, 129.0, 136.1, 137.0, 140.1, 149.1, 163.9. HR-MS (EI). Calcd for $C_{16}H_{14}ClNS$ (M): 287.0535. Found: *m/z* 287.0545. Anal. Calcd for $C_{16}H_{14}ClNS$: C, 66.77; H, 4.90; N, 4.87. Found: C, 66.48; H, 5.02; N, 4.83.

(*Z*)-*N*-Ethyl-5-methoxy-3-phenylbenzo[*c*]thiophen-1(3*H*)-imine (4h): a yellow oil; R_f 0.46 (AcOEt/hexane 1:3); IR (neat) 1633, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, *J* = 7.4 Hz, 3H), 3.43–3.54 (m, 2H), 3.74 (s, 3H), 5.77 (s, 1H), 6.57 (d, *J* = 1.7 Hz, 1H), 6.94 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.5, 51.8, 55.2, 55.5, 110.0, 114.9, 123.8, 127.9, 128.2, 128.8, 130.4, 141.0, 149.6, 162.1, 164.7. HR-MS (EI). Calcd for $C_{17}H_{17}NOS$ (M): 283.1031. Found: *m/z* 283.1031.

(*Z*)-*N*-Ethyl-4-methoxy-3-phenylbenzo[*c*]thiophen-1(3*H*)-imine (4i): a white solid; mp 115–117 °C (hexane/CH_2Cl_2); IR (KBr) 1630, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, *J* = 7.4 Hz, 3H), 3.41–3.55 (m, 2H), 3.60 (s, 3H), 5.86 (s, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 7.16 (dd, *J* = 6.9, 1.7 Hz, 2H), 7.20 (tt, *J* = 6.9,

1.7 Hz, 1H), 7.25 (t, *J* = 6.9 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.3, 51.9, 53.4, 55.5, 112.5, 115.0, 127.2, 127.4, 128.3, 129.9, 135.4, 139.7, 141.4, 156.1, 165.8. HR-MS (EI). Calcd for $C_{17}H_{17}NOS$ (M): 283.1031. Found: *m*/*z* 283.1026. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 71.99; H, 6.08; N, 4.91.

Typical Procedure for the Preparation of *N*-Alkyl-2,3-dihydro-1*H*-isoindole-1-thiones (5). 2-Ethyl-3-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (5a). To a stirred suspension of NaH (60% in mineral oil; 87 mg, 2.2 mmol) in DMF (2 mL) at 0 °C was added a solution of **3a** (0.30 g, 1.1 mmol) dropwise. After evolution of H_2 gas had ceased, $ClCO_2Ph$ (0.17 g, 1.1 mmol) was added dropwise. Stirring was continued at the same temperature for 1.5 h before saturated aqueous NH_4Cl (25 mL) was added. The mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with H_2O (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 (AcOEt/hexane 1: 10) to give **5a** (0.17 g, 61%); a yellow solid; mp 100–102 °C (hexane/CH_2Cl_2); IR (KBr) 1477, 1279 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7.4 Hz, 3H), 3.31–3.38 (m, 1H), 4.46–4.54 (m, 1H), 5.67 (s, 1H), 7.12–7.13 (m, 2H), 7.19 (dd, *J* = 8.6, 3.4 Hz, 1H), 7.37–7.38 (m, 3H), 7.47–7.51 (m, 2H), 8.12 (dd, *J* = 8.6, 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 39.8, 71.4, 122.3, 125.5, 127.5, 128.6, 129.1, 129.3, 131.7, 135.6, 138.8, 144.6, 182.6. HR-MS (EI). Calcd for $C_{16}H_{15}NS$ (M): 253.0925. Found: *m*/*z* 253.0929. Anal. Calcd for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53. Found: C, 76.00; H, 5.98; N, 5.45.

3-(4-Chlorophenyl)-2-ethyl-2,3-dihydro-1*H*-isoindole-1-thione (5b): yellow needles; mp 115–117 °C (hexane/CH_2Cl_2); IR (KBr) 1475, 1281 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7.4 Hz, 3H), 3.28–3.35 (m, 1H), 4.44–4.51 (m, 1H), 5.64 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.15 (dd, *J* = 8.0, 3.4 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.47–7.51 (m, 2H), 8.10 (dd, *J* = 8.0, 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 39.8, 70.6, 122.2, 125.6, 128.9, 129.1, 129.5, 131.8, 134.2, 135.0, 138.7, 144.2, 192.8. HR-MS (EI). Calcd for $C_{16}H_{14}ClNS$ (M): 287.0535. Found: *m*/*z* 287.0533.

2-Ethyl-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-isoindole-1-thione (5c): a pale-yellow solid; mp 98–100 °C (hexane/CH_2Cl_2); IR (KBr) 1611, 1485, 1262 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, *J* = 7.4 Hz, 3H), 3.32–3.38 (m, 1H), 3.80 (s, 3H), 4.40–4.47 (m, 1H), 5.61 (s, 1H), 6.88 (d, *J* = 9.2 Hz, 2H), 7.02 (d, *J* = 9.2 Hz, 2H), 7.16 (dd, *J* = 8.6, 3.4 Hz, 1H), 7.46–7.49 (m, 2H), 8.09–8.12 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 39.7, 55.3, 71.0, 114.6, 122.3, 125.5, 127.3, 128.6, 129.1, 131.6, 138.8, 144.8, 160.2, 192.3. HR-MS (EI). Calcd for $C_{17}H_{17}NOS$ (M): 283.1031. Found: *m*/*z* 283.1041. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 71.67; H, 5.95; N, 4.81.

