New Routes to Selectively Methylated Benzimidazoles

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Received December 9, 1993

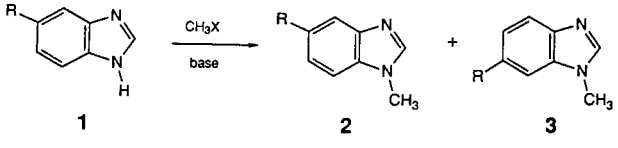
The use of intermediate benzotriazol-1-yl derivatives simplified the procedures for the preparation of 5-methoxy-1-methylbenzimidazole and 6-methoxy-1-methylbenzimidazole starting from 4-methoxy-2-nitroaniline. This strategy represents a novel and potentially general method for synthesis of 5- and 6-substituted-1-methylbenzimidazoles from 4-substituted anilines. Preparation of 1-methyl-5-nitrobenzimidazole by reaction of 2-chloro-5-nitroaniline with methylamine and condensation of the obtained diamine with formic acid represents a special case.

J. Heterocyclic Chem., **31**, 775 (1994).

Introduction.

Methylation of a benzimidazole bearing a substituent on the benzenoid ring produces a mixture of two isomers. When a 5-substituted benzimidazole **1** is methylated, isomers **2** and **3** (Scheme 1) are formed in an approximate 1:1 ratio [1]. Even one of the strongest electron withdrawing substituents, the nitro group does not differentiate the benzimidazole nitrogen atoms as 5-nitrobenzimidazole is reported to give a 1:1 mixture of **2** and **3** (R = NO_2) upon methylation with dimethyl oxalate [2] or methyl iodide in methanol in the presence of potassium hydroxide [3].

Scheme 1



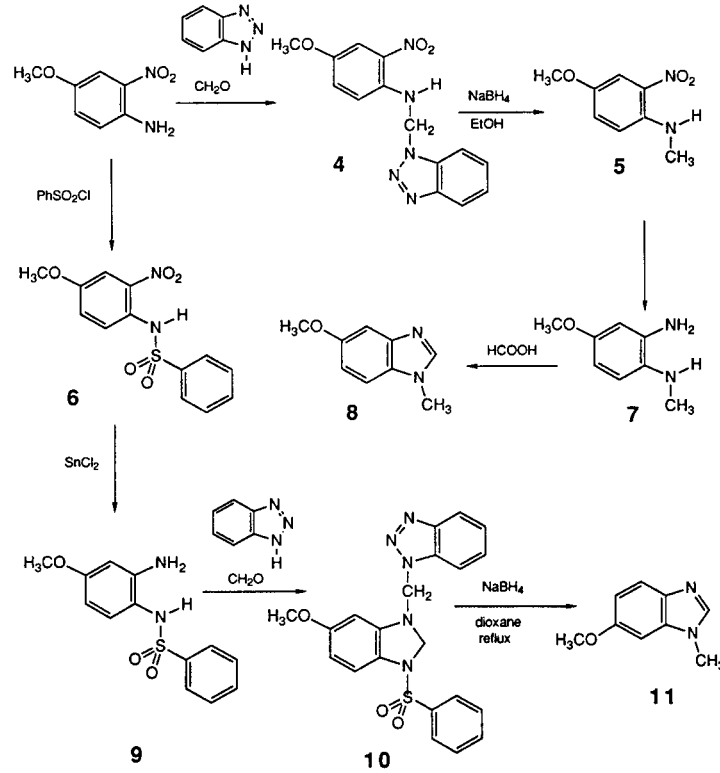
1 2 3

Because the separation of mixtures of **2** and **3** is usually difficult [3,4] complex multistep procedures have been elaborated for the preparation of the individual isomers. For example, 1,5-dimethylbenzimidazole was prepared from 2-nitro-4-toluidine in a five step process involving protection of the amino group with tosyl chloride, methylation with dimethyl sulfate in the presence of a base, hydrolysis of the sulfonamido protection with concentrated sulfuric acid, reduction of the nitro group and final cyclocondensation with formic acid [5]. In this paper, we describe our modifications in the preparation of selectively methylated benzimidazoles **2** and **3** by giving examples of the synthesis of each with R = OCH_3. Other derivatives of benzimidazole of this type should be obtainable by similar procedures.

Results and Discussion.

Benzotriazolylmethylation [6] of 4-methoxy-2-nitroaniline gave the stable derivative **4** (Scheme 2). Reduction of **4** with sodium borohydride in ethanol yielded the substituted *N*-methylaniline **5**. Reduction of the nitro group of **5** by tin(II) chloride afforded diamine **7**; the structure of **7** was confirmed by nmr but due to its sensitivity to air oxidation it was condensed directly with formic acid to give 5-methoxy-1-methylbenzimidazole (**8**) with an overall yield for the 4 steps of 62%. The literature method for the preparation of **8** involves a laborious methylation of 4-methoxy-2-nitroaniline *via* tosylation of the amino group and no yield is quoted [7].

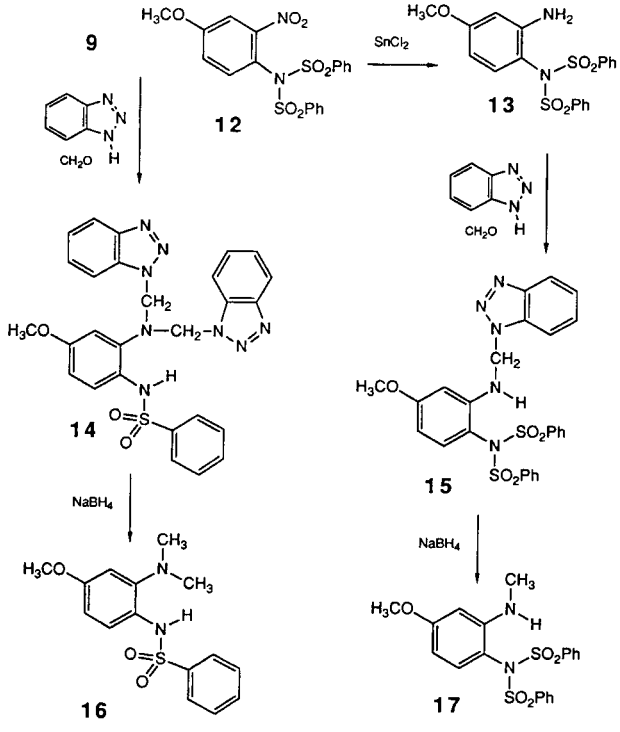
Scheme 2



The same starting material, 4-methoxy-2-nitroaniline, was used for the preparation of 6-methoxy-1-methylbenzimidazole (**11**). First, the amino group was protected by treatment with benzenesulfonyl chloride to give sulfonamide **6**. Reduction of the nitro group of **6** with tin(II) chloride afforded amine **9**. Attempted benzotriazolylmethylation of **9** under the standard conditions gave a complex product mixture, however, use of two moles of formaldehyde per one mole of amine **9** and one mole of benzotriazole gave the substituted benzimidazoline **10** in good yield. Reduction of **10** with sodium borohydride in ethanol caused its decomposition to the starting material **9**, but sodium borohydride in refluxing dioxane converted **10** directly into benzimidazole **11**. The intermediate 1-(phenylsulfonyl)-6-methoxy-3-methylbenzimidazoline is evidently unstable under the reaