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Synthesis and Reactivity of 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole. A Novel One-pot Synthesis of N-Substituted Indole-2-thiols†

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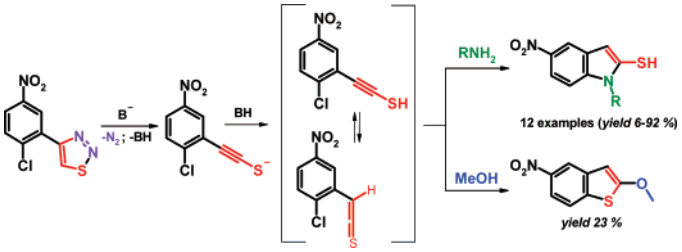

4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole undergoes ring opening to produce a thioketene intermediate that reacts with an O- or N-nucleophile, forming an ester or an amide of the aryl-substituted thioacetic acid. Intermolecular cyclization of the thioacetic acid derivative via nucleophilic substitution of halogen in the aromatic ring gives an N-substituted indole-2-thiol (in case of an N-nucleophile) or a 2-alkoxy-substituted benzo[*b*]thiophene (in case of an O-nucleophile). The reaction is also applicable to the synthesis of heterocyclic analogues of N-substituted indole-2-thiols: 1-butyl-1,3-dihydropyrrolo[2,3-*b*]pyridine-2-thione was synthesized as an example. In the presence of potassium thioacetate (an S-nucleophile) 4-nitro-2-(1,2,3-thiadiazol-4-yl)benzenethiol is formed more quickly than thiadiazole ring opening occurs, making the heterocyclic ring tolerant toward the base.

Introduction

The indole nucleus is ubiquitous among natural products, and its synthesis has attracted synthetic chemists.[1,2] There are several problematic procedures that have been documented for the introduction of the sulfur-containing substituents at the C2 position of the indole ring: coupling of protected tryptophan derivatives with sulfenyl chloride[3] or dialkyl disulfides in the presence of the silver salt of trifluoromethanesulfonic acid,[4] thiol-mediated radical cyclization of 2-alkenylphenyl isocyanides,[5] treatment of 2-oxyindole[6−8] or its derivative[9] with Lawesson's reagent, and isomerization of 5-chloro-3-(phenylthio)-1*H*-indole into the corresponding 5-chloro-2-(phenylthio)-1*H*-indole in the polyphosphoric acid.[10] The substituents that can be incorporated are few, and/or the stability of the substrates can be an issue. Furthermore, the only general method for the synthesis of indole-2-thiols having no substituents at the C3 position is the thionation of 2-oxyindoles.[6−8]

Several natural products having specific biological activity contain the indole-2-thiol fragment. For example, cruciferous sulfur-containing phytoalexins, such as brassilexin, sinalexin, and cyclobrassinin occurring in plants, have a broad antimicrobial activity, playing crucial roles in their resistance to pathogen invasion.[8,9,11,12] Indole-2-thiol derivatives[13] have, for

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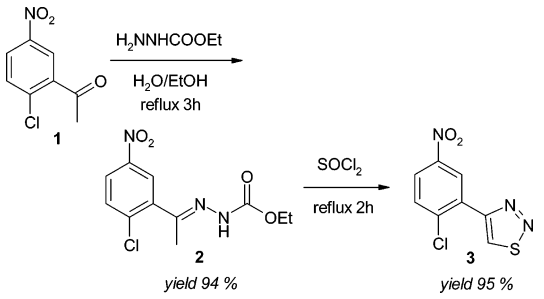
SCHEME 1



example, been demonstrated as useful intermediates in the synthesis of 2,2′-dithiobisindole tyrosine kinase inhibitors.[7,14,15] Wieland et al.[16−19] carried out notable synthetic work on phalloidin as well as natural and nonnatural analogues of the phallotoxins. Phalloidine is a cyclic heptapeptide fungal toxin produced by *Amanita Phalloides* (the Death Cap mushroom) comprised of a 2-thioindole fragment as a cross-linker. This compound is a potent stabilizer of filamentous actin, and fluorescently labeled phallotoxins have been used in cellular biology to study the actin system.[20] Some perspective small-molecule motilin agonists contain the 2-thioindole unit. These motilin analogues have been suggested as potential drugs for the treatment of patients with hypomotility syndromes.[4]

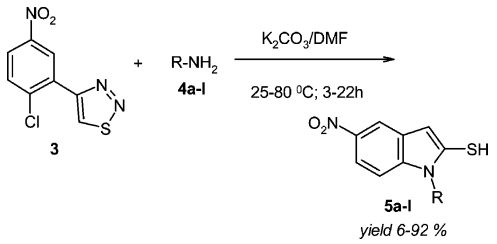
Herein we report a new, simple, and convenient approach to a variety of N-substituted indole-2-thiols based on a one-pot transformation of 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole in the presence of primary amines. We have investigated the mechanism of this reaction. It has been shown that the reaction is applicable to the synthesis of 2-thioindole analogues having heteroatoms in six-membered rings as well as to the synthesis of 2-alkoxybenzo[*b*]thiophenes.

Results and Discussion

The Hurd−Mori reaction gives access to 4-substituted 1,2,3-thiadiazoles from methyl ketones via the reaction of the corresponding ethyl carbazones or tosyl hydrazones with thionyl chloride.[21,22] This procedure was used to obtain the previously unknown 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole (**3**) from the starting 1-(2-chloro-5-nitrophenyl)ethanone (**1**) in 89% overall yield (Scheme 1).

When we carried out the base-catalyzed (K_2CO_3) alkylamination of **3** with a variety of primary alkylamines **4a**−**l** in DMF at moderate temperature (50−80 °C), the unexpected N-substituted indole-2-thiols **5a**−**l** were isolated (Scheme 2). Additionally, we found that the reaction is tolerant to the

SCHEME 2



medium and MeCN, Me_2CO, MeOH, and EtOH could be used as solvents. The use of DMF allows the reaction even at room temperature (20−25 °C). Generally, we did not optimize the reaction conditions (ratio of reagents, choice of solvent, temperature) in each particular case. However, according to our observations the yield of desirable indole-2-thiol can be increased at lower reaction temperature (92% (22 h; 25 °C) vs 44% (3 h; 50 °C) for product **5a**). Reaction of **3** with aniline and *N*-phenylhydrazine under the same conditions gave none of the desired indole-2-thiols.

The mechanism of this reaction was studied by ^{1}H NMR monitoring of a reaction mixture containing **3**, **4a**, and K_2CO_3 in DMF at 25 °C (Scheme 3). Initially thiadiazole ring opening was indicated by the disappearance of the thiadiazole H5 at δ_H 9.19. Decomposition of the electron-withdrawing thiadiazole ring is accompanied by nitrogen evolution and formation of the thioamide **3-V.** The appearance of N*H* at δ_H 7.44 and an upfield shift of phenyl protons at the 3-, 4-, and 6-positions by 0.30, 0.16, and 0.89 ppm, respectively, were observed. We also followed the progress of the reaction by GC/MS. This supports formation of the intermediate **3-V** (*m*/*z* 286). After 22 h the transformation was complete and the NMR spectrum showed a clean absorption pattern of 1-butyl-5-nitro-1*H*-indole-2-thiol (**5a**) with δ_H 0.97 ($CH_3CH_2CH_2CH_2N$), 1.46 ($CH_3CH_2CH_2CH_2N$), 1.67 ($CH_3CH_2CH_2CH_2N$), 3.24 ($CH_3CH_2CH_2CH_2N$), 4.28 (S*H*), 6.12 (H3), 7.59 (H7), 7.87 (H6), and 8.21 (H4). There were no detectable impurities present. The supposed intermediates **3-I**−**3-IV**, **3-VI**, and **3-VII** were not detected by ^{1}H NMR, but their formation is not in conflict with our observations (see Scheme 8) and has been documented by data on the reactivity of 5-unsubstituted 1,2,3-thiodiazoles.[23−25]

The dynamics of the transformation of thiadiazole **3** into indole **5a** via thioamide **3-V** is shown in Figure 1.

In order to understand how the electron-withdrawing nitro group exerts an influence on the reaction, we prepared 4-(2-chlorophenyl)-1,2,3-thiadiazole (**8**) (overall yield 37%) from 1-(2-chlorophenyl)ethanone **6** by the Hurd−Mori[22] procedure. After heating **8** in the presence of *n*-$BuNH_2$ and K_2CO_3 at 70 °C for 24 h, only the starting material **8** and thioamide **9** was detected. Complete conversion of **8** into **9** was achieved at elevated temperature (130 °C), but no trace of cyclized product **10** was found. Thus, the presence of the activating nitro group at the phenyl ring makes the thiadiazole ring susceptible to proton abstraction, facilitating anionic ring opening. Additionally, heterocyclization of **9** into **10** does not occur, since the chlorine atom is inactive to intramolecular nucleophilic attack by amide nitrogen under the reaction conditions (Scheme 4).

We synthesized 2-chloro-3-(1,2,3-thiadiazol-4-yl)pyridine (**13**; overall yield 79%) from 1-(chloropyridin-3-yl)ethanone (**11**)

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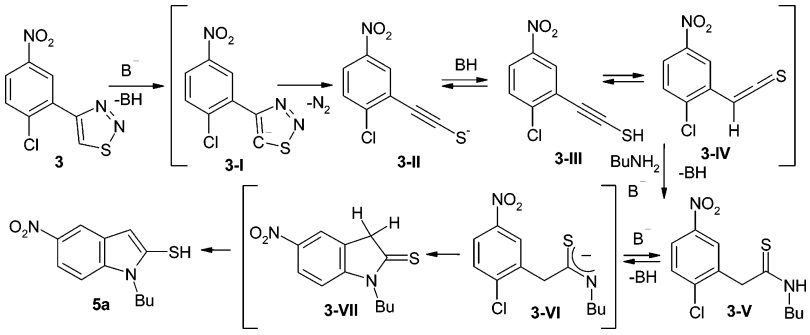
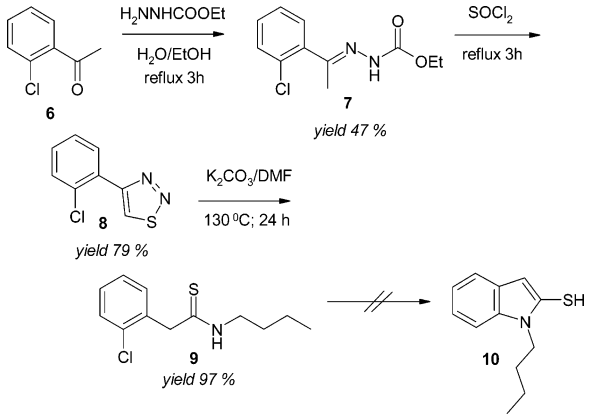
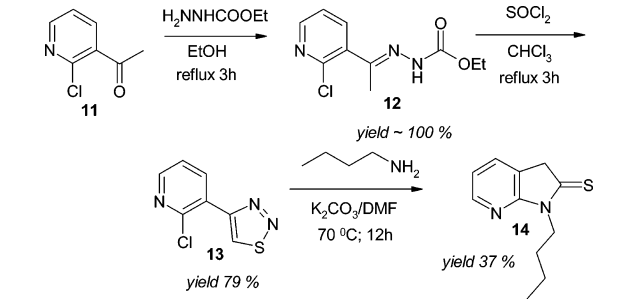
SCHEME 3



SCHEME 4



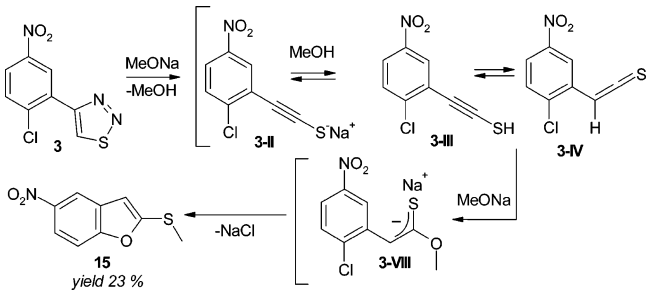
SCHEME 5



according to the Hurd−Mori[22] procedure. The reaction of **13** with *n*-$BuNH_2$ in the presence of K_2CO_3 (DMF; 70 °C; 12 h) resulted in 1-butyl-1,3-dihydropyrrolo[2,3-*b*]pyridine-2-thione (**14**; yield 37%). Interestingly, **14** exists as the thione tautomer, in contrast to compound **5a**, which is in the thiol configuration under the same conditions ($CDCl_3$; 25 °C) (Scheme 5).

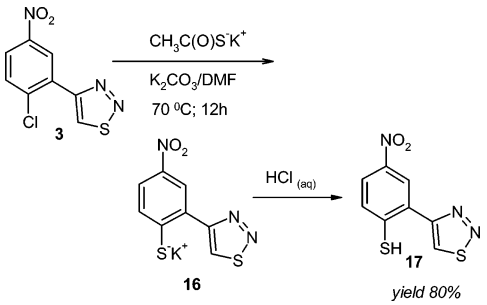
Treatment of **3** with MeONa in MeOH under an inert atmosphere led to the unexpected 2-methoxy-5-nitrobenzo[*b*]-thiophene (**15**; yield 23%). Formation of **15** can be explained by relying on already known data on the reactivity of 5-unsubstituted 1,2,3-thiadiazoles.[23−25] In analogy with Scheme 3, after

SCHEME 6 [a]



[a] Conditions: MeONa/MeOH, reflux, 24 h.

SCHEME 7



the addition of nucleophile (MeONa) to the thioketene **3-IV**, the enethiol anion **3-VIII**, stabilized by conjugation, is formed and the route of the subsequent reaction is cyclization to the benzothiophene **15** (Scheme 6).

Our attempt to introduce the sulfur-containing nucleophile potassium thioacetate by reaction with **3** in the presence of K_2CO_3 resulted in the product of nucleophilic substitution in the benzene ring. This gave thiophenolate **16** (Scheme 7) without decomposition of the heterocyclic ring. Anion **16** can be isolated as the thiol **17** (yield 80%) after addition of dilute HCl.

