JOC*Note*

Synthesis of 1,1-Dialkylindolium-2-thiolates via Base-Induced Transformation of 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole in the Presence of Secondary Amines

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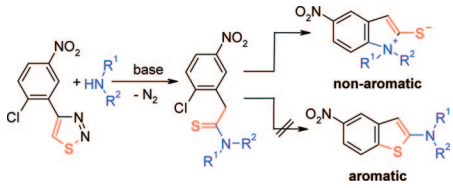
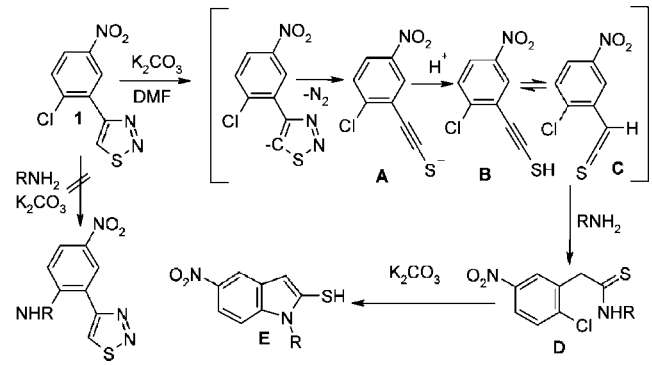


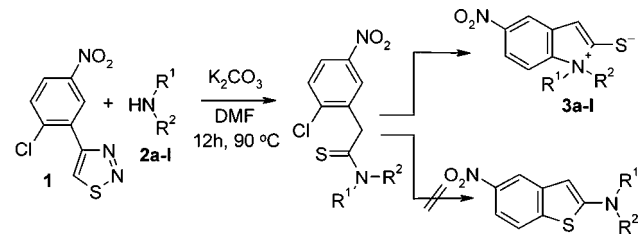
4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole undergoes ring-opening to produce a thioketene intermediate that reacts with secondary amines forming 2-(2-chloro-5-nitrophenyl)-*N*,*N*-dialkylthioacetamides. Intramolecular cyclization of these thioamides via nucleophilic substitution of the halogen on the aromatic ring affords nonaromatic 1,1-dialkylindolium-2-thiolates instead of the expected aromatic *N*,*N*-dialkylaminobenzo[*b*]thiophenes.

The indole nucleus is ubiquitous among natural products, and its synthesis has often attracted organic chemists.[1,2] There are several procedures that have been documented for the introduction of 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 with Lawesson's reagent[6] or phosphorus pentasulfide,[7] and isomerization of 5-chloro-3-phenylthio-1*H*-indole into the corresponding 5-chloro-2-phenylthio-1*H*-indole in the polyphosphoric acid.[8] However, 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.[6,7]

SCHEME 1. Reaction of 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole with Primary Amines



SCHEME 2. Reaction of 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole with Secondary Amines



Recently, we have reported a 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. The mechanism of this reaction was investigated.[9] Base-induced deprotonation of the thiadiazole ring causes anionic ring-opening, accompanied by a loss of nitrogen to yield acetylene thiolate **A**. Protonation of thiolate **A** produces a tautomeric mixture of acetylene thiol **B** and thioketene **C**. Primary amine traps the highly reactive thioketene **C** to form corresponding thioamide **D**. Finally, intramolecular cyclization of thioamide **D** affords *N*-substituted indole-2-thiol **E** (Scheme 1).

In an attempt to expand the scope of this reaction we were surprised to find the base-induced reaction of 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole with secondary amines selectively afforded nonaromatic 1,1-dialkylindolium-2-thiolates instead of the expected *N*,*N*-dialkylaminobenzo[*b*]thiophenes (Scheme 2).[10] The results of our study are summarized in Table 1.

Compound **3g** was obtained in low yield (7%) due to the relatively high nucleophilicity of pyrrolidine which displaces the chlorine atom on the benzene ring faster than cyclization occurs, resulting in thioamide **4** (62%) as a major product (Scheme 3).

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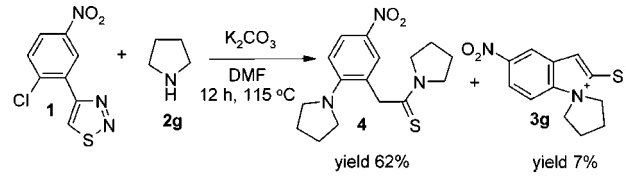
TABLE 1. Synthesis of 1,1-Dialkylindolium-2-thiolates

entry	ratio **1**/K_2CO_3	amine	product
1	1/5/7	NH_4OAc **2a**	**3a** (75%)
2	1/5/3	**2b**	**3b** (55%)
3	1/5/3	**2c**	**3c** (33%)
4	1/5/5	**2d**	**3d** (25%)
5	1/5/5	**2e**	**3e** (38%)
6	1/3/3	**2f**	**3f** (41%)
7	1/5/5	**2g**	**3g** (7%)
8	1/5/5	**2h**	**3h** (17%)
9	1/3/3	**2i**	**3i** (63%)
10	1/3/3	**2j**	**3j** (20%)
11	1/5/5	**2k**	**3k** (49%)
12	1/3/3	**2l**	**3l** (74%)

