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ONE-POT SYNTHESIS OF 2-SUBSTITUTED 1*H*-ISOINDOLE-1,3(2*H*)-DITHIONES FROM SECONDARY BENZOTHIOAMIDES AND ISOTHIOCYANATES

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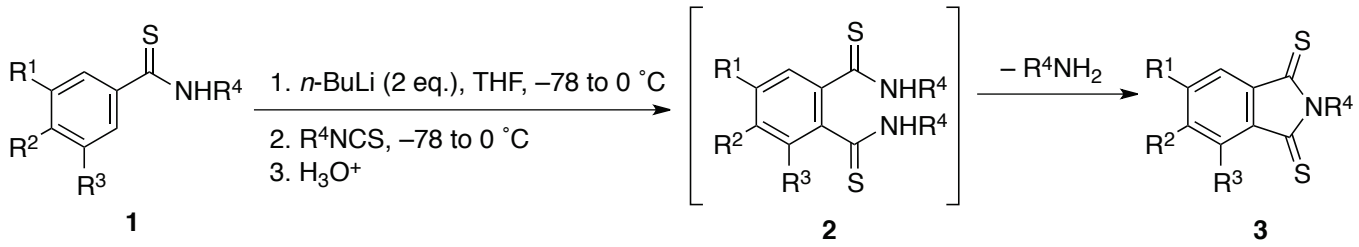
Abstract – The reaction of 2,*N*-dilithiobenzothioamides, generated from readily available secondary benzothioamides and two equivalents of butyllithium, with isothiocyanates, followed by aqueous workup, gives the corresponding N^1,N^2-disubstituted benzene-1,2-dicarbothioamides, which undergo intramolecular attack of one of the thioamide nitrogen on the adjacent thiocarbonyl moiety with loss of primary amines to provide 2-substituted 1*H*-isoindole-1,3(2*H*)-dithiones.

1*H*-Isoindole-1,3(2*H*)-dithione derivatives have recently held considerable interest because of their diverse biological properties, such as TNF-α inhibitory,[1a] fungicidal[1c,d] and other activities.[1] Materials with high electron affinity including the 1*H*-isoindole-1,3(2*H*)-dithione structure have also been reported.[2] Moreover, 1*H*-isoindole-1,3(2*H*)-dithiones have been utilized for the preparation of structurally more complex molecules.[3] However, there are few methods for the general preparation of these heterocycles in the literature. This class of molecules have been conventionally prepared by the treatment of the respective phthalimide with Lawesson's reagent,[4] though recently the synthesis of 1*H*-isoindole-1,3(2*H*)-dithione along with 3-thioxo-2,3-dihydro-1*H*-isoindol-1-one by the reaction of phthalic acid with ammonium *O*,*O*-diethyl dithiophosphate.[5] These methods, however, involves rather harsh conditions and/or incomplete generality. For these reasons, we embarked upon development of a new and facile method for the general preparation of 1*H*-isoindole-1,3(2*H*)-dithiones.

We recently demonstrated that *N*-substituted 2,*N*-dilithiobenzamides, generated from secondary benzamides and two equivalents of butyllithium, react with the respective isothiocyanates to afford 2-substituted 3-thioxo-2,3-dihydro-1*H*-isoindol-1-ones.[6] As an extension of this study, we became interested in the reaction of *N*-substituted 2,*N*-dilithiobenzothioamides with the respective isothiocyanates.

It was anticipated that it would provide 2-substituted 1*H*-isoindole-1,3(2*H*)-dithione derivatives. In this paper, we wish to report the results of our investigations, which offer a new and efficient method for the synthesis of 2-substituted 1*H*-isoindole-1,3(2*H*)-dithiones (**3**) from secondary benzothioamides (**1**) using an operationally easy one-pot procedure.

