JOC The Journal of Organic Chemistry

Note

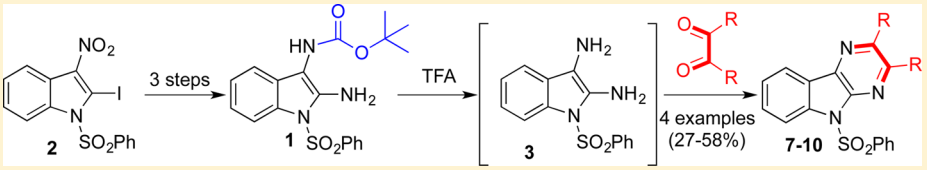
pubs.acs.org/joc

Synthesis of a Masked 2,3-Diaminoindole

Philip Z. Mannes, Evans O. Onyango, and Gordon W. Gribble*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755-3564, United States

Supporting Information



ABSTRACT: A three-step synthesis of masked 2,3-diaminoindole **1** from 2-iodo-3-nitro-1-(phenylsulfonyl)indole (**2**) has been developed. Treatment of **1** with trifluoroacetic acid generates the unstable 2,3-diamino-1-(phenylsulfonyl)indole (**3**), which can be trapped with α-dicarbonyl compounds to afford 5*H*-pyrazino[2,3-*b*]indoles **7**−**10**.

Although *functionalized* 3- and 2-aminoindoles are well established in synthesis (e.g., 3-acylaminoindoles, 2-amino-3-cyanoindoles) and several synthetic routes are known,[1,2] the parent 3- and 2-aminoindoles are labile and only rarely have been isolated.[3] In contrast to the situation with 3- and 2-aminoindoles, 2,3-diaminoindoles, functionalized or not, are virtually unknown compounds.[4] In an extension of our study of the synthesis and chemistry of 3- and 2-nitroindoles,[1d,2e,5] we now describe the synthesis of a masked *N*-protected 2,3-diaminoindole that can serve, for example, as a precursor to 5*H*-pyrazino[2,3-*b*]indoles, imidazo[4,5-*b*]indoles, 6*H*-indolo[2,3-*b*]quinoxalines, and similarly fused indoles that exhibit cytotoxicity, antiviral, antibacterial, and other biological activities (Figure 1).[6]

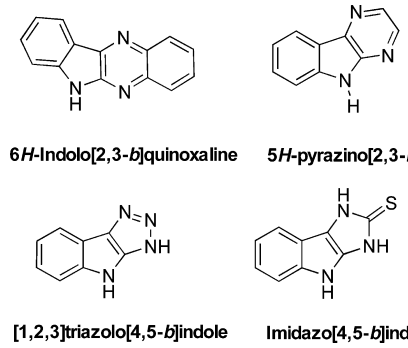
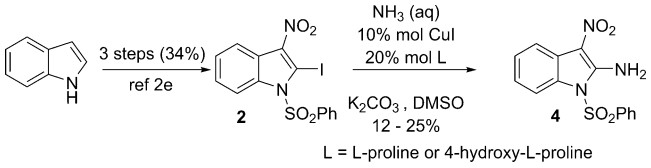


Figure 1. Representative compounds bearing the 2,3-diaminoindole scaffold.

We envisioned a route to a 2,3-diaminoindole, such as 2,3-diamino-1-(phenylsulfonyl)indole (**3**), from indole via 2-amino-3-nitro-1-(phenylsulfonyl)indole (**4**) as depicted in Scheme 1.