Decomposition of **3** under the influence of base (K_2CO_3, MeCN; 80 °C, 6 h) in the absence of a nucleophile affords the

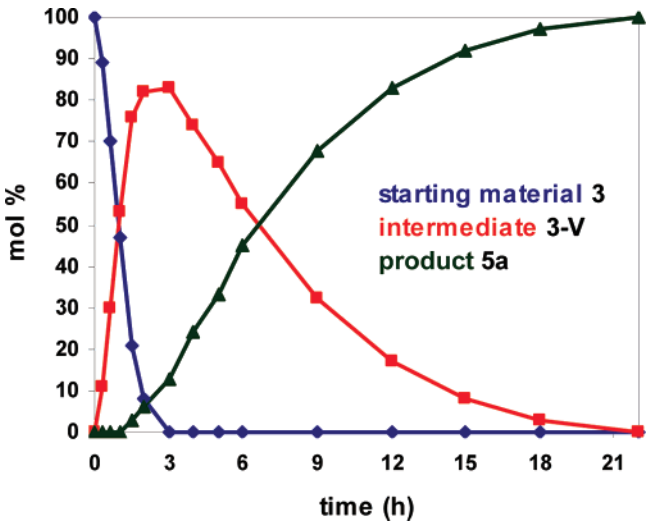
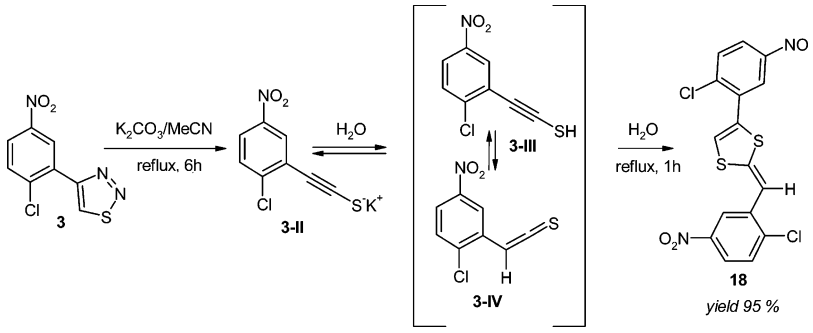


FIGURE 1. Transformation of thiadiazole **3** into indole **5a** via intermediate formation of thioamide **3-V** in DMF at 25 °C, as monitored by ^1H NMR spectroscopy.

SCHEME 8



alkynethiolate **3-II**, which converts into thioketene **3-IV** after addition of water with subsequent dimerization to the dithiafulvene **18** (Scheme 8).

Conclusion

We have synthesized and studied the reactivity of 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole **3** with N,O,S-nucleophiles. The unusual base-induced transformation of **3** in the presence of various primary aliphatic amines uncovered a simple and convenient route to potentially important indole-2-thiols and their heterocyclic analogues. A similar transformation of **3** in the presence of methanol produces 2-methoxy-5-nitrobenzo[*b*]-thiophene. This might be developed for the synthesis of various 2-alkoxybenzo[*b*]thiophenes in the future.

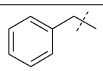
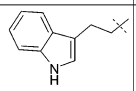
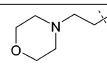
Experimental Section

***N*-Ethoxycarbonyl Hydrazone of 1-(2-Chloro-5-nitrophenyl)-ethanone (2).** A mixture of 28.1 g (0.14 mol) of 1-(2-chloro-5-nitrophenyl)ethanone, 17.5 g (0.17 mol) of ethyl carbazate, and 1 mL of AcOH in 800 mL of EtOH/H_2O (1:1) was refluxed for 3 h and left overnight at room temperature. The precipitate was filtered, washed with EtOH/H_2O (1:1), and dried to give 37.8 g (94%) of **2** as a white solid, mp 169−170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, 3H), 4.34 (q, 4H), 7.55 (d, 1H), 7.98 (s, 1H, NH), 8.16 (dd, 1H), 8.31 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 16.4, 62.5, 124.5, 125.8, 130.8, 139.3, 140.0, 146.6. MS (EI$^+$ mode): *m*/*z* 285 (M^+, 20%), 250 (7), 195 (47), 178 (100), 166 (75), 151 (22), 137 (37), 102 (67). HRMS (EI$^+$ mode): *m*/*z* calcd for M^+ 285.0516, found 285.0514.

4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole (3). A solution of 37.5 g (0.13 mol) of **2** in 60 mL of $SOCl_2$ was refluxed for 2 h, cooled, and poured into water. The precipitate was thoroughly washed with water and dried to give 30.2 g (95%) of pure **3** as light yellow crystals. Product **3** can be crystallized from $CHCl_3$/MeOH (via azeotropic substitution of MeOH for $CHCl_3$); mp 121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 1H) 8.26 (dd, 1H), 9.07 (d, 1H), 9.19 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 124.6, 126.8, 131.0, 131.7, 135.9, 138.8, 146.9, 156.9. MS (EI$^+$ mode): *m*/*z* 241 (M^+, 2%), 213 (71), 167 (100), 155 (21), 132 (50), 123 (47). HRMS (EI$^+$ mode) *m*/*z* calcd for M^+ 240.9713, found 240.9710.

General Procedure for the Synthesis of Indole-2-thiols (5a−l). 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole (**3**; 0.5 g, 2.07 mmol), K_2CO_3 (0.57 g, 4.13 mmol), the corresponding amine **4a−l** (1.05−3.0 equiv), and 10 mL of DMF (in that order; for molar ratios see Table 1) were charged into a 50 mL round-bottom flask. The mixture was stirred for 3−22 h at 25−80 °C. DMF was removed under reduced pressure and the residue purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:1), $CHCl_3$/hexane (2:1), or $CHCl_3$/MeOH (100:1)), affording the corresponding indole-2-thiol **5a−l** (yields 6−92%; see Table 1).

