Amination of Arenes with Electron-Deficient Azodicarboxylates

Helen Mitchell and Yves Leblanc*

Merck Frosst Centre for Therapeutic Research, P.O. Box 1005, Pointe Claire-Dorval, Quebec, Canada H9R 4P8

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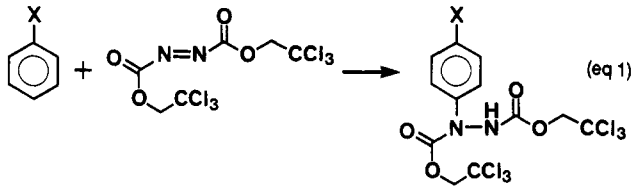
The concept of making use of azodicarboxylates as an electrophilic source of nitrogen NH_2^+ has been well established over the last few years.[1-5] More recently, we reported the amination of electron-rich arenes 1 by an electron-deficient azodicarboxylate, namely bis(2,2,2-trichloroethyl) azodicarboxylate (2) (eq 1).[6] The amination



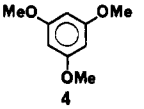
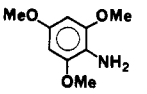
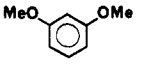
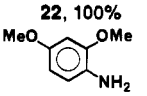
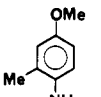
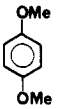
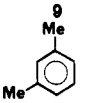
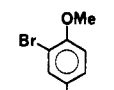
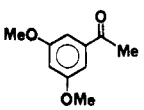
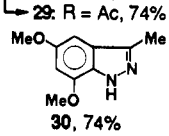
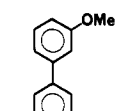
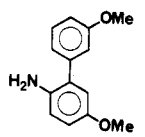
1 2 3

reactions were conducted in 3 M lithium perchlorate–diethyl ether or acetone solution.[7] However, with less-reactive substrates such as anisole (6) (Table 1), the reaction required heating for several hours, whereas with poorly reactive compounds like xylene (10) or dimethoxyacetophenone (12) the formation of aminated products was not observed at all. Thus, there was a need to develop other experimental conditions for this amination reaction. Herein, we describe more practical conditions for the amination of arenes including indole and 2-methylindole.[8] In addition, the synthesis and the reactivity of an unsymmetrical azo reagent toward arenes is reported. The advantage of this new reagent is that it is now possible to convert the hydrazides to their corresponding hydrazines without reduction of the N–N bond.

Results and Discussion

Amination of Arenes by Bis(2,2,2-trichloroethyl) Azodicarboxylate (BTCEAD). We observed that electron-rich arene molecules can be aminated with a catalytic amount of Lewis acid such as ZnI_2 or $ZnCl_2$ in CH_2Cl_2 solution. For example, 1,3,5-trimethoxybenzene (4) was aminated on a gram scale by BTCEAD (1.2 equiv) in the presence of 0.1 equiv of ZnI_2 as an activator. The reaction was complete within 20 min at room temperature to provide the hydrazide 14 in 95% yield. Similarly, 1,3-dimethoxybenzene (5) was converted to the hydrazide 15 in quantitative yield. With anisole (6) as a substrate, the reaction

Table 1

arene	hydrazide[b] no.	condtn	time	% yield	aniline[f]
 4	14	*a*	20 min	95	 **22**, 100%
 5	15	*a*	15 min	100	 **23**, 85%
 6	16	*b*	18 h	91	 **24**, 67%
 7	17	*c*	30 min	92	 **25**, 76%
 8	–				
 9	–				
 10	18	*d*	18 h	86	 *g* → **26**: R = H, 85%; **27**: R = Ac, 93%
 11	19	*e*	8 h	80	 *g* → **28**: R = H, 75%; **29**: R = Ac, 74%
 12	20	*e*	24 h	77	 **30**, 74%
 13	21	*c*	18 h	100	 **31**, 99%

[a] BTCEAD, 1 equiv of ZnI_2, CH_2Cl_2, 25 °C. [b] BTCEAD, 1.0 equiv of $ZnCl_2$, CH_2Cl_2, 25 °C. [c] BTCEAD, 0.1 equiv of $ZnCl_2$, CH_2Cl_2, 25 °C. [d] BTCEAD, BF_3·Et_2O, 25 °C. [e] BTCEAD, BF_3·Et_2O, CH_2Cl_2, 25 °C. [f] Zn, AcOH. [g] Ac_2O/CH_2Cl_2. [h] A single regioisomer was detected by TLC in each case.

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0022-3263/94/1959-0682$04.50/0

was performed with $ZnCl_2$ as Lewis acid to afford the hydrazide **16** in 91% yield.[9] As observed with the 3 M $LiClO_4$–ether conditions,[6] the reaction is strongly para-directed to yield exclusively the para-isomer. The present electrophilic aromatic substitution reaction still remains highly regioselective with unsymmetrical electron-rich arenes. A single regioisomer was produced from the reaction of BTCEAD and 3-methylanisole (**7**). In this case, the hydrazide moiety is incorporated into the molecule exclusively para to the oxygen substituent to yield adduct **17** in 92%. Poor reactivity was anticipated with 1,4-disubstituted arenes as a consequnce of this para-oxygen-directed reaction. With 1,4-dimethoxybenzene (**8**) and 4-methylanisole (**9**) as substrates, the reactions were much slower with BTCEAD and mixtures of mono- and bis-aminated compounds were produced.

Having shown the effectiveness of the present amination conditions toward electron-rich substrates we turned our attention to poorly reactive substrates. With *m*-xylene used as a solvent, the hydrazide **18** was isolated in very good yield with $BF_3{\cdot}Et_2O$ as an activator. From our observations, *m*-xylene appeared to be the limit in terms of reactivity since toluene was inert toward BTCEAD. Compounds containing both an electron-withdrawing and donating group such as 2-bromoanisole (**11**) and 3,5-dimethoxyacetophenone (**12**) gave the adducts **19** and **20** in 80 and 77% yields, respectively.

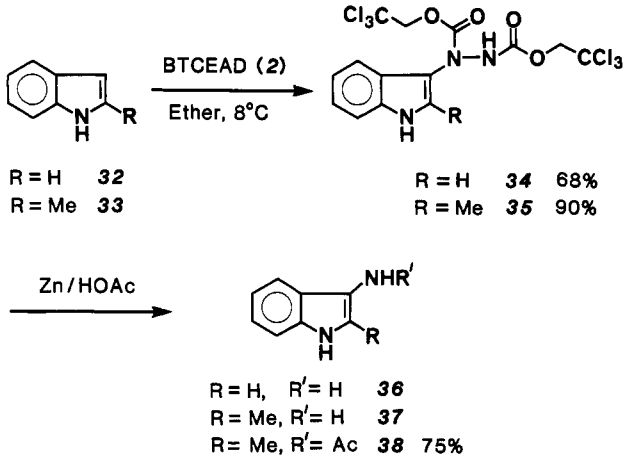
It is noteworthy that exclusively mono-hydrazide compounds were produced from this electrophilic amination reaction. The hydrazide group appears to deactivate the aromatic ring sufficiently to prevent further amination. The same rule applies to biphenyl compounds. 3,3′-Dimethoxybiphenyl (**13**) was converted in quantitative yield to the hydrazide **21** under the same conditions as for anisole (**6**). In this latter case, the regiochemistry was assigned based on NOEs and COSY experiments.

The hydrazides obtained in the present study were easily converted to their corresponding anilines (**22–31**) by zinc in acetic acid, except for hydrazide **20** where the indazole **30** was isolated instead.

Amination of Indole and 2-Methylindole. It is known that the nitration of indoles unsubstituted at the 2-position is problematic. In some cases only polymeric compounds are produced.[10] A few reports exist on the reaction of diethyl azodicarboxylate and indole molecules.[11] In these reports, refluxing conditions in toluene or dioxane were required for the reaction to take place. It was found that BTCEAD adds to indole (**32**) in ether at 8 °C to provide the 3-hydrazidoindole (**34**) (Scheme 1) in 68% yield. Unfortunately, all attempts to isolate 3-aminoindole[12] (**36**) after the standard deprotection failed, and only decomposition products were detected.

It was anticipated that 3-aminoindoles substituted at C-2 may be more stable toward the deprotection conditions.

Scheme 1



The nitration of 2-methylindole (**33**) in H_2SO_4 is reported to afford 2-methyl-5-nitroindole and in AcOH to produce dinitro derivatives.[13] 2-Methylindole was aminated with BTCEAD in ether at 8 °C to yield exclusively the 3-hydrazido compounds (**35**). As anticipated with zinc in acetic acid, the hydrazide **35** was converted to the corresponding 3-amino-2-methylindole (**37**). Due to its poor stability, the free amine **37** was characterized as the acetamido derivative **38**.

Preparation and Use of an Unsymmetrical Azo Reagent. In our study, aniline compounds were produced exclusively from the reduction of hydrazides using the Zn/AcOH conditions. Several attempts were made to control the reduction reaction in order to obtain the corresponding hydrazines which are useful precursors for the Fisher indole synthesis.[14] However, all reductive conditions lead to the formation of anilines for BTCEAD adducts. As we had previously observed,[2] the cleavage of the N–N bond took place concomitant to the removal of the two trichloroethyl ester groups in the case of bis-trichloroethyl hydrazides. It was anticipated that the unsymmetrical 2-(trimethylsilyl)ethyl 2,2,2-trichloroethyl azodicarboxylate (**43**) may be useful to achieve the present goal. This compound contains both the trichloroethyl ester group to maintain the reactivity and a trimethylsilylethyl ester group which can be removed under nonreductive conditions. This reagent was prepared as shown in Scheme 2. The hydrazide **41** was obtained by using a standard technique described by Carpino.[15] Condensation of 2-(trimethylsilyl)ethanol (**39**) with ethyl chlorothioformate in pyridine/$CHCl_3$ under reflux afforded the thiocarbonate **40** (Scheme 2). After refluxing compound **40** with hydrazine, the hydrazide **41** was obtained in 97% yield. This hydrazide **41** was converted in high yield to the bis-hydrazide **42** by treatment at 0 °C with 2,2,2-trichloroethyl chloroformate in $CHCl_3$–H_2O. The oxidation to the SEMTROC azo reagent **43** was achieved with N_2O_4 in CH_2Cl_2.[16]

1,3,5-Trimethoxybenzene (**4**) adds to the more electron-deficient nitrogen of the azo reagent **43** to provide

(9) The superiority of electron-deficient azo compounds over standard azo reagents (diethyl azodicarboxylate) for the amination reaction was verified with anisole as a substrate. When diethyl azodicarboxylate was used as a reagent, the hydrazide was formed in only 7% yield under identical conditions.