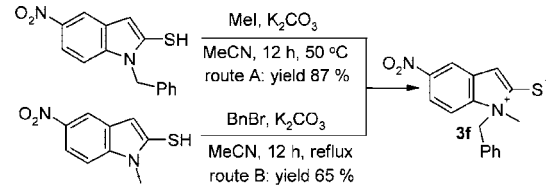
The formation of 1,1-dialkylindolium-2-thiolates **3a**−***l*** was unambiguously supported by counter-synthesis of compound **3f** from two different precursors. Surprisingly, quaternization of the endocyclic *N*-atom and loss of aromaticity is preferable to alkylation of the exocyclic *S*-atom, when aromaticity remains intact (Scheme 4).

It is worthy of note that the best result for the synthesis of compound **3a** was achieved by using the combination NH_4OAc/K_2CO_3/DMF that made it possible to generate dimethylamine in situ (Scheme 5).

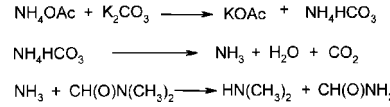
SCHEME 3. Reaction of 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole with Pyrrolidine



SCHEME 4. Counter-Synthesis of 1-Benzyl-1-methyl-5-nitro-1*H*-indoliumthiolate



SCHEME 5. Convenient in Situ Generation of Dimethylamine



In summary, we have found and developed a convenient one-pot synthesis of 1,1-dialkylindolium-2-thiolates, accomplished with easily accessible starting materials. This procedure provides a simple and practical approach to the construction of novel polyfunctional indoles. Further studies of this reaction (reaction conditions optimization, scope, and application) are underway.

Experimental Section

General Procedure for the Synthesis of 1,1-Dialkylindolium-2-thiolates (3a−*l*). 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole **1** (0.5 g; 2.07 mmol), K_2CO_3 (3−7 equiv), the corresponding amine **2a**−***l*** (3−5 equiv), and 10 mL of DMF (in that order; for molar ratios see Table 1) were charged into a 50-mL round-bottomed flask. The mixture was stirred for 12 h at 90 °C. DMF was removed under reduced pressure and the residue was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:3), (1:2), (1:1) (2:1), or $CHCl_3$/MeOH (40:1), (100:1)) affording the corresponding 1,1-dialkylindolium-2-thiolate **3a**−***l*** (yields 7−75%, see Table 1).

1,1-Dimethyl-5-nitro-1*H*-indolium-2-thiolate (3a). 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole **1** (0.5 g; 2.07 mmol), K_2CO_3 (2 g; 14.49 mmol; 7 equiv), ammonium acetate **2a** (0.8 g; 10.35 mmol; 5 equiv), and 10 mL of DMF were charged into a 50-mL round-bottomed flask. The mixture was stirred for 12 h at 90 °C. DMF was removed under reduced pressure and the residue was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:2)) to afford red crystalline solid, 0.35 g (75%), mp 133−134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04 (s, 6H), 5.97 (s, 1H), 7.59 (d, 1H), 7.82 (dd, 1H), 8.20 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.2, 95.5, 114.4, 114.7, 121.5, 138.3, 141.8, 145.9, 159.9; *m*/*z* (EI, 70 eV) 222 (M^+, 100%), 207 (3), 192 (6), 176 (60), 146 (27); HRMS (EI, 70 eV) calcd for $C_{10}H_{10}N_2O_2S$ M^+ 222.0463, found 222.0464.

1,1-Diethyl-5-nitro-1*H*-indolium-2-thiolate (3b). 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole **1** (0.5 g; 2.07 mmol), K_2CO_3 (0.86 g; 6.21 mmol; 3 equiv), diethylamine **2b** (0.76 g; 10.35 mmol; 5 equiv), and 10 mL of DMF were charged into a 50-mL round-bottomed flask. The mixture was stirred for 12 h at 90 °C. DMF was removed under reduced pressure and the residue was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:3), (1:2), (1:1)) to afford red crystalline solid, 0.29 g (55%), mp 41−42 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6H), 3.40 (q, 4H), 5.97 (s,

1H), 7.58 (d, 1H), 7.81 (dd, 1H), 8.18 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 47.0, 94.2, 114.08, 114.13, 121.3, 137.7, 142.1, 145.9, 157.9; *m*/*z* (EI, 70 eV) 250 (M^+, 66%), 235 (100), 207 (25), 189 (23), 161 (20). Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C 57.58; H 5.64; N 11.19. Found: C 57.74; H 5.60; N 11.25.

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Supporting Information Available: General information, characterization data for compounds **3c**−***l*** and **4** along with copies of ^{1}H and ^{13}C NMR and mass spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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