As we described earlier,[2e] indole was converted to 2-iodo-3-nitro-1-(phenylsulfonyl)indole (**2**) by a sequence of *N*-phenylsulfonylation, C2-iodination, and C-3 nitration (34% overall yield) (Scheme 1). We initially attempted to aminate **2**

Scheme 1. Synthesis of 4 via CuI Catalyzed Amination of 2-Iodo-3-nitroindole 2



with ammonium salts[7] and aqueous ammonia[8] as the nitrogen source and with CuI as the catalyst. However, under various conditions only 25% of the desired 2-amino-3-nitroindole **4** was obtained. We also attempted a direct amination of **2** using a palladium-catalyzed coupling of ammonia ($Pd[(P(o\text{-}tol)_3)]_2$, CyPF-*t*-Bu, NaO-*t*-Bu, 0.5 M ammonia solution in 1,4-dioxane, 50−80 °C).[9] Under these conditions, we isolated a mixture of unidentified products, without any evidence of **4**. In contrast, treatment of **2** with *tert*-butylamine under our standard conditions[2e] gave **5**, which was further exposed to HCl to induce cleavage of the *tert*-butyl group (Scheme 2).[10] This gave **4** in 47% yield for the two steps. The attempted amination of **2** with *p*-methoxybenzylamine only resulted in removal of the phenylsulfonyl group.

With the desired 2-amino-3-nitroindole **4** in hand, the stage was set for the reduction of the nitro group. Classical metal based methods[11] and metal catalytic hydrogenation[12] methods only returned the starting material and in some cases formation of intractable mixtures (Table 1). We ultimately achieved the reduction of the nitro group by employing a combination of indium/Boc_2O/AcOH in MeOH, which we used previously to reduce 3-nitroindoles.[1d] Given the known instability of 2-and 3-aminoindoles, and the inherent advantage of indium as a reducing agent,[13] the success of this reaction depended on the *in situ* trapping of the amino group as it formed.[1d,14] No reduction product was isolated in the absence of the Boc

Received: September 21, 2016
Published: November 7, 2016

DOI: 10.1021/acs.joc.6b02318
J. Org. Chem. 2016, 81, 12478−12481

Scheme 2. Synthesis of 4 via S_NAr Displacement of 2-Iodo-3-nitroindole 2

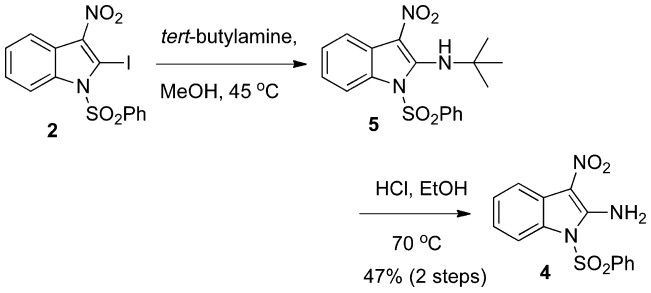


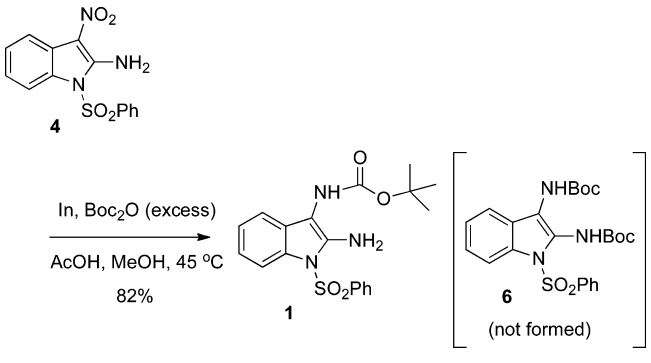
Table 1. Reaction Conditions for the Reduction of the C-3 Nitro Group of 4

conditions	Boc_2O	time	yield of **1** (%)
H_2/Pd−C/EtOH/25 °C	no	overnight	0[a]
H_2/Pd−C/MeOH/60 °C	yes	overnight	16
Fe/EtOH/AcOH/70 °C	no	overnight	0[a,b]
Fe/EtOH/AcOH/45 °C	yes	overnight	0[a]
Sa/NH_4Cl/$I_{2(cat)}$/THF/25 °C	no	48 h	0[a]
Sa/NH_4Cl/$I_{2(cat)}$/THF/45 °C	yes	48 h	0[a]
$SnCl_2$/EtOH/reflux	no	overnight	0[a,b]
$SnCl_2$EtOH/45 °C	yes	5 h	0[a]
NH_2NH_2/Pd−C/MeOH/80 °C	no	5 min	0[a,b]
In/AcOH/MeOH/45 °C	yes	10 h	82
In/AcOH/MeOH/45 °C	no	4 h	0[b]

[a]Starting material recovered. [b]Unidentified compound isolated.