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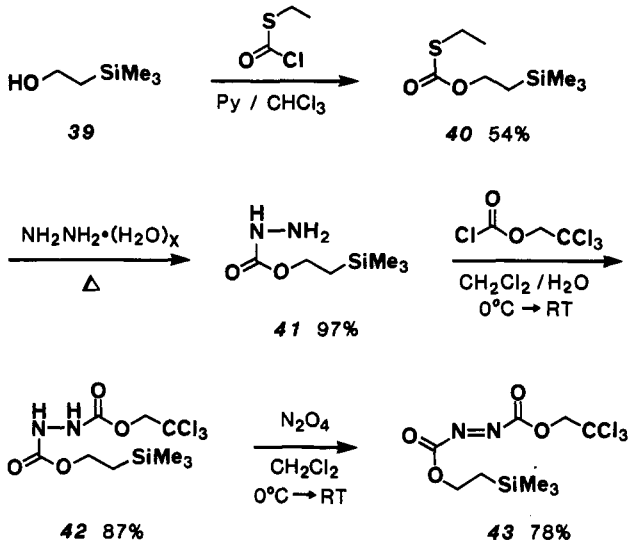
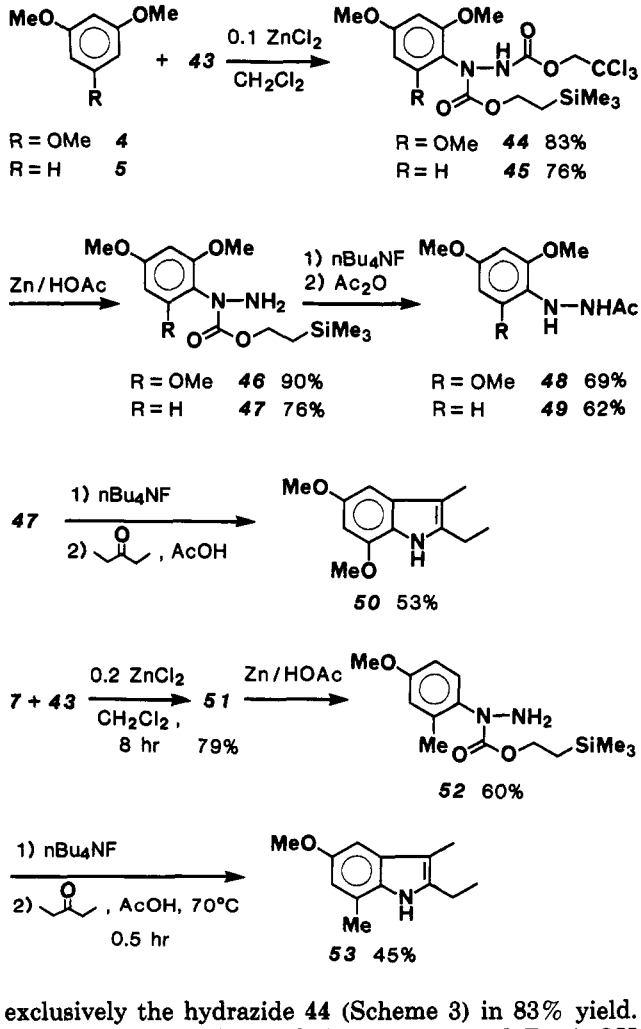
Scheme 2



Scheme 3



exclusively the hydrazide **44** (Scheme 3) in 83% yield. Removal of the trichloroethyl ester group with Zn–AcOH followed by treatment with nBu_4NF provided the hydrazine compound. The hydrazine was acetylated to give the *N*-acylhydrazine **48**. Similarly, protected hydrazine **49** was obtained from 1,3-dimethoxybenzene (**5**). In the latter case the hydrazine can be trapped by 3-pentanone in acetic acid to provide the indole **50**. The same sequence was repeated with 3-methylanisole (**7**) to yield the indole **53**.

In summary, it has been shown that electron-deficient azodicarboxylates can be used for the amination of arenes under extremely mild conditions. This amination reaction is potentially very useful for acid-sensitive molecules where nitration conditions are unsuitable. The new unsymmetrical azo reagent **43** is very useful for the synthesis of arylhydrazines and work is presently being extended to other systems.

Experimental Section

Bis(2,2,2-trichloroethyl) azodicarboxylate was purchased from Aldrich Chemical Co. or Fluka Chemical Co. Ethyl chlorothioformate was purchased from American Bioorganics.

Amination of Arenes with BTCEAD. Workup Procedure. The reaction mixture is quenched with a 25% aqueous ammonium acetate solution and extracted with ethyl acetate. The organic layer is dried over Na_2SO_4 and the solvent removed under reduced pressure.

Method A. Preparation of 1-(2,4,6-Trimethoxyphenyl)-1,2-hydrazinedicarboxylic Acid Bis(2,2,2-trichloroethyl) Ester (14). To a solution of 1,3,5-trimethoxybenzene (2.00 g, 11.9 mmol) in CH_2Cl_2 (60.0 mL) was added BTCEAD (5.40 g, 14.3 mmol) and ZnI_2 (379 mg, 1.19 mmol); workup procedure. The crude mixture was purified by flash chromatography (20% ethyl acetate in hexane) to give 6.30 g (95%) of the adduct: mp 147–149 °C (ethyl acetate–hexane); IR 3300 (N–H), 1770 (C=O), 1740 (C=O) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6, 325 K) δ 3.82 (s, 9H), 4.81 (s, 4H), 6.25 (s, 2H), 8.79 (bs, 1H); ^{13}C NMR (100 MHz, toluene-d_8, 378 K) δ 55.15, 56.04 (2), 75.65, 76.33, 92.40, 96.03 (2), 113.73, 153.59, 154.50, 158.06 (2), 162.17. Anal. Calcd for $C_{15}H_{16}Cl_6N_2O_7$: C, 32.78; H, 2.91; N, 5.10. Found: C, 32.90; H, 3.00; N, 4.93.

1-(2,4-Dimethoxyphenyl)-1,2-hydrazinedicarboxylic Acid Bis(2,2,2-trichloroethyl) Ester (15): mp 99–100 °C (ethyl acetate–hexane); IR 3400, 3300 (N–H), 1750 (C=O) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6, 325 K) δ 3.82 (s, 3H), 3.85 (s, 3H), 4.85 (s, 4H), 6.52 (d, 1H), 6.61 (s, 1H), 6.61 (s, 1H), 7.47 (bd, 1H), 9.39 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ 55.42, 55.70, 75.92, 76.48, 96.01 (2), 100.40, 105.41, 124.09, 131.15, 154.39, 156.71, 162.10 (2). Anal. Calcd for $C_{14}H_{14}Cl_6N_2O_6$: C, 32.40; H, 2.72; N, 5.40. Found: C, 32.57; H, 2.73; N, 5.35.