TABLE 1. Reaction Conditions and Yields of Indole-2-thiols

Entry	Amine R-NH_2	R	Product	Ratio **3**/**4**/K_2CO_3 (eq)	Time (h)	Temp. (°C)	Yield (%) [a]
1	*n*-Butylamine		**5a**	1/3/2	3	50	44
					22	25	92 (~100) [b]
2	*tert*-Butylamine		**5b**	1/3/2	3	70	39
3	Allylamine		**5c**	1/3/2	3	70	42
4	Benzylamine		**5d**	1/3/2	3	70	33
5	Cyclohexylamine		**5e**	1/3/2	3	70	38
6	Cyclopentylamine		**5f**	1/3/2	3	70	33
7	*iso*-Propylamine		**5g**	1/4/2	6	60	29
8	Methylamine hydrochloride		**5h**	1/3/2	6	60	6
9	Glycine ethyl ester hydrochloride		**5i**	1/1.05/3	3	80	9
10	Tryptamine		**5j**	1/2/2	3	70	23
11	1-Adamantylamine		**5k**	1/3/2	9	80	26
12	4-(2-Aminoethyl)-morpholine		**5l**	1/3/2	3	80	61

[a] Yield after column chromatography. [b] Conversion of **3** into **5**, as monitored by ^{1}H NMR spectroscopy.

1-Butyl-5-nitro-1*H*-indole-2-thiol (5a). 5a was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:1)), giving red crystals: yield 0.52 g (92%); mp 74−75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (t, 3H), 1.40−1.52 (m, 2H), 1.63−1.72 (m, 2H), 3.25 (q, 2H), 4.27 (br t, 1H), 6.12 (s, 1H), 7.59 (d, 1H), 7.87 (dd, 1H), 8.21 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 20.2, 31.4, 46.7, 96.0, 114.9, 115.1, 121.6, 138.0, 141.6, 145.9, 156.5. MS (EI$^+$ mode): *m*/*z* 250 (M^+, 75%), 207 (100), 194 (15), 161 (65), 148 (22), 134 (16), 120 (9). HRMS (EI$^+$ mode): *m*/*z* calcd for M^+ 250.0776, found 250.0776.

1-*tert*-Butyl-5-nitro-1*H*-indole-2-thiol (5b). 5b was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:1)), giving yellow crystals: yield 0.20 g (39%); mp 114−115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 9H), 4.18 (br s, 1H), 6.31 (s, 1H), 7.61 (d, 1H),

7.90 (dd, 1H), 8.26 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.3, 53.6, 101.2, 115.3, 115.6, 121.4, 138.9, 141.1, 145.8, 153.8. MS (EI^+ mode): *m*/*z* 250 (M^+, 37%), 194 (100), 148 (46), 121 (12), 57 (69). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 250.0776, found 250.0775.

1-Allyl-5-nitro-1*H*-indole-2-thiol (5c). 5c was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:1)), giving dark red crystals: yield 0.20 g (42%); mp 67−68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (br s, 2H), 4.50 (br s, 1H), 5.23−5.38 (m, 2H), 5.89−6.01 (m, 1H), 6.13 (s, 1H), 7.57 (d, 1H), 7.85 (dd, 1H), 8.19 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.2, 96.8, 115.0, 115.3, 117.5, 121.6, 133.7, 138.2, 141.4, 145.8, 156.0. MS (EI^+ mode): *m*/*z* 234 (M^+, 100%), 207 (23), 188 (13), 161 (20). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 234.0463, found 234.0463.

1-Benzyl-5-nitro-1*H*-indole-2-thiol (5d). 5d was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:1)), giving red crystals: yield 0.194 g (33%); mp 99−100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (d, 2H), 4.72 (br t, 1H), 6.10 (s, 1H), 7.26−7.40 (m, 5H), 7.52 (d, 1H), 7.82 (dd, 1H), 8.13 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.9, 96.9, 115.0, 115.3, 121.5, 127.6, 127.9, 128.8, 137.5, 138.2, 141.3, 145.8, 155.9. MS (EI^+ mode): *m*/*z* 284 (M^+, 22%), 91 (100), 65 (20). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 284.0620, found 284.0619.

1-Cyclohexyl-5-nitro-1*H*-indole-2-thiol (5e). 5e was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:1)), giving red crystals: yield 0.217 g (38%); mp 130−131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17−1.48 (m, 5H), 1.60−1.66 (m, 1H), 1.76−1.83 (m, 2H), 2.10−2.15 (m, 2H), 3.22−3.33 (br m, 1H), 4.23 (br d, 1H), 6.11 (s, 1H), 7.57 (d, 1H), 7.85 (dd, 1H), 8.19 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 25.6, 33.0, 55.7, 96.0, 114.6, 114.8, 121.4, 138.0, 141.6, 145.8, 155.6. MS (EI^+ mode): *m*/*z* 276 (M^+, 52%), 233 (17), 194 (100), 166 (10), 148 (47), 136 (8), 121 (12), 83 (9), 55 (87). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 276.0933, found 276.0932.