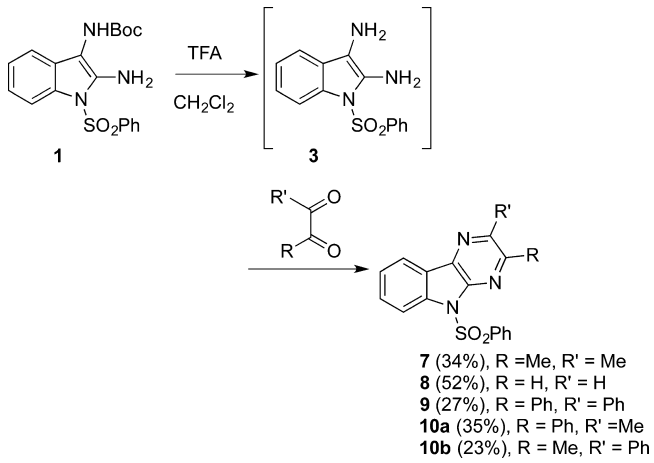
anhydride. Although we initially assigned the crude product of this reaction as the desired 2,3-diaminoindole **3** based on HRMS analysis,[15] we overlooked a broader and less pronounced *tert*-butyl ^1H NMR peak.[16−19] Thus, after further spectral analysis and high temperature ^1H NMR experiments,[20] the structure of the product resulting from treatment of the **4** with indium/Boc_2O/AcOH was assigned as **1** isolated in 82% yield (Scheme 3). Despite using excess Boc anhydride, both ^1H and ^{13}C NMR strongly supported the presence of a single Boc group (no **6** was formed). The regioselectivity of this reaction can be attributed to two factors: (i) the C-3 amine is probably inherently more reactive than the C-2 amine due to the inductive effect of the SO_2Ph group, and (ii) steric interaction from the SO_2Ph group makes the C-2 amine less accessible. A NOESY NMR analysis of **1** showed correlations between the C-3 *tert*-butylcarboxamide proton and that of the C-4 indole ring, as well as between the C-2 amino group and the aromatic protons of the *N*-phenylsulfonyl group. We also attempted the indium reduction in the presence of acetic anhydride, but an intractable mixture of polar compounds was isolated.

Scheme 3. Synthesis of 1 via Indium Mediated Reduction of 4



When the Boc protected aminoindole **1** was treated with trifluoroacetic acid (TFA), TLC analysis showed complete consumption of the starting material and the formation of a new polar compound. However, workup gave a yellow residue that quickly turned into black tar (^1H NMR analysis showed an intractable mixture). In a separate experiment, when **1** was treated with TFA and 2,3-butanedione was added after 15 min (when TLC analysis showed no remaining **1**), the pyrazino[2,3-*b*]indole **7** was formed in 34% yield (Scheme 4). Similarly,

Scheme 4. Condensation of Diamine 3 with Various α-Dicarbonyl Compounds

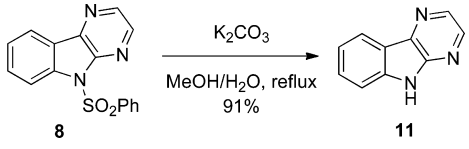


pyrazino[2,3-*b*]indoles **8** and **9** were obtained by trapping diaminoindole **3** with glyoxal and benzil, respectively. Condensation of **3** with 1-phenyl-1,2-propanedione gave separable pyrazino[2,3-*b*]indoles **10a** and **10b** in 35 and 23% yields, respectively. Based on the product ratio, the more nucleophilic C-3 indole amino group reacts with the more reactive ketone carbonyl of 1-phenyl-1,2-propanedione. The isomers were fully characterized and distinguished by X-ray crystallography of the major isomer **10a** (cf. Supporting Information). Attempted condensation of *in situ* generated **3** with 2-oxopropanal and 2-oxophenylacetaldehyde gave low yields of inseparable isomeric mixtures.