Method B. 1-(4-Methoxyphenyl)-1,2-hydrazinedicarboxylic Acid Bis(2,2,2-trichloroethyl) Ester (16). As in method A except that 1.0 equiv of a 1 M solution of $ZnCl_2$ in ether was added: mp 112 °C (ether–hexane); ^1H NMR (300 MHz, acetone-d_6, 325 K) δ 3.80 (s, 3H), 4.87 (s, 2H), 4.88 (s, 2H), 6.40 (d, 2H), 7.46 (d, 2H), 9.64 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ 55.37, 75.98, 76.52, 95.86 (2), 114.82, 127.20, 134.97, 153.60, 154.55, 159.86. Anal. Calcd for $C_{13}H_{12}Cl_6N_2O_5$: C, 31.93; H, 2.47; N, 5.73. Found: C, 31.97; H, 2.55; N, 5.62.

Method C. 1-(4-Methoxy-2-methylphenyl)-1,2-hydrazinedicarboxylic Acid Bis(2,2,2-trichloroethyl) Ester (17). As in method B except that 0.1 equiv of a 1 M solution of $ZnCl_2$ in ether was added: ^1H NMR (300 MHz, acetone-d_6, 325 K) δ 2.37 (s, 3H), 3.80 (s, 3H), 4.97 (s, 4H), 6.78 (dd, 1H), 6.84 (d, 1H), 7.50 (bd, 1H), 9.60 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ 18.07, 55.28, 76.03, 76.52, 95.52 (2), 112.72, 116.74, 129.83, 133.63, 154.40, 154.63, 160.69. Anal. Calcd for $C_{14}H_{14}Cl_6N_2O_5$: C, 33.42; H, 2.78; N, 5.56. Found: C, 33.35; H, 2.74; N, 5.62.

1-[2-(3′-Methoxyphenyl)-4-methoxyphenyl]-1,2-hydrazinedicarboxylic acid bis(2,2,2-trichloroethyl) ester (21): mp 134–136 °C (ether, hexane); ^1H NMR (200 MHz, acetone-d_6) δ 3.82 (s, 3H), 3.88 (s, 3H), 4.73 to 4.83 (m, 4H), 6.89 to 7.04 (m, 5H), 7.30 (bt, 1H), 7.73 (d, 1H), 9.65 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ 55.27 (2), 75.83, 76.43, 95.78 (2), 114.09, 114.32, 115.28, 116.52, 121.26, 130.10, 131.39, 132.42, 141.21, 141.79, 154.09, 154.24, 160.56, 160.95. Anal. Calcd for $C_{20}H_{18}Cl_6N_2O_6$: C, 40.37; H, 3.05; N, 4.71. Found: C, 40.53; H, 2.97; N, 4.61.

Method D. 1-(2,4-Dimethylphenyl)-1,2-hydrazinedicarboxylic Acid Bis(2,2,2-trichloroethyl) Ester (18). To *m*-xylene (10 mL) were added BTCEAD 2.00 g, 5.53 mmol) and BF_3·Et_2O (650 μL, 5.52 mmol). After a period of 18 h at room temperature, the excess of *m*-xylene was removed under reduced pressure; workup procedure. The crude mixture was purified by

flash chromatography (20% ether in hexane) to give 2.15 g (86%) of the adduct: mp 55–59 °C; ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ 2.21 (s, 3H), 2.37 (s, 3H), 4.88 (s, 4H), 7.04 (d, 1H), 7.10 (s, 1H), 7.45 (bd, 1H), 9.60 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ 17.79, 19.95, 76.02, 76.48, 95.85 (2), 127.85, 131.90, 135.92, 138.09, 139.00, 153.90, 154.57. Anal. Calcd for $C_{14}H_{14}Cl_6N_2O_4$: C, 34.53; H, 2.90; N, 5.75. Found: C, 34.44; H, 2.70; N, 5.55.

Method E. 1-(3-Bromo-4-methoxyphenyl)-1,2-hydrazinedicarboxylic Acid Bis(2,2,2-trichloroethyl) Ester (19). To a solution of 2-bromoanisole (500 mg, 2.68 mmol) in CH_2Cl_2 (4.0 mL) were added BTCEAD (400 mg, 5.26 mmol) and BF_3·Et_2O (280 μL, 2.26 mmol); workup procedure. The crude mixture was purified by flash chromatography (15–20% ethyl acetate, hexane) to give 1.20 g (80%) of a white foam: ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ 3.93 (s, 3H), 4.90 (m, 4H), 7.15 (d, 1H), 7.52 (bd, 1H), 7.80 (bs, 1H), 8.80 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ 56.50, 76.04, 76.64, 95.75 (2), 112.52, 112.67, 125.76, 131.00, 135.49, 153.37, 154.55, 156.32. Anal. Calcd for $C_{13}H_{11}BrCl_6N_2O_5$: C, 27.51; H, 1.94; N, 4.94. Found: C, 25.71; H, 2.05; N, 5.14.

1-(2-Acetyl-4,6-dimethoxyphenyl)-1,2-hydrazinedicarboxylic Acid Bis(2,2,2-trichloroethyl) Ester (20). To a solution of 3,5-dimethoxyacetophenone (500 mg, 2.78 mmol) in CH_2Cl_2 (14.0 mL) were added BTCEAD (1.30 g, 3.42 mmol) and BF_3·Et_2O (0.170 mL, 1.39 mmol). After a period of 18 h additional BTCEAD (211 mg, 0.555 mmol) was added; workup procedure. The crude mixture was purified by flash chromatography (33% ethyl acetate in hexane) to give 1.20 g (77%) of the adduct as a white foam: ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ 2.55 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.87 (4H), 6.75 (d, 1H), 6.82 (d, 1H), 8.85 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ 29.57, 55.50, 56.48, 75.81, 76.60, 97.0 (2), 103.33, 106.49, 123.00, 140.01, 148.00, 153.82, 161.48. Anal. Calcd for $C_{16}H_{16}Cl_6N_2O_7$: C, 34.24; H, 2.88; N, 4.99. Found: C, 34.08; H, 2.92; N, 4.71.