The one-pot preparation of **3** from **1** was conducted according to the procedure depicted in Scheme 1. The starting materials (**1**) were readily prepared from phenyllithiums and isothiocyanates as described by us in another previous paper.[7] Treatment of these compounds with two equivalents of butyllithium in THF at –78 to 0 ˚C generated the corresponding 2,*N*-dilithiobenzothioamides as described previously,[7] which, after cooling to –78 ˚C, were treated with the respective isothiocyanates. Then, the temperature was again raised to 0 ˚C gradually and the mixture was worked up usually to give the desired isoindoledithiones (**3**). Initially formed N^1,N^2-disubstituted benzene-1,2-dicarbothioamides (**2**) are thought to undergo elimination of primary amines (R^4NH_2) to provide **3**.



Scheme 1

Table 1. Preparation of 1*H*-isoindole-1,3(2*H*)-dithiones (**3**)

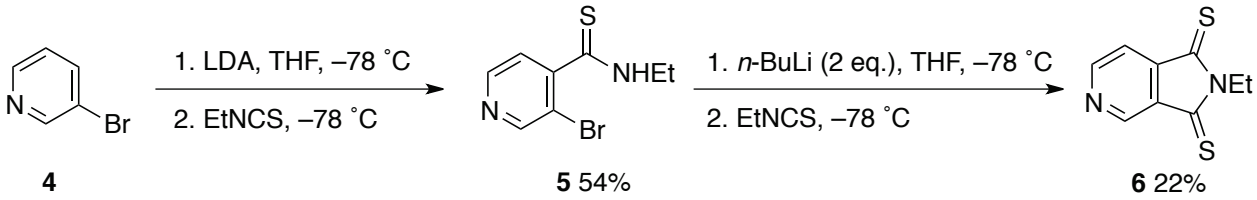
Entry	**1**	R^1	R^2	R^3	R^4	**3**	Yield/%[a]
1	**1a**	H	H	H	Me	**3a**	72
2	**1b**	H	H	H	Et	**3b**	56
3	**1c**	Me	H	Me	Et	**3c**	59
4	**1d**	H	Cl	H	Et	**3d**	63
5	**1e**	H	OMe	H	Et	**3e**	76
6	**1f**	H	H	OMe	Et	**3f**	62
7	**1g**	H	OMe	OMe	Et	**3g**	75
8	**1h**	OMe	OMe	OMe	Et	**3h**	68
9	**1i**	H	H	H	Ph	**3i**	20
10	**1j**	H	H	H	4-ClC_6H_4	**3j**	17
11	**1k**	H	Cl	H	4-$MeOC_6H_4$	**3k**	25

[a] Yields of isolated products.

The results are summarized in Table 1. The yields of the products (**3a-h**) from *N*-alkylbenzothioamides (**1a-h**) were generally moderate to fair (Entries 1–8). On the other hand, the reactions using *N*-arylbenzothioamides (**1i-k**) gave the corresponding desired products (**3i-k**) in rather lower yields (Entries 9–11). Since considerable amounts of the starting thioamides were recovered in these reactions,

these results may be ascribed to the lower coordinative ability of the arylamino groups compared to the alkylamino groups during the generation of 2,*N*-dilithio intermediates and/or the lower reactivity of aryl isothiocyanates. It should be noted that compounds (**3f)** and (**3g**) were obtained as a single regioisomer (Entries 6 and 7). These results indicate that 3-methoxy substituent of **1f** and **1g** worked as a good orientation group for the selective lithiation at the 2-position.

Subsequently, a 1*H*-pyrrolo[3,4-*c*]pyridine-1,3(2*H*)-dithione derivative proved to be also accessible by a similar reaction. An analogous substrate, *N*-ethylpyridine-4-carbothioamide did not work well in the reaction with *n*-BuLi/EtNCS under the same conditions to result in the formation of an intractable mixture of products. However, treatment of 3-bromo-*N*-ethylpyridine-4-carbothioamide (**5**), prepared by the reaction between 3-bromo-4-lithiopyridine[8] and ethyl isothiocyanate, with two equivalents of butyllithium followed by ethyl isothiocyanate gave the desired 2-ethyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3(2*H*)-dithione (**6**) albeit in a low yield, as shown in Scheme 2. These results including the low yield of **6** may be ascribed to the addition of the second butyllithium to the thioamide moieties of these thioamides.[9]



Scheme 2

In summary, we have shown that the reaction of *N*-substituted 2,*N*-dilithiobenzothioamides with the respective isothiocyanates provides an efficient method to prepare 2-substituted 1*H*-isoindole-1,3(2*H*)-dithiones. Since the method employs readily available starting materials and is experimentally simple, it may be of value in organic synthesis. Future contribution from this laboratory will describe utilization of these dilithium compounds in the synthesis of other useful heterocyclic derivatives.