Cleavage of the SO_2Ph group in pyrazino[2,3-*b*]indole **8** with K_2CO_3 in MeOH/H_2O afforded the known pyrazino[2,3-*b*]indole (**11**) in 91% yield (Scheme 5).[21d]

In conclusion, we have synthesized the masked 2,3-diaminoindole **1** and demonstrated that it can be converted *in situ* to 2,3-diaminoindole **3** with TFA and subsequently trapped with α-dicarbonyl compounds to generate 5*H*-pyrazino[2,3-*b*]indoles. Our general method complements the

Scheme 5. Cleavage of the *N*-Phenylsulfonyl Protecting Group To Afford 11



DOI: 10.1021/acs.joc.6b02318
J. Org. Chem. 2016, 81, 12478−12481

well-known syntheses of 5*H*-pyrazino[2,3-*b*]indoles and related fused indoles via the condensation of isatins with phenylenediamines.[21]

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed in the appropriate oven-dried glass apparatus under a balloon of nitrogen gas (N_2). Solvents were reagent grade and in most cases rigorously dried before use. Methylene chloride and THF were dried and stored over molecular sieves. Furan was distilled and dried from potassium hydroxide. All reagents were obtained commercially as reagent grade and, unless otherwise noted, used without further purification. The organolithium reagents were titrated with *N*-benzylamide prior to use. All glassware utilized for Diels–Alder reactions was flame-dried. Reactions were monitored by TLC silica gel plates (0.25 mm) and visualized by UV light or *p*-anisaldehyde. Column chromatography was performed using silica gel (60, particle size 40–60 mm). Additionally, flash column chromatography was performed on Biotage Automated Liquid Chromatography System Isolera One using Biotage SNAP Ultra 25 um HP-Sphere 10 g silica gel cartridges. The organic extracts were dried over anhydrous $MgSO_4$. Proton (^{1}H), carbon (^{13}C), and fluorine (^{19}F) nuclear magnetic resonance spectra were recorded at 500 or 600, 150, or 565 MHz, respectively. Chemical shifts are reported in parts per million (ppm, δ) with the residual deuterated solvent as an internal standard (7.26 ppm for chloroform, 5.32 ppm for methylene chloride, 2.50 for dimethyl sulfoxide). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra (HRMS) were obtained employing electron ionization (EI) or electrospray (ES), with TOF as the mass analyzer. Infrared (IR) spectroscopy was conducted using Fourier transform infrared spectrometers using the cast film procedure.

Procedures. *N-(tert-Butyl)-3-nitro-1-(phenylsulfonyl)-1H-indol-2-amine (**5**).* A stirred suspension of **2** (284 mg, 0.67 mmol) in MeOH (4.5 mL) at 0 °C was treated dropwise with *tert*-butylamine (0.210 mL, 2.01 mmol) and subsequently warmed to 38 °C for 7 h. The reaction mixture was then loaded directly onto silica gel (SiO_2, ~0.5 g). Dry-pack purification (10:1 hexanes/ethyl acetate) afforded **5** as a bright yellow solid (124 mg, 50%). Recrystallization from hexanes/ethyl acetate gave **5** as a yellow crystals, R_f = 0.54 (3:1 hexanes/ethyl acetate): mp dec 148 °C; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.20 (s br, 1H), 7.99–7.98 (m, 1H), 7.84–7.83 (m, 1H), 7.48–7.47 (m, 3H), 7.30–7.27 (m, 4H), 1.58 (s, 9H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 151.8, 134.8, 134.6, 131.9, 129.3, 128.8, 127.2, 126.8, 124.9, 124.3, 119.5, 117.7, 62.2, 30.80; UV (EtOH) λ_{max} 201, 203, 206, 215, 217, 262, 268, 273 nm; HRMS (ES) calcd for $C_{18}H_{20}N_3O_4S$ 374.1175, $[M + 1]^+$ found 374.1175.