Conversion of Hydrazides to Anilines. 2,4,6-Trimethoxyaniline (22). To a solution of the hydrazide **14** (5.00 g, 9.11 mmol) in glacial acetic acid (45.5 mL), under a nitrogen atmosphere, was added zinc dust (5.00 g) portionwise over 5 min. The resulting mixture was stirred at room temperature for 45 min. The reaction was quenched by adding water and sodium hydroxide (10 N) to pH 10 and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent removed under vacuum. The crude mixture was then purified by flash chromatography to give 2.12 g (100%) of the aniline as a colorless liquid: bp 113 °C at 0.5 torr (lit.[17] 125 °C at 0.8 torr.).

2,4-Dimethoxyaniline (23). To a solution of the hydrazide **15** (200 mg, 0.390 mmol) in glacial acetic acid (2.0 mL) was added zinc dust (200 mg) portionwise over 3 min. The resulting mixture was stirred at room temperature for 30 min. The reaction was quenched by adding sufficient 3 N HCl to dissolve the remaining zinc and extracted with ethyl acetate. Water and sodium hydroxide (10 N) were added to the aqueous layer, and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent removed under vacuum. The crude mixture was purified by flash chromatography (30% ethyl acetate in hexane) to give 50 mg (85%) of the aniline **23** as a beige solid identical to an authentic sample: mp 33–35 °C.

4-Methoxyaniline (24). As for compound **23**; beige solid identical to an authentic sample: mp 56–58 °C.

4-Methoxy-2-methylaniline (25). As for compound **22**; brown liquid identical to an authentic sample.

2,4-Dimethylaniline (26). As for compound **22**; colorless liquid: bp 197 °C at 1 atm (lit.[18] 212–214 °C at 1 atm).

2,4-Dimethylacetanilide (27). To a solution of the aniline **26** (75 mg, 0.62 mmol) in pyridine (1.0 mL) was added an excess of Ac_2O. The mixture was stirred at room temperature for 45 min and then the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and 1 N sodium hydroxide solution. The organic layer was dried over Na_2SO_4 and the solvent evaporated under vacuum. The acetamide was recrystallized from ethyl acetate–hexane to give 94 mg (93%) of white needles: mp 129–131 °C (lit.[19] 127–128 °C).

3-Bromo-4-methoxyaniline (28). As for compound **23**: mp 62 °C (ethanol), lit.[20] 60–62 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 3.72 (s, 3H), 4.45 (bs, 2H), 6.62 (dd, 1H), 7.80 (d, 1H), 6.90 (d, 1H), high-resolution mass spectrum, m/z calcd for C_7H_9BrNO-$(M + H)^+$ 201.9867, found 201.9866.

3-Bromo-4-methoxyacetanilide (29). As for compound **26**, the aniline **28** was converted to the crystalline derivative **29**: mp 115 °C (ether–CH_2Cl_2); IR 3240, 3220 (NH), 1660 (NHAc) cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.05 (s, 3H), 3.85 (s, 3H), 7.00 (d, 1H), 7.50 (dd, 1H), 7.98 (d, 1H), 9.05 (bs, 1H). Anal. Calcd for $C_9H_{10}BrNO_2$: C, 44.44; H, 4.11; N, 5.76. Found: C, 44.42; N, 4.24; H, 5.70.

5,7-Dimethoxy-3-methylindazole (30). To a solution of hydrazide **20** (500 mg, 0.892 mmol) in glacial acetic acid (5.00 mL) was added zinc dust (500 mg). After a period of 1 h, water and 10 N NaOH were added until pH 10 and the product was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent evaporated under vacuum. The indazole **30** was purified by flash chromatography (30% ethyl acetane in hexane) to afford 126 mg (74%) of a white solid: mp 155–156 °C (MeOH); IR 3300 (NH) cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.48 (s, 3H), 2.90 (bs, 1H), 3.85 (s, 3H), 3.98 (s, 3H), 6.48 (d, 1H), 6.70 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.99, 55.51, 55.75, 90.80, 98.60, 123.36, 129.41, 142.67, 145.67, 155.41. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25; N, 14.58. Found: C, 62.87; H, 6.40; N, 14.51.

2-Amino-5,3′-dimethoxybiphenyl (31). As for compound **22**; mp 97–99 °C (ether–hexane); ^{1}H NMR (500 MHz, acetone-d_6, 325 K) δ 3.71 (s, 3H), 3.82 (s, 3H), 4.08 (bs, 2H), 6.67 (s, 1H), 6.71 (d, 1H), 6.75 (d, 1H), 6.89 (d, 1H), 6.99 (s, 1H), 7.01 (d, 1H), 7.33 (t, 1H); ^{13}C NMR (100.0 MHz, acetone-d_6) δ 55.47, 55.84, 113.43, 115.17, 116.11, 117.42, 121.84, 128.33, 130.52, 139.31, 142.32, 153.03, 160.90, 206.13. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.40; H, 6.59; N, 6.10. Found: C, 72.95; H, 6.84; N, 5.98. High-resolution mass spectrum, m/z calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ 230.1181, found 230.1181.

Amination of Indole (32) and 2-Methylindole (33). 1-(3-Indolyl)-1,2-hydrazinedicarboxylic Acid Bis(2,2,2-trichloroethyl) Ester (34). To a solution of indole (**32**) (250 mg, 2.13 mmol) in ether (3.0 mL), under nitrogen at 8 °C, was added BTCEAD (1.63 g, 4.27 mmol) portionwise over 20 min. The resulting yellow solution was stirred for 10 min; workup procedure. The crude mixture was purified by flash chromatography (20% ethyl acetate in hexane) to give 718 mg (68%) of the adduct: mp 128–130 °C (ethyl acetate–hexane, white needles); IR 3340 (N–H), 1740 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ 4.90 (s, 4H), 7.07 (t, 1H), 7.13 (t, 1H), 7.42 (d, 1H), 7.52 (bs, 1H), 7.75 (d, 1H), 9.79 (bs, 1H), 10.18 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ 75.95, 76.65, 95.96 (2), 111.96, 119.17, 119.38, 121.03, 121.96, 123.24, 124.10, 135.39, 154.64, 154.74. Anal. Calcd for $C_{14}H_6Cl_6N_3O_4$: C, 33.77; H, 2.22; N, 8.44. Found: C, 34.02; H, 2.27; N, 8.38.