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 and ^{13}C NMR spectra were recorded in $CDCl_3$ 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 (ESI and DART) 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 (**1b**), (**1d-f**), (**1i**), and (**1j**) were prepared according to the procedure described previously.[7] *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals were commercially available. All other chemicals used in this study were commercially available.

***N*-Substituted Benzothioamides Other than (1b), (1d-f), (1i), and (1j).** These compounds were prepared from the respective bromobenzenes and isothiocyanate as described for the preparation of **1b**, **1d-f**, **1i**, and **1j**.[7]

***N*-Methylbenzothioamide (1a):**[10] yield; 57%; a yellow solid; mp 82–83 °C (hexane/CH_2Cl_2); (lit.,[10] mp 81.5 °C). The ^{1}H NMR data for this product were identical to those reported previously.[11]

***N*-Ethyl-3,5-dimethylbenzothioamide (1c):** yield; 93%; a yellow oil; R_f 0.41 (Et_2O/hexane 1:2); IR (neat) 3246, 1605, 1525, 1196 cm^{-1}; ^{1}H NMR δ 1.36 (t, *J* = 7.4 Hz, 3H), 2.33 (s, 6H), 3.84 (q, *J* = 7.4 Hz, 2H), 7.08 (s, 1H), 7.03 (s, 2H), 7.53 (br s, 1H); ^{13}C NMR δ 13.3, 21.5, 41.5, 124.3, 132.5, 138.1, 142.1, 199.4. HR-MS (ESI). Calcd for $C_{11}H_{16}NS$: (M+H): 194.1003. Found: *m*/*z* 194.0995.

***N*-Ethyl-3,4-dimethoxybenzothioamide (1g):** yield: 70%; a pale-yellow solid; mp 87–89 °C (hexane/CH_2Cl_2); IR (KBr) 3208, 1597, 1532, 1176 cm^{-1}; ^{1}H NMR δ 1.38 (t, *J* = 7.4 Hz, 3H), 3.84–3.89 (m, 2H), 3.91 (s, 3H), 3.93 (s, 3H), 6.80 (d, *J* = 8.6 Hz, 1H), 7.23 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.51 (d, *J* = 2.3 Hz, 1H), 7.57 (br, 1H); ^{13}C NMR δ 13.4, 41.6, 55.97, 56.01, 110.0, 111.6, 117.9, 134.6, 148.6, 151.6, 197.9. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.38; H, 6.71; N, 6.16.

***N*-Ethyl-3,4,5-trimethoxybenzothioamide (1h):**[12] yield; 53%; a yellow solid; mp 111–113 °C (hexane/CH_2Cl_2); IR (KBr) 3318, 1587, 1530, 1138 cm^{-1}; ^{1}H NMR δ 1.38 (t, *J* = 7.4 Hz, 3H), 3.82–3.91 (m including 2s at 3.85 and 3.88, combined 11H), 6.92 (s, 2H), 7.63 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 41.7, 56.2, 60.8, 104.1, 137.8, 140.3, 152.8, 198.6.