*3-Nitro-1-(phenylsulfonyl)-1H-indol-2-amine (**4**).* Concentrated HCl (2 mL) was added dropwise to a stirred suspension of **5** (108 mg, 0.29 mmol) in EtOH (3 mL) and heated to 70 °C overnight. After cooling to rt, the reaction was diluted with ethyl acetate and then the pH was adjusted to 7 with a saturated solution of $NaHCO_3$. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Concentration of the solvent *in vacuo* gave **4** as a dark-yellow solid (86 mg, 94%). Recrystallization of **4** from ethanol/ethyl acetate gave **4** as a yellow crystals, R_f = 0.59 (1:1 hexanes/ethyl acetate): mp 198–199 °C; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.02 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 8.5, 2H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 148.9, 136.4, 135.6, 129.9, 129.4, 127.1, 126.0, 124.6, 122.1, 119.3, 113.2; IR (KBr) 3442, 3311, 1630 cm^{-1}; UV (EtOH) λ_{max} 202, 204, 219, 238, 267, 275 nm; HRMS (ES) calcd for $C_{14}H_{12}N_3O_4S$ 318.0549, $[M + 1]^+$ found 318.0550.

*tert-Butyl (2-amino-1-(phenylsulfonyl)-1H-indol-3-yl)carbamate (**1**).* To a stirred suspension of **4** (889 mg, 2.8 mmol), AcOH (1.6 mL, 28 mmol), and di-*tert*-butyl dicarbonate (3.05 g, 14 mmol) in MeOH (17 mL) at rt was added indium metal (1.6 g, 14 mmol). The reaction mixture was stirred for 10 h at 45 °C. After cooling to rt, the opaque solution was filtered through Celite and the filtrate was concentrated *in vacuo*. The resulting residue was with diluted with ethyl acetate and washed with saturated $NaHCO_3$ to remove the acetic acid. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Column purification (5:1 hexanes/ethyl acetate) gave **1** as a light brown/orange solid (885 mg, 82%). The compound was resistant to crystallization, R_f = 0.26 (3:1 hexanes/ethyl acetate): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.18–7.11 (m, 1H), 7.11–7.03 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.7, 137.7, 136.6, 134.0, 130.6, 129.2, 127.8, 126.8, 124.2, 121.5, 114.5, 114.1, 97.9, 80.9, 28.3; IR (KBr) 3372, 2977, 1699, 1651, 1459, 1365 cm^{-1}; HRMS (ES) calcd for $C_{19}H_{21}N_3O_4S$ 387.1253, $[M]^+$ found 387.1260.

*2,3-Dimethyl-5-(phenylsulfonyl)-5H-pyrazino[2,3-b]indole (**7**).* Trifluoroacetic acetic acid (0.15 mL) was added dropwise to a stirred solution of **1** (20 mg, 0.052 mmol) in methylene chloride (1 mL) under nitrogen. The reaction proceeded for 15 min, and then 2,3-butanedione (0.005 mL, 0.052 mmol) was added dropwise. After 30 min, the reaction mixture was diluted with ethyl acetate and poured onto a saturated solution of $NaHCO_3$ (~10 mL). The organic layer was then washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Column purification (5:1 hexanes/ethyl acetate) gave **7** as an off-white solid (6 mg, 34%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 7.7 Hz, 1H), 8.14 (d, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 1H), 7.47–7.37, (m, 3H), 2.70 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.1, 148.5, 143.3, 138.6, 138.5, 134.8, 134.1, 129.5, 128.9, 127.7, 124.3, 122.6, 120.8, 114.9, 22.9, 22.1; HRMS (EI) calcd for $C_{18}H_{16}N_3O_2S$ 338.0964, $[M + 1]^+$ found 338.0963.

*5-(Phenylsulfonyl)-5H-pyrazino[2,3-b]indole (**8**).* Trifluoroacetic acid (0.30 mL) was added dropwise to a stirred solution of **1** (40 mg, 0.10 mmol) in methylene chloride (2 mL) under nitrogen. The reaction proceeded for 45 min, and then glyoxal (40% in water, 0.010 mL) was added dropwise. After 20 min, the reaction mixture was diluted with ethyl acetate and poured onto a saturated solution of $NaHCO_3$ (~10 mL). The organic layer was then washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Column purification (3:1 hexanes/ethyl acetate) gave **8** as a light yellow solid (16 mg, 52%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.4 Hz, 1H), 8.52 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 2.4 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 2H), 7.72–7.69 (m, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.2, 140.5, 140.3, 139.1, 138.4, 134.4, 130.8, 129.2, 127.5, 124.7, 122.2, 121.6, 114.9; HRMS (EI) calcd for $C_{16}H_{11}N_3O_2S$ 309.0572, $[M]^+$ found 309.0573.

*2,3-Diphenyl-5-(phenylsulfonyl)-5H-pyrazino[2,3-b]indole (**9**).* Trifluoroacetic acid (0.018 mL, 0.23 mmol) was added slowly to a stirred solution of **1** (30 mg, 0.078 mmol) and benzil (18 mg, 0.086 mmol) in methylene chloride (2 mL) under nitrogen. After 16 h, the reaction mixture was diluted with ethyl acetate and poured onto a saturated solution of $NaHCO_3$ (~5 mL). The organic layer was then washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography on a Biotage SNAP HP Sphere 10 g cartridge with 94:6 to 50:50 (hexanes–EtOAc) gradient elution afforded **9** as a white solid (9 mg, 27%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.5 Hz, 1H), 8.31 (d, *J* = 7.5 Hz, 1H), 8.25–8.21 (m, 2H), 7.71–7.68 (m, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.52–7.42 (m, 7H), 7.36–7.30 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4, 148.8, 143.4, 139.7, 139.3, 138.8, 138.6, 135.7, 134.3, 130.4, 130.3, 130.0, 129.0, 128.6, 128.4, 128.3, 128.1, 124.4, 122.3, 121.7, 114.9; HRMS (EI) calcd for $C_{28}H_{19}N_3O_2S$ 461.1198, $[M]^+$ found 461.1203.

*2-Methyl-3-phenyl-5-(phenylsulfonyl)-5H-pyrazino[2,3-b]indole (**10a**) and 3-Methyl-2-phenyl-5-(phenylsulfonyl)-5H-pyrazino[2,3-b]indole (**10b**).* Trifluoroacetic acid (0.036 mL) was dropwise added to a stirring solution of **1** (60 mg, 0.156 mmol) and 1-phenyl-1,2-propanedione (46 mg, 0.312 mmol) in methylene chloride (6 mL) under nitrogen. After 16 h, the reaction mixture was diluted with ethyl acetate and poured onto a saturated solution of $NaHCO_3$ (~5 mL). The organic layer was then washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (15:1 hexanes/ethyl acetate) afforded **10a** as a white solid (22 mg, 35%) and

DOI: 10.1021/acs.joc.6b02318
J. Org. Chem. 2016, 81, 12478–12481

10b as a white solid (14 mg, 23%). Recrystallization from methylene chloride gave **10a** as white crystals, mp 193−194 °C. **10a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (dt, J = 8.5 Hz, 0.9 Hz, 1H), 8.21 (d, J = 7.5 Hz, 1H), 8.12−8.07 (m, 2H), 7.63−7.55 (m, 3H), 7.54−7.38 (m, 5H), 7.38−7.32 (m, 2H), 2.70 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.0, 147.6, 143.2, 139.4, 138.9, 138.8, 138.6, 135.5, 134.2, 130.1, 129.6, 128.9, 128.7, 128.3, 128.0, 124.4, 121.3, 114.9, 23.5; HRMS (EI) calcd for $C_{23}H_{18}N_3O_2S$ 400.1120, $[M + 1]^+$ found 400.1116. **10b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (dt, J = 8.5 Hz, 0.8 Hz, 1H), 8.36−8.04 (m, 3H), 8.12−8.07 (m, 2H), 7.63−7.30 (m, 8H), 2.69 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.2, 148.4, 143.5, 139.0, 138.6, 135.2, 134.2, 130.0, 134.2, 129.9, 128.9, 129.9, 129.0, 128.9, 128.6, 128.5, 128.3, 128.0, 124.4, 121.4, 114.9, 24.0; HRMS (EI) calcd for $C_{23}H_{18}N_3O_2S$ 400.1120, $[M + 1]^+$ found 400.1115.