1-(2-Methyl-3-indolyl)-1,2-hydrazinedicarboxylic Acid Bis(2,2,2-trichloroethyl) Ester (35). To a solution of 2-methylindole (**33**) (250 mg, 1.91 mmol) in ether (9.5 mL), under nitrogen in a cold water bath (8 °C), was added BTCEAD (870 mg, 2.29 mmol) portionwise over 10 min. The reaction mixture was stirred for 1.5 h; workup procedure. The crude mixture was purified by flash chromatography (40% ether in hexane) to give 877 mg (90%) of the adduct as a yellow foam: ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ 2.51 (s, 3H), 4.87 (s, 4H), 7.01 (t, 1H), 7.06 (t, 1H), 7.30 (d, 1H), 7.73 (d, 1H), 9.70 (bs, 1H), 10.00 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ 11.41, 75.94, 76.62, 95.94, 96.02, 111.16, 115.45, 118.06, 121.01, 122.40, 133.00, 134.67, 137.79, 154.65 (2). Anal. Calcd for $C_{15}H_{13}Cl_6N_3O_4$: C, 35.19; H, 2.56; N, 8.21. Found: C, 35.60; H, 2.69; N, 8.06.

3-Acetamido-2-methylindole (38). To a solution of the hydrazide **35** (1.00 g, 1.95 mmol) in glacial acetic acid (10.0 mL), under nitrogen at 20 °C was added zinc dust (1.00 g) portionwise

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over 5 min. After a period of 45 min at room temperature, EtOAc (15.0 mL) and H_2O (5.0 mL) were added. To the resulting mixture was added 10 N KOH until pH 8 and it was extracted twice with EtOAc. The organic layer was dried over Na_2SO_4 and the solvent evaporated under vacuum. The mixture was purified by flash chromatography (EtOAc) to yield 270 mg (75%) of the title compound: mp 156–157 °C (ethyl acetate–hexane); IR 3400 (N–H), 3250 (N–H), 1700 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, 393 K) δ 2.01 (s, 3H), 2.28 (s, 3H), 6.93 (t, 1H), 7.00 (t, 1H), 7.25 (d, 1H), 7.31 (d, 1H), 8.50 (bs, 1H), 10.35 (bs, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 410 K) δ 10.11, 21.29, 109.94, 110.44, 116.42, 117.74, 119.52, 124.90, 129.30, 133.44. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.24; H, 6.57; N, 14.80.

Synthesis and Reactivity of the SEM TROC Azodicarboxylate Reagent 43. *S*-Ethyl 2-(Trimethylsilyl)ethyl Thiocarbonate (40). To a solution of 2-(trimethylsilyl)ethanol (42.0 mL, 296 mmol) in chloroform (90 mL) was added pyridine (24.0 mL, 296 mmol). Over a period of 30 min, ethyl chlorothioformate (33.42 g, 269 mmol) was added dropwise. After a period of 18 h at reflux, the reaction mixture was poured on water and washed with 5% HCl solution, followed by saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was distilled (115 °C, 18 mmHg) to give 30.0 g (54%) of the title compound as a colorless oil: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.08 (s, 9H), 1.08 (t, 2H), 1.25 (t, 3H), 2.75 (q, 2H), 4.32 (t, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ −1.52, 15.48, 18.03, 25.57, 66.13, 171.04. Anal. Calcd for $C_8H_{18}SSiO_2$: C, 46.60; H, 8.73. Found: C, 46.29; H, 8.87.

1-Hydrazinecarboxylic Acid 2-(Trimethylsilyl)ethyl Ester (41). To the thiocarbamate **40** (38.60 g, 0.18 mol) was added $NH_2NH_2{\cdot}XH_2O$ (10.0 mL, 0.209 mmol) and the mixture was refluxed overnight; workup procedure. The crude mixture was purified by flash chromatography (100% ethyl acetate) to give 32.0 g (97%) of the monohydrazide **41** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$, 325 K) δ 0.02 (s, 9H), 0.98 (t, 2H), 4.19 (t, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.50 (−1.83), 17.74 (17.61), 63.83 (64.59), 159.32 (158.00). Anal. Calcd for $C_6H_{16}N_2O_2Si$: C, 40.90; H, 9.09. Found: C, 40.85; H, 8.87.

1,2-Hydrazinedicarboxylic Acid 1-[2-(Trimethylsilyl)-ethyl]-2-(2,2,2-Trichloroethyl) Ester (42). To a solution of the mono-hydrazide **41** (32.0 g, 0.181 mol) in water (227 mL) and $CHCl_2$ (32.0 mL), under argon at 0 °C, was added 2,2,2-trichloroethyl chloroformate (28.1 mL, 0.199 mmol) dropwise over 10 min. After a period of 8 h at room temperature, the reaction was quenched with a 25% aqueous NH_4OAc solution, extracted with CH_2Cl_2, and dried over Na_2SO_4. The crude mixture was concentrated under reduced pressure and an ether–hexane mixture was added to give 55.0 g (87%) of the bis-hydrazide after standing at 0 °C followed by filtration: mp 84–86 °C; ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ 0.06 (s, 9H), 1.01 (t, 2H), 4.20 (s, 2H), 4.82 (s, 2H), 8.04 (bs, 1H), 8.56 (bs, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ −1.44, 18.22, 64.04, 75.14, 96.50, 155.97, 157.29. Anal. Calcd for $C_9H_{17}Cl_3N_2O_4Si$: C, 30.74; H, 4.87; N, 7.97. Found: C, 30.58; H, 4.76; N, 8.09.