4-Chloro-*N*-(4-methoxyphenyl)benzothioamide (1k):[13] yield: 70%; a yellow solid; mp 172–174 °C (hexane/CH_2Cl_2) (lit.,[14] mp 171–173 °C). The ^{1}H NMR data for this compound were identical to those reported previously.[15]

Typical Procedure for the Preparation of 1*H*-Isoindole-1,3(2*H*)-dithiones (3). 2-Ethyl-1*H*-isoindole-1,3(2*H*)-dithione (3b).[16] To a stirred solution of **1b** (0.17 g, 1.0 mmol) in THF (10 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 at the same temperature. The mixture was cooled to –78 °C and EtNCS (87 mg, 1.0 mmol) was added dropwise, and then the temperature was again raised to 0 °C gradually. Saturated aqueous NH_4Cl (15 mL) was added and the resulting mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated by

evaporation. The residue was purified by column chromatography on SiO_2 (CH_2Cl_2/hexane 1:20) to afford **3b** (0.12 g, 56%); a brown solid; mp 72–74 ˚C (hexane) (lit.,[16] mp 75–76 ˚C); IR (KBr) 1353, 1065 cm^{-1}; ^1H NMR δ 1.30 (t, *J* = 7.4 Hz, 3H), 4.51 (q, *J* = 7.4 Hz, 2H), 7.67 (dd, *J* = 5.7, 2.8 Hz, 2H), 7.86 (dd, *J* = 5.7, 2.8 Hz, 2H).

2-Methyl-1*H*-isoindole-1,3(2*H*)-dithione (3a):[17] a dark yellow solid; mp 97–99 ˚C (hexane) (lit.,[16] mp 81–83 ˚C); IR (KBr) 1323, 1056 cm^{-1}; ^1H NMR δ 3.83 (s, 3H), 7.66 (dd, *J* = 5.7, 3.4 Hz, 2H), 7.85 (dd, *J* = 5.7, 3.4 Hz, 2H).

2-Ethyl-4,6-dimethyl-1*H*-isoindole-1,3(2*H*)-dithione (3c): a brown solid; mp 79–81 ˚C (hexane); IR (KBr) 1610, 1341, 1057 cm^{-1}; ^1H NMR δ 1.25 (t, *J* = 7.4 Hz, 3H), 2.42 (s, 3H), 2.74 (s, 3H), 4.47 (q, *J* = 7.4 Hz, 2H), 7.25 (s, 1H), 7.55 (s, 1H); ^{13}C NMR δ 12.8, 19.5, 21.8, 38.6, 122.2, 129.1, 136.6, 137.3, 137.8, 142.9, 196.5, 197.1. HR-MS (EI). Calcd for $C_{12}H_{13}NS_2$: (M): 235.0489. Found: *m/z* 235.0496. Anal. Calcd for $C_{12}H_{13}NS_2$: C, 61.24; H, 5.57; N, 5.95. Found: C, 61.07; H, 5.60; N, 5.93.

5-Chloro-2-ethyl-1*H*-isoindole-1,3(2*H*)-dithione (3d): a dark brown solid; mp 64–66 ˚C (hexane); IR (KBr) 1363, 1078 cm^{-1}; ^1H NMR δ 1.29 (t, *J* = 7.4 Hz, 3H), 4.48 (q, *J* = 7.4 Hz, 2H), 7.61 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR δ 12.9, 39.2, 123.2, 124.4, 132.9, 133.1, 136.0, 139.5, 195.1, 195.4. HR-MS (EI). Calcd for $C_{10}H_8ClNS_2$: (M): 240.9787. Found: *m/z* 240.9779. Anal. Calcd for $C_{10}H_8ClNS_2$: C, 49.68; H, 3.34; N, 5.79. Found: C, 49.97; H, 3.51; N, 5.80.

2-Ethyl-5-methoxy-1*H*-isoindole-1,3(2*H*)-dithione (3e): a dark brown solid; mp 87–89 ˚C (hexane/CH_2Cl_2); IR (KBr) 1604, 1352, 1030 cm^{-1}; ^1H NMR δ 1.28 (t, *J* = 7.4 Hz, 3H), 3.93 (s, 3H), 4.46 (q, *J* = 7.4 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.27 (s, 1H), 7.74 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR δ 13.0, 38.9, 56.1, 106.7, 119.8, 125.0, 128.6, 137.3, 164.1, 196.4, 196.5. HR-MS (ESI). Calcd for $C_{11}H_{12}NOS_2$: (M+H): 238.0360. Found: *m/z* 238.0355. Anal. Calcd for $C_{11}H_{11}NOS_2$: C, 55.67; H, 4.67; N, 5.90. Found: C, 55.60; H, 4.65; N, 5.79.