1-Cyclopentyl-5-nitro-1*H*-indole-2-thiol (5f). 5f was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:1)), giving dark green crystals: yield 0.179 g (33%); mp 124−125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69−1.82 (m, 5H), 2.02−2.12 (m, 2H), 3.78−3.88 (br m, 1H), 4.31 (br d, 1H), 6.11 (s, 1H), 7.57 (d, 1H), 7.86 (dd, 1H), 8.20 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.0, 33.2, 58.1, 96.6, 114.8, 115.1, 121.5, 138.2, 141.6, 145.9, 155.8. MS (EI^+ mode): *m*/*z* 262 (M^+, 65%), 233 (14), 194 (100), 166 (8), 148 (58), 136 (10), 121 (16), 69 (21). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 262.0776, found 262.0778.

1-Isopropyl-5-nitro-1*H*-indole-2-thiol (5g). 5g was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:1)), giving brown crystals: yield: 0.142 g (29%); mp 84−85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, 6H), 3.62−3.69 (br m, 1H), 4.15 (br d, 1H), 6.14 (s, 1H), 7.61 (d, 1H), 7.88 (dd, 1H), 8.23 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ: 22.8, 48.5, 96.4, 114.8, 115.1, 121.5, 138.1, 141.6, 145.9, 155.4. MS (EI^+ mode): *m*/*z* 236 (M^+, 97%), 221 (100), 194 (27), 175 (18), 166 (10), 148 (63), 136 (10), 121 (19), 69 (8). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 236.0620, found 236.0619.

1-Methyl-5-nitro-1*H*-indole-2-thiol (5h). 5h was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:1)), giving red crystals: yield 0.026 g (6%); mp 163−164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (d, 3H), 4.31 (br s, 1H), 6.13 (s, 1H), 7.60 (d, 1H), 7.89 (dd, 1H), 8.24 (d, 1H). ^{13}C NMR ($CDCl_3$): δ 33.2, 95.9, 115.0, 115.3, 121.6, 138.2, 141.5, 145.9, 157.3. MS (EI^+ mode): *m*/*z* 208 (M^+, 100%), 178 (10), 162 (64), 146 (14), 128 (12), 69 (13). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 208.0307, found 208.0307.

(2-Mercapto-5-nitroindol-1-yl)acetic Acid Ethyl Ester (5i). 5i was purified via column chromatography (SiO_2, $CHCl_3$/hexane (2:1)), giving yellow crystals: yield 0.052 g (9%); mp 163−164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, 3H), 4.01 (d, 2H), 4.29 (q, 2H), 4.95 (br t, 1H), 6.13 (s, 1H), 7.62 (d, 1H), 7.91 (dd, 1H), 8.25 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 47.8, 61.9, 97.4, 115.5, 115.8, 121.7, 138.4, 141.1, 145.9, 154.7, 169.7. MS (EI^+ mode): *m*/*z* 280 (M^+, 30%), 207 (100), 161 (34), 134 (10). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 280.0519, found 280.0519.

1-[2-(1*H*-Indol-3-yl)ethyl]-5-nitro-1*H*-indole-2-thiol (5j). 5j was purified via column chromatography (SiO_2, $CHCl_3$/MeOH (100:1)), giving yellow crystals: yield 0.20 g (23%); mp 160−161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15 (t, 2H), 3.57 (q, 2H), 4.35 (br t, 1H), 6.13 (s, 1H), 7.08 (d, 1H), 7.13−7.18 (m, 1H), 7.21−7.27 (m, 1H), 7.40 (d, 1H), 7.57 (d, 1H), 7.62 (d, 1H), 7.86 (dd, 1H), 8.09 (br s, 1H), 8.20 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0, 46.9, 96.5, 111.4, 112.5, 115.0, 115.2, 121.6, 122.3, 122.5, 127.2, 136.5, 138.2, 141.5, 145.9, 156.3. MS (EI^+ mode): *m*/*z* 337 (M^+, 8%), 207 (7), 143 (8), 130 (100). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 337.0885, found 337.0882.

1-(Adamantan-1-yl)-5-nitro-1*H*-indole-2-thiol (5k). 5k was purified via column chromatography (SiO_2, $CHCl_3$/hexane (2:1)), giving dark yellow crystals: yield 0.177 g (26%); mp 126−127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 (m, 6H), 1.95 (d, 6H), 2.16 (br s, 3H), 4.11 (br s, 1H), 6.34 (s, 1H), 7.58 (d, 1H), 7.88 (dd, 1H), 8.24 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.6, 36.3, 42.6, 53.9, 102.4, 115.2, 115.5, 121.4, 139.2, 140.8, 145.7, 153.2. MS (EI^+ mode): *m*/*z* 328 (M^+, 46%), 193 (6), 166 (17), 135 (100), 107 (35). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 328.1246, found 328.1244.