2-(Trimethylsilyl)ethyl 2,2,2-Trichloroethyl Azodicarboxylate (43). A solution of the bis-hydrazide **42** (18.91 g, 53.8 mmol) in CH_2Cl_2 (225 mL), at 0 °C, was saturated with nitrogen dioxide and stirred overnight at room temperature. To the reaction mixture was added $NaHCO_3$ solution and it was extracted with ethyl acetate. The EtOAc solution was dried over Na_2SO_4 and concentrated under reduced pressure to give 14.6 g (78%) of the azo reagent as an orange oil sufficiently pure for use in the next step. An analytical sample was distilled (150 °C at 0.1 mmHg) on a Kugelrohr apparatus: ^{1}H NMR (400 MHz, acetone-d_6) δ 0.10 (s, 9H), 1.13 (t, 1H), 4.63 (t, 2H), 5.18 (s, 2H). ^{13}C NMR (100.0 MHz, acetone-d_6) δ −1.50, 17.98, 69.42, 77.47, 94.66, 159.79, 160.87, 206.04. Anal. Calcd for $C_9H_{15}Cl_3N_2O_4Si$: C, 30.91; H, 4.32; N, 8.01. Found: C, 30.93; H, 4.47; N, 7.99.

1-(2,4,6-Trimethoxyphenyl)-1,2-hydrazinedicarboxylic Acid 1-[2-(Trimethylsilyl)ethyl]-2-(2,2,2-Trichloroethyl) Ester (44). To a solution of 1,3,5-trimethoxybenzene (1.00 g, 5.94 mmol) in dichloromethane (30.0 mL) under argon at room temperature were added the azo reagent **43** (2.50 g, 7.13 mmol) and $ZnCl_2$ (594 μL of a 1 M solution in ether, 0.594 mmol). The reaction mixture was stirred for 3 h; workup procedure. The crude mixture was purified by flash chromatography (30% ether in hexane) to give 2.50 g (83%) of the adduct: mp 112–115 °C (ether–hexane); ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ −0.04 (bs, 9H), 0.89 (bt, 2H), 3.81 (s, 9H), 4.15 (bt, 2H), 4.79 (s, 2H), 6.23 (s, 2H), 8.40 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ −1.50 (3), 55.35, 56.29, 65.01, 75.78, 93.03 (2), 96.00, 115.00, 154.18, 158.44 (2), 161.98. Anal. Calcd for $C_{18}H_{27}Cl_3N_2O_7Si$: C, 41.75; H, 5.26; N, 5.41. Found: C, 41.73; H, 5.46; N, 5.21.

1-(2,4-Dimethoxyphenyl)-1,2-hydrazinedicarboxylic acid 1-[2-(trimethylsilyl)ethyl] 2-(2,2,2-trichloroethyl) ester (45): mp 68–70 °C (ether–hexane) ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ 0.01 (s, 9H), 0.95–1.05 (m, 2H), 3.85 and 3.88 (2s, 6H), 4.20 (m, 2H), 4.85 (s, 2H), 6.50 (dd, 1H), 6.60 (d, 1H), 7.40 (d, 1H), 9.00 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K), δ −1.48 (3), 55.41, 55.63, 65.17, 75.81, 100.53, 105.40, 131.43, 150.00, 156.84, 161.72. Anal. Calcd for $C_{17}H_{25}Cl_3N_2SiO_6$: C, 41.88; H, 5.13; N, 5.74. Found: C, 41.80; H, 5.06; N, 5.66.

1-(4-Methoxy-2-methylphenyl)-1,2-hydrazinedicarboxylic acid 1-[2-(trimethylsilyl)ethyl] 2-(2,2,2-trichloroethyl) ester (51): ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ 0.01 (s, 9H), 0.93–1.05 (m, 2H), 2.30 (s, 3H), 3.82 (s, 3H), 4.25 (bt, 2H), 4.85 (bs, 2H), 6.75 (dd, 1H), 6.80 (d, 1H), 7.45 (bd, 1H), 9.35 (bs, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ −1.48, 18.18, 18.40, 55.31, 65.44, 75.93, 96.1, 112.67, 116.71, 129.86, 134.60, 155.12, 155.89, 160.34 (2). Anal. Calcd for $C_{17}H_{25}Cl_3N_2O_5Si$: C, 43.31; H, 5.30; N, 5.95. Found: C, 43.14; H, 5.50; N, 5.92.

1-(2,4,6-Trimethoxyphenyl)-1-hydrazinecarboxylic Acid 1-[2-(Trimethylsilyl)ethyl] Ester (46). To a solution of the hydrazide **44** (2.00 g, 3.86 mmol) in glacial acetic acid (19.3 mL) under argon at 10 °C was added zinc dust (2.0 g) portionwise over 10 min. After a period of 1 h, the reaction was quenched by adding water and sodium hydroxide (10 N) to pH 10 and it was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent evaporated under vacuum. The crude mixture was purified by flash chromatography (65% ethyl acetate in hexane) to give 1.19 g (90%) of the hydrazide **46** as a yellow oil which solidified on standing: ^{1}H NMR (400 MHz, acetone-d_6) δ −0.60 (s, 9H), 0.87 (t, 2H), 3.80 (s, 9H), 4.08 (t, 2H), 4.50 (bs, 2H), 6.21 (s, 2H); ^{13}C NMR (125 MHz, toluene-d_8, 383 K) δ −1.43 (3), 18.44, 55.38, 56.17, 63.97, 93.22 (2), 128.14, 129.22, 158.48 (2), 161.39; low-resolution mass spectrum, m/z calcd for $C_{15}H_{27}N_2O_5Si$ $(M + H)^+$ 343, found 343. Anal. Calcd for $C_{15}H_{26}N_2O_5Si$: C, 52.61; H, 7.65; N, 8.18. Found: C, 52.33; H, 7.77; N, 8.05.