5H-Pyrazino[2,3-b]indole (11). To a stirring solution of **8** (6 mg, 0.019 mmol) in MeOH/H_2O (1 mL:0.300 mL) was added K_2CO_3 (36 mg, 0.26 mmol). The reaction mixture was then heated at reflux for 30 min. After cooling to rt, the reaction mixture was diluted with ethyl acetate and poured onto brine. The organic layer was separated, dried over $MgSO_4$, and subsequently concentrated *in vacuo* to give **11** as a yellow solid (3 mg, 91%): ^{1}H NMR (600 MHz, DMSO) δ 12.14 (br s, 1H), 8.50 (d, J = 2.7 Hz, 1H), 8.44 (d, J = 2.7 Hz, 1H), 8.23 (d, J = 7.9 Hz, 1H), 7.63−7.58 (m, 2H), 7.36−7.32 (m, 1H); ^{13}C NMR (150 MHz, DMSO) δ 146.0, 140.7, 140.4, 136.9, 135.7, 129.5, 121.4, 121.0, 119.8, 112.6. These spectral data matched those reported.[21d]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02318.

^{1}H and ^{13}C NMR spectra for new compounds (PDF)

X-ray data for **10a** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gordon.w.gribble@dartmouth.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by the Donors of the Petroleum Research Fund administered by the American Chemical Society. P.Z.M. acknowledges support from the Zabriskie Fellowship from Dartmouth College. We are grateful to Dr. Jerry Jasinski of Keene State University for X-ray analyses.

■ REFERENCES

(1) 3-Aminoindoles: (a) Velezheva, V. S.; Yarosh, A. V.; Kozik, T. A.; Suvorov, N. N. *J. Org. Chem. USSR (Engl. Transl.)* **1978**, 1596−1607. (b) Bailey, A. S.; Buckley, A. J.; Warr, W. A.; Wedgwood, J. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2411−2415. (c) Nettekoven, M. *Tetrahedron Lett.* **2000**, *41*, 8251−8254. (d) Roy, S.; Gribble, G. W. *Heterocycles* **2006**, *70*, 51−56. (e) Roy, S.; Roy, S.; Gribble, G. W. *Tetrahedron Lett.* **2008**, *49*, 1531−1533.

(2) 2-Aminoindoles: (a) Snyder, H. R.; Merica, E. P.; Force, C. G.; White, E. G. *J. Am. Chem. Soc.* **1958**, *80*, 4622−4625. (b) Becher, J.; Pluta, K.; Krake, N.; Brøndum, K.; Christensen, N. J.; Vinader, M. V. *Synthesis* **1989**, *1989*, 530−533. (c) Bata, I.; Korbonits, D.; Kolonits, P.; Podányi, B.; Takácsy-Erös, T.; Simon, K. *Chem. Ber.* **1993**, *126*, 1835−1841. (d) Landwehr, J.; Troschütz, R. *Synthesis* **2005**, 2414−2420. (e) Roy, S.; Gribble, G. W. *Tetrahedron Lett.* **2007**, *48*, 1003−1005 and references cited therein.

(3) (a) Pschorr, R.; Hoppe, G. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2543−2552. (b) Madelung, W. *Liebigs Ann. Chem.* **1914**, *405*, 58−95. (c) Hiremath, S. P.; Kaddargi, S. S.; Mruthyunjayaswamy, B. H. M.; Purohit, M. G. *Indian J. Chem.* **1980**, *19B*, 767−769.

(4) Wang and colleagues recently reported the synthesis of functionalized 2,3-diaminoindoles en route to imidazo[4,5-*b*]indoles: (a) Sheng, G.; Huang, K.; Chi, Z.; Ding, H.; Xing, Y.; Lu, P.; Wang, Y. *Org. Lett.* **2014**, *16*, 5096−5099. Jeffry has noted that a straightforward synthesis of 2,3-diaminoindoles is still largely undeveloped: (b) Anumandla, D.; Acharya, A.; Jeffrey, C. S. *Org. Lett.* **2016**, *18*, 476−479.