2-Ethyl-4-methoxy-1*H*-isoindole-1,3(2*H*)-dithione (3f): a brown solid; mp 103–105 ˚C (hexane); IR (KBr) 1606, 1354, 1050 cm^{-1}; ^1H NMR δ 1.25 (t, *J* = 7.4 Hz, 3H), 4.02 (s, 3H), 4.47 (q, *J* = 7.4 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.58 (dd, *J* = 8.0, 7.4 Hz, 1H); ^{13}C NMR δ 12.8, 38.5, 56.2, 115.8, 117.0, 121.0, 134.2, 137.5, 156.8, 193.8, 195.7. HR-MS (ESI). Calcd for $C_{11}H_{12}NOS_2$: (M+H): 238.0360. Found: *m/z* 238.0353. Anal. Calcd for $C_{11}H_{11}NOS_2$: C, 55.67; H, 4.67; N, 5.90. Found: C, 55.66; H, 4.78; N, 5.94.

2-Ethyl-4,5-dimethoxy-1*H*-isoindole-1,3(2*H*)-dithione (3g): a brown solid; mp 103–105 ˚C (hexane/CH_2Cl_2); IR (KBr) 1357, 1045 cm^{-1}; ^1H NMR δ 1.26 (t, *J* = 7.4 Hz, 3H), 3.97 (s, 6H), 4.47 (q, *J* = 7.4 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 12.8, 38.6, 56.6, 61.2, 115.2, 120.2, 126.5, 129.7, 146.3, 159.0, 193.4, 195.6. HR-MS (ESI). Calcd for $C_{12}H_{14}NO_2S_2$: (M+H): 268.0466.

Found: *m/z* 268.0453. Anal. Calcd for $C_{12}H_{13}NO_2S_2$: C, 53.91; H, 4.90; N, 5.24. Found: C, 53.84; H, 4.93; N, 5.22.

2-Ethyl-4,5,6-trimethoxy-1*H*-isoindole-1,3(2*H*)-dithione (3h): a brown solid; mp 78–80 °C (hexane/CH_2Cl_2); IR (KBr) 1600, 1357, 1066 cm^{-1}; ^1H NMR δ 1.25 (t, *J* = 7.4 Hz, 3H), 3.94 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 4.44 (q, *J* = 7.4 Hz, 2H), 7.20 (s, 1H); ^{13}C NMR δ 12.9, 38.6, 56.7, 61.4, 61.6, 102.6, 120.2, 132.6, 147.5, 151.0, 157.5, 193.6, 195.7. HR-MS (DART, positive). Calcd for $C_{13}H_{16}NOS_2$: (M+H): 298.0571. Found: *m/z* 298.0559. Anal. Calcd for $C_{13}H_{15}NO_3S_2$: C, 52.50; H, 5.08; N, 4.71. Found: C, 52.56; H, 5.13; N, 4.70.

2-Phenyl-1*H*-isoindole-1,3(2*H*)-dithione (3i):[18] a brown solid; mp 138–140 °C (hexane/CH_2Cl_2); IR (KBr) 1600, 1353, 1082 cm^{-1}; ^1H NMR δ 7.29 (dd, *J* = 8.0, 1.1 Hz, 2H), 7.49–7.57 (m, 3H), 7.76 (dd, *J* = 5.9, 2.9 Hz, 2H), 7.95 (dd, *J* = 5.9, 2.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.6, 129.1, 129.3, 133.4, 134.8, 136.1, 198.1.