1-(2,4-Dimethoxyphenyl)-1-hydrazinecarboxylic acid 1-[2-(trimethylsilyl)ethyl] ester (47): ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ −0.05 (s, 9H), 0.900 (t, 2H), 3.80 and 3.85 (2s, 6H), 4.15 (t, 2H), 4.55 (bs, 2H), 6.45 (dd, 2H), 6.58 (d, 1H), 7.10 (d, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 383 K) δ −1.42 (3), 18.43, 55.42, 55.74, 64.15, 100.92, 105.52, 127.63, 130.22, 157.22, 158.32, 161.06. Anal. Calcd for $C_{14}H_{24}N_2O_4Si$: C, 53.84; H, 7.69; H, 8.97. Found: C, 53.61; H, 7.56; N, 9.39.

1-(4-Methoxy-2-methylphenyl)-1-hydrazinecarboxylic acid 1-[2-(trimethylsilyl)ethyl] ester (52): ^{1}H NMR (400 MHz, acetone-d_6) δ 0.01 (s, 9H), 0.90 (bs, 2H), 2.22 (s, 3H), 3.75 (s, 3H), 4.15 (bt, 1H), 4.80 (bs, 2H), 6.68 (dd, 1H), 6.75 (d, 1H), 7.10 (d, 1H); ^{13}C NMR (125 MHz, toluene-d_8, 378 K) δ −1.47, 18.05, 18.48, 55.29, 64.35, 112.39, 116.70, 136.15, 137.38, 157.59, 159.78. Anal. Calcd for $C_{14}H_{24}N_2O_3Si$: C, 56.75; H, 8.11; N, 9.46. Found: C, 57.14; H, 8.07; N, 9.45.

2-Acetyl-(2,4,6-trimethoxyphenyl)hydrazine (48). A solution of hydrazide **46** (370 mg, 1.08 mmol) in THF (5.00 mL) was purged with argon for 5 min. A solution of 1 N *n*-Bu_4NF in THF (1 M, 3.20 mL, 3.20 mmol), under argon, was then added. After a period of 3 h, the reaction mixture was poured into 200 mL of CH_2Cl_2 and then Ac_2O was added (2.0 mL). After 10 min, MeOH (20.0 mL) was added and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed three times with saturated NaCl, dired over Na_2SO_4, and evaporated under vacuum. After flash chromatography (15% acetone in ethyl acetate), 180 mg (69%) of the title compound was obtained: mp 123–124 °C (ethyl acetate–ether); IR 3300, 3320 (NH), 1670 (NHCO); ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ 1.80 and 2.10 (2s, 3H), 3.70 and 3.88 (2s, 9H), 6.25 (s, 2H), 7.00 (d, 1H), 8.60 (bs, 1H); ^{13}C NMR (100 MHz, toluene-d_8) δ 21.26, 55.77, 56.67 (56.31), 92.88 (92.33), 122.04 (119.88), 152.54 (153.91), 156.90

(157.89), 167.89 (175.93). Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.74; H, 6.80; N, 11.33.

2-Acetyl-1-(2,4-dimethoxyphenyl)hydrazine (49): mp 143–144 °C (ethyl acetate); ^{1}H NMR (300 MHz, acetone-d_6, 325 K) δ 1.92 (s, 3H), 3.70 (s, 3H), 3.85 (s, 3H), 6.40 (dd, 1H), 6.45 (bs, 1H), 6.52 (bd, 1H), 6.75 (d, 1H), 8.75 (bs, 1H). ^{13}C NMR (100 MHz, toluene-d_8) δ 26.37, 55.84, 55.90, 100.01 (100.24), 104.87, 113.82 (112.92), 133.77 (132.83), 148.95 (148.42), 155.04, 169.37 (176.16). Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.14; H, 6.66; N, 13.33. Found: C, 57.24; H, 6.91; N, 13.14.

5,7-Dimethoxy-2-ethyl-3-methylindole (50).[21] To the hydrazide **47** (500 mg, 1.46 mmole) in THF (10.0 mL) was added a solution of *n*-Bu_4NF in THF (1 M) (4.70 mL, 4.70 mmol). After a period of 1 h at room temperature, the solvent was removed under reduced pressure. AcOH (10.0 mL) was then added to the crude mixture followed by 3-pentanone (200 μL). The reaction was stirred at room temperature for 2 h. The reaction mixture was neutralized by the addition of a solution of KOH (8 N) and extracted with Et_2O. The organic layer was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. After flash chromatography (10% ethyl acetate in hexane), the title compound was obtained as a brown oil (170 mg, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H), 2.15 (s, 3H), 2.75 (q, 2H), 3.80 (s, 3H), 3.90 (s, 3H), 6.28 (bs, 1H), 6.50 (bs, 1H), 7.80 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.62, 13.97, 19.49, 55.36, 55.98, 92.12, 93.25, 106.57, 120.40, 129.99, 136.70, 145.86, 154.65; HRMS calcd for $C_{13}H_{18}NO_2$ $(M + H)^+$ 220.1338, found 220.1338.

3,7-Dimethyl-2-ethyl-5-methoxyindole (53):[21] ^{1}H NMR (400 MHz, acetone-d_6) δ 1.22 (t, 3H), 2.15 (s, 3H), 2.40 (s, 3H), 2.75 (q, 2H), 3.75 (s, 3H), 6.50 (bs, 1H), 6.75 (bs, 1H), 9.45 (bs, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.69, 14.78, 16.93, 20.05, 55.80, 98.40, 106.09, 111.77, 121.15, 130.28, 131.09, 138.42, 154.78. HRMS calcd for $C_{13}H_{18}NO$ $(M + H)^+$ 204.1388, found 204.1388.

(21) Compounds **50** and **53** must be stored, under nitrogen, at −78 °C.

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Supplementary Material Available: Copies of ^{1}H NMR spectra of **14–21**, **28–31**, **34**, **35**, **38**, **43**, **48–50**, and **53** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.