2,3-Diethyl-2,3-dihydro-1*H*-isoindole-1-thione (5d): a yellow oil; R_f 0.29 (AcOEt/hexane 1:10); IR (neat) 1614, 1479, 1290 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.53 (t, *J* = 7.4 Hz, 3H), 1.35 (t, *J* = 7.4 Hz, 3H),

2.12–2.17 (m, 2H), 3.53–3.60 (m, 1H), 4.57–4.60 (m, 1H), 4.85 (dd, *J* = 4.5, 4.0 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.47 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 6.5, 12.5, 23.5, 39.4, 67.1, 121.2, 125.5, 128.4, 131.2, 139.8, 142.9, 192.5. HR-MS (EI). Calcd for $C_{12}H_{15}NS$ (M): 205.0925. Found: *m/z* 205.0927.

2-Butyl-3-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (5e): a yellow oil; R_f 0.23 (AcOEt/hexane 1:20); IR (neat) 1477, 1293 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.28–1.37 (m, 2H), 1.59–1.69 (m, 2H), 3.14–3.20 (m, 1H), 4.46–4.52 (m, 1H), 5.65 (s, 1H), 7.08–7.10 (m, 2H), 7.16 (dd, *J* = 8.0, 2.9 Hz, 1H), 7.33–7.37 (m, 3H), 7.44–7.49 (m, 2H), 8.10 (dd, *J* = 8.6, 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.1, 29.5, 44.6, 71.8, 122.2, 125.5, 127.6, 128.6, 129.0, 129.2, 131.6, 135.6, 138.7, 144.6, 193.0. HR-MS (EI). Calcd for $C_{18}H_{19}NS$ (M): 281.1238. Found: *m/z* 281.1230.

2-Butyl-3-(pyridin-3-yl)-2,3-dihydro-1*H*-isoindole-1-thione (5f): a yellow oil; R_f 0.26 (AcOEt/hexane 1:2); IR (neat) 1476, 1318 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.32–1.37 (m, 2H), 1.58–1.72 (m, 2H), 3.12–3.17 (m, 1H), 4.48–4.53 (m, 1H), 5.70 (s, 1H), 7.16–7.29 (m, 3H), 7.48–7.53 (m, 2H), 8.12 (dd, *J* = 8.6, 2.9 Hz, 1H), 8.58 (s, 1H), 8.63 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.1, 29.5, 44.6, 69.0, 122.2, 124.3, 125.8, 129.1, 131.9, 132.0, 135.0, 138.8, 143.7, 149.3, 150.6, 193.5. HR-MS (EI). Calcd for $C_{17}H_{18}N_2S$ (M): 282.1191. Found: *m/z* 282.1188.

5-Chloro-2-ethyl-3-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (5g): an orange oil; R_f 0.28 (AcOEt/hexane 1:15); IR (neat) 1471, 1321 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, *J* = 7.4 Hz, 3H), 3.28–3.35 (m, 1H), 4.41–4.49 (m, 1H), 5.63 (s, 1H), 7.10–7.12 (m, 2H), 7.16 (d, *J* = 1.7 Hz, 1H), 7.38–7.40 (m, 3H), 7.46 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 40.0, 71.0, 122.7, 126.7, 127.7, 129.3, 129.37, 129.43, 134.8, 137.3, 138.1, 145.9, 191.5. HR-MS (EI). Calcd for $C_{16}H_{14}ClNS$ (M): 287.0535. Found: *m/z* 287.0539. Anal. Calcd for $C_{16}H_{14}ClNS$: C, 66.77; H, 4.90; N, 4.87. Found: C, 66.63; H, 5.02; N, 4.74.

2-Ethyl-5-methoxy-3-phenyl-2,3-dihydro-1*H*-isoindole-1-thione (5h): a yellow solid; mp 97–99 °C (hexane/CH_2Cl_2); IR (neat) 1610, 1469, 1323 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, *J* = 7.4 Hz, 3H), 3.26–3.33 (m, 1H), 3.78 (s, 3H), 4.42–4.49 (m, 1H), 5.60 (s, 1H), 6.63 (d, *J* = 1.7 Hz, 1H), 7.00 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.11–7.13 (m, 2H), 7.36–7.38 (m, 3H), 8.02 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.6, 39.7, 55.6, 71.0, 106.9, 115.2, 127.0, 127.7, 129.0, 129.3, 132.1, 135.7, 146.8, 163.0, 192.1. HR-MS (EI). Calcd for $C_{17}H_{17}NOS$ (M): 283.1031. Found: *m/z* 283.1030. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 71.95; H, 6.10; N, 4.89.

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