2-(4-Chlorophenyl)-1*H*-isoindole-1,3(2*H*)-dithione (3j):[18] a yellow solid; mp 159–161 °C (hexane/CH_2Cl_2) (lit.,[18] mp 138–139 °C); IR (KBr) 1601, 1317, 1293, 1160 cm^{-1}; ^1H NMR δ 7.25 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.77 (dd, *J* = 5.9, 2.9 Hz, 2H), 7.96 (dd, *J* = 5.9, 2.9 Hz, 2H); ^{13}C NMR δ 122.7, 129.4, 130.7, 133.6, 134.5, 134.8, 135.4, 197.9. HR-MS (DART, negative). Calcd for $C_{14}H_8ClNS_2$: (M): 288.9787. Found: *m/z* 288.9792.

5-Chloro-2-(4-methoxyphenyl)-1*H*-isoindole-1,3(2*H*)-dithione (3k): a brown solid; mp 121–123 °C (hexane/CH_2Cl_2); IR (KBr) 1610, 1310, 1290, 1104 cm^{-1}; ^1H NMR δ 3.80 (s, 3H), 6.97 (d, *J* = 9.2 Hz, 2H), 7.12 (d, *J* = 9.2 Hz, 2H), 7.62 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 1.1 Hz, 1H); ^{13}C NMR δ 55.4, 114.4, 123.6, 124.9, 128.3, 130.2, 132.9, 133.3, 135.9, 139.9, 160.1, 196.7, 197.0. HR-MS (DART, negative). Calcd for $C_{15}H_{10}ClNOS_2$: (M): 318.9892. Found: *m/z* 318.9898. Anal. Calcd for $C_{15}H_{10}ClNOS_2$: C, 56.33; H, 3.15; N, 4.38. Found: C, 56.16; H, 3.47; N, 4.33.

3-Bromo-*N*-ethylpyridine-4-carbothioamide (5). 3-Bromo-4-lithiopyridine was generated by treating 3-bromopyridine (**4**) (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,[8] 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 **3b**. The residue was purified by column chromatography on SiO_2 (Et_2O/hexane 1:4) to give **5** (0.40 g, 54%); a pale-yellow solid; mp 108–110 °C (hexane/CH_2Cl_2); IR (KBr) 3187, 1562, 1400, 1251 cm^{-1}; ^1H NMR δ 1.38 (t, *J* = 7.4 Hz, 3H), 3.82–3.87 (m, 2H), 7.34 (d, *J* = 5.2 Hz, 1H), 7.98 (br s, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 8.61 (s, 1H); ^{13}C NMR δ 12.9, 41.1, 115.8, 123.2, 148.2, 150.6, 152.3, 194.6. Anal. Calcd for $C_8H_9BrN_2S$: C, 39.20; H, 3.70; N, 11.43. Found: C, 39.16; H, 3.76; N, 11.37.

2-Ethyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3(2*H*)-dithione (6). To a stirred solution of **5** (0.17 g, 0.69 mmol) in THF (8 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 1.4 mmol) dropwise. After 3 min, EtNCS (60 mg, 0.69 mmol) was added dropwise, and stirring was continued for an additional 5 min before addition of saturated aqueous NH_4Cl (15 mL). The resulting mixture was worked up as described for the preparation of **3b**. The residue was purified by column chromatography on SiO_2 (AcOEt/hexane 1:5) to afford **6** (32 mg, 22%); a brown solid; mp 67–69 ˚C (hexane); IR (KBr) 1600, 1357, 1276, 1090 cm^{-1}; ^1H NMR δ 1.30 (t, *J* = 6.3 Hz, 3H), 4.52 (q, *J* = 6.3 Hz, 2H), 7.72 (br s, 1H), 9.01 (d, *J* = 2.3 Hz, 1H), 9.16 (s, 1H); ^{13}C NMR δ 12.8, 38.9, 115.9, 128.4, 140.3, 145.0, 154.0, 194.6, 195.0. HR-MS (DART, negative). Calcd for $C_9H_8N_2S_2$: (M): 208.0129. Found: *m/z* 208.0131. Anal. Calcd for $C_9H_8N_2S_2$: C, 51.90; H, 3.87; N, 13.45; S, 30.78. Found: C, 51.75; H, 4.05; N, 13.48; S, 30.98.

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