1-(2-(Morpholin-4-yl)ethyl)-5-nitro-1*H*-indole-2-thiol (5l). 5l was purified via column chromatography (SiO_2, $CHCl_3$/MeOH (100:1)), giving orange crystals: yield 0.388 g (61%); mp 159−160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (t, 4H), 2.69 (t, 2H), 3.29 (q, 2H), 3.75 (t, 4H), 5.03 (br t, 1H), 6.13 (s, 1H), 7.61 (d, 1H), 7.88 (dd, 1H), 8.23 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.6, 53.3, 56.6, 67.0, 96.3, 115.0, 115.3, 121.6, 138.2, 141.5, 146.0, 156.3. MS (EI^+ mode): *m*/*z* 307 (M^+, 30%), 207 (7), 161 (31), 100 (100). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 307.0991, found 307.0992.

***N*-Ethoxycarbonyl Hydrazone of 1-(2-Chlorophenyl)ethanone (7).** A mixture of 3 g (19.4 mmol) of 1-(2-chlorophenyl)ethanone (**6**), 2.42 g (23.3 mmol) of ethyl carbazate, and 1 drop of AcOH in 40 mL of EtOH/H_2O (1:1) was refluxed for 3 h and left overnight at room temperature. The precipitate was filtered, washed with EtOH/H_2O (1:1), and dried to give 2.19 g (47%) of **7** as white crystals, mp 130−131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, 3H), 4.33 (q, 4H), 7.26−7.30 (m, 2H), 7.35−7.38 (m, 1H), 7.41−7.44 (m, 1H), 7.93 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 16.8, 62.2, 126.9, 129.7, 129.9, 130.5, 132.3, 138.8, 149.5. MS (EI^+ mode): *m*/*z* 240 (M^+, 13%), 205 (33), 161 (30), 152 (26), 133 (100), 126 (25), 111 (7). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 240.0666, found 240.0664.

4-(2-Chlorophenyl)-1,2,3-thiadiazole (8). A solution of **3** (2.0 g, 8.32 mmol) in 6 mL of $SOCl_2$ was refluxed for 2 h, cooled, and poured into water. The precipitate was thoroughly washed with water and dried to give 1.3 g (79%) of pure **8** as light brown crystals, mp 30−31 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.47 (m, 2H), 7.55 (dd, 1H), 8.14 (dd, 1H), 9.05 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 127.4, 129.6, 130.4, 130.6, 131.9, 132.3, 134.6, 159.1. MS (EI^+ mode): *m*/*z* 196 (M^+, 5%), 168 (100), 133 (49), 89 (48). HRMS (EI^+ mode): *m*/*z* calcd for M^+ 195.9862, found 195.9862.

***N*-Butyl-2-(2-chlorophenyl)thioacetamide (9).** A mixture of **8** (0.086 g, 0.43 mmol), K_2CO_3 (0.18 g, 1.3 mmol), and *n*-butylamine (0.16 g, 2.19 mmol) in 10 mL of DMF was heated and stirred at 130 °C for 24 h. After the mixture was cooled to room temperature, the solvent was evaporated under vacuum. The residue was dissolved in $CHCl_3$ and the solution thoroughly washed with water. Evaporation of the $CHCl_3$ gave 0.088 g (97%) of pure **9** as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H), 1.30 (m, 2H), 1.56 (m, 2H), 3.61 (t, 2H), 7.29 (m, 2H), 7.40 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 20.0, 29.8, 45.9, 50.2, 127.5, 129.3, 129.8, 131.9, 133.3, 134.3, 200.2. MS (EI^+ mode): *m*/*z* 206 (M^+, 100%), 164 (7), 150 (27), 134 (9), 125 (15), 89 (15), 57 (16).

2-Chloro-3-(1,2,3-thiadiazol-4-yl)pyridine (13). A mixture of 1.62 g (10.4 mmol) of 1-(2-chloropyridin-3-yl)-ethanone (**11**), 1.14 g (11 mmol) of ethyl carbazate, and 3 drops of AcOH in 20 mL of EtOH was refluxed for 5 h. The solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (100 mL), and the solution was thoroughly washed with water and dried over Na_2SO_4. Thionyl chloride (3.8 mL, 52 mmol) was added to the dried chloroform solution. The mixture was refluxed for 3 h, cooled to room temperature, and poured into water (200 mL). The chloroform layer was thoroughly washed with water (4 × 200 mL) and dried over Na_2SO_4. The solvent was evaporated to yield 1.5 g (74%) of **13** as a brown solid. The product can be crystallized from MeOH to give light gray crystals, mp 70−72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (m, 1H), 8.51 (dd, 1H), 8.60 (dd, 1H), 9.22 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ: 123.0, 126.7, 135.5, 140.4, 148.8, 149.9, 157.4. MS (EI$^+$ mode): *m*/*z* 197 (M^+, 8%), 169 (95), 133 (100), 106 (24), 63 (39). HRMS (EI$^+$ mode): *m*/*z* calcd for M^+ 196.9814, found 196.9814.