(5) (a) Roy, S.; Gribble, G. W. *Tetrahedron Lett.* **2007**, *48*, 1003−1007. (b) Roy, S.; Kishbaugh, T. L. S.; Jasinski, J. P.; Gribble, G. W. *Tetrahedron Lett.* **2007**, *48*, 1313−1316. (c) Androsov, D. A.; Kishbaugh, T. L. S.; Gribble, G. W. *Tetrahedron Lett.* **2008**, *49*, 6621−6623.

(6) (a) Manna, K.; Agrawal, Y. K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2688−2692. (b) Pai, N. R.; Pusalkar, D. A. *J. Chem. Pharm. Res.* **2010**, *2*, 485−493. (c) Rane, A. R.; Jain, K.; Shaikh, M.; Hampannavar, G.; Karpoormath, R. A. *Curr. Top. Med. Chem.* **2016**, *16*, 1262−1289.

(7) Kim, J.; Chang, S. *Chem. Commun.* **2008**, 3052−3054.

(8) Jiang, L.; Lu, X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2009**, *74*, 4542−4546.

(9) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049−11061.

(10) Lee, L.; Kreutter, K. D.; Pan, W.; Crysler, C.; Spurlino, J.; Player, M. R.; Tomczuk, B.; Lu, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6266−6269.

(11) Lu, H.; Geng, Z.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Org. Lett.* **2016**, *18*, 2774−2776.

(12) Schabel, T.; Belger, C.; Plietker, B. *Org. Lett.* **2013**, *15*, 2858−2861.

(13) Li, C. *Tetrahedron* **1996**, *52*, 5643−5668.

(14) Kim, B. H.; Han, R.; Piao, F.; Jun, Y. M.; Baik, W.; Lee, B. M. *Tetrahedron Lett.* **2003**, *44*, 77−79.

(15) Analysis of both the HRMS and MS showed a fragmentation pattern reminiscent of loss of CO_2 and *tert*-butyl to account for the observed HRMS (EI) calcd for $C_{18}H_{16}N_3O_2S$ 338.0964, $[M + 1]^+$; found 338.0963.

(16) A literature search revealed that similarly broadened *tert*-butyl peaks have been observed for *tert*-butyl groups attached to aromatic rings, and this phenomenon is attributed to restricted bond rotation: refs 17−19.

(17) Yamamoto, G.; Ōki, M. *Tetrahedron Lett.* **1986**, *27*, 49−50.

(18) Gribble, G. W.; Olson, E. R.; Brown, J. H.; Bushweller, C. H. *J. Org. Chem.* **1993**, *58*, 1631−1634.

(19) Kuznetsov, N. Y.; Khrustalev, V. N.; Godovikov, I. A.; Bubnov, Y. N. *Eur. J. Org. Chem.* **2006**, *2006*, 113−120.

(20) We performed high temperature (up to 45 °C in $CDCl_3$) NMR experiments and observed better resolution and sharpening of the peaks.

(21) (a) Buu-Hoi, N. P.; Saint-Ruf, G. *Bull. Soc. Chim. Fr* **1960**, 1920−1922. (b) Sarkis, G. Y.; Al-Badri, H. T. *J. Heterocycl. Chem.* **1980**, *17*, 813−815. (c) Bergman, J.; Damberg, C.; Vallberg, H. *Rec. Trav. Chim. Pays-Bas* **1996**, *115*, 31−36. (d) Alphonse, F.-A.; Routier, S.; Coudert, G.; Mérour, J.-Y. *Heterocycles* **2001**, *55*, 925−940. (e) Avula, S.; Komsani, J. R.; Koppireddi, S.; Yadla, R. *J. Heterocycl. Chem.* **2015**, *52*, 1737−1742.

DOI: 10.1021/acs.joc.6b02318
J. Org. Chem. 2016, 81, 12478−12481