1-Butyl-1,3-dihydropyrrolo[2,3-*b*]pyridine-2-thione (14). A mixture of compound **13** (0.88 g, 4.45 mmol), K_2CO_3 (1.84 g, 13.4 mmol), and *n*-butylamine (1.63 g, 22.3 mmol) in DMF (10 mL) was stirred and heated at 70 °C for 12 h. The solution was cooled to room temperature and poured into 200 mL of water. The water layer was extracted with EtOAc (2 × 100 mL). The resulting organic solution was washed with water (3 × 200 mL) and dried over Na_2SO_4. Solvent was evaporated to yield 0.72 g (78%) of crude **14**. After purification via column chromatography (SiO_2, EtOAc/hexane (1:2)), 0.34 g (37%) of pure **14** was obtained. Product **14** is an oil that slowly crystallizes as a yellow solid, mp 172−173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H), 1.33−1.41 (m, 2H), 1.60−1.65 (m, 2H), 3.65 (q, 2H), 4.11 (s, 2H), 7.26−7.30 (m, 1H), 7.85 (dd, 1H), 8.34 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 20.1, 29.8, 46.2, 49.5, 123.0, 131.3, 140.6, 148.4, 151.0, 199.1. MS (EI$^+$ mode): *m*/*z* 207 ([M + 1]$^+$, 100%), 191 (12), 151 (16), 134 (14), 127 (34), 91 (13). HRMS (EI$^+$ mode): *m*/*z* calcd for M^+ 206.0878, found 206.0880.

2-Methoxy-5-nitrobenzo[*b*]thiophene (15). Na (0.29 g, 12.42 mmol) was dissolved in 50 mL of dry MeOH. Compound **3** (1.0 g, 4.14 mmol) was added to the resulting solution, and the mixture was stirred and refluxed for 24 h under an atmosphere of argon. After the mixture was cooled, several drops of AcOH were added to neutralize it. Solvent was evaporated under reduced pressure and the residue chromatographed (SiO_2, EtOAc/hexane (1:8)) to give 0.2 g (23%) of **15** as yellow crystals, mp 118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.04 (s, 3H), 6.46 (s, 1H), 7.70 (d, 1H), 8.04 (dd, 1H), 8.40 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 60.0, 98.3, 116.9, 117.0, 122.3, 138.2, 138.7, 145.7, 168.1. MS (EI$^+$ mode): *m*/*z* 209 (M^+, 100%), 194 (15), 166 (55), 136 (22), 120 (85). HRMS (EI$^+$ mode): *m*/*z* calcd for M^+ 209.0147, found 209.0148.

4-Nitro-2-(1,2,3-thiadiazol-4-yl)benzenethiol (17). A mixture of **3** (0.3 g, 1.24 mmol), K_2CO_3 (0.52 g, 3.73 mmol), and potassium thioacetate (0.42 g, 3.73 mmol) in DMF (10 mL) was stirred and heated at 70 °C for 12 h. The solvent was evaporated under reduced pressure. The residue was dissolved in 200 mL of water, and the solution was stirred with charcoal for 10 min at room temperature. The charcoal was filtered and the resulting solution acidified with aqueous HCl (3 M) to form a yellow precipitate. The precipitate was filtered and thoroughly washed with water to yield 1.9 g (80%) of **17** as a yellow powder, mp 116−117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.77 (s, 1H), 7.60 (d, 1H), 8.15 (dd, 1H), 8.54 (d, 1H), 8.92 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.9, 125.8, 116.9, 129.4, 131.1, 135.1, 142.2, 159.4. MS (EI$^+$ mode): *m*/*z* 237 ([M − 2]$^+$, 52%), 209 (74), 165 (84), 153 (24), 132 (17), 121 (100). HRMS (EI$^+$ mode): *m*/*z* calcd for M^+ 238.9823, found 238.9825.

2-[(*E*)-2-Chloro-5-nitrobenzylidene]-4-[2-chloro-5-nitrophenyl]-1,3-dithiole (18). A mixture of compound **3** (0.5 g, 2.07 mmol) and K_2CO_3 (0.86 g, 6.21 mmol) in MeCN (20 mL) was stirred and refluxed for 6 h. After it was cooled to room temperature, the mixture was poured into water (200 mL) and refluxed for an additional 1 h. The precipitate was filtered and thoroughly washed with water to yield 0.42 g (95%) of **18** as an orange powder, mp 220−223 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 1H), 7.36 (s, 1H), 7.79 (d, 1H), 7.89 (d, 1H), 8.02 (dd, 1H), 8.24 (d, 1H), 8.27 (dd, 1H), 8.34 (d, 1H). MS (EI$^+$ mode): *m*/*z* 426 (M^+, 100%), 390 (18), 298 (8), 264 (13), 199 (58), 164 (19), 155 (43), 132 (28), 123 (19). HRMS (EI$^+$ mode): *m*/*z* calcd for M^+ 425.9303, found 425.9305.

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Supporting Information Available: Text giving general information and figures giving MS, HRMS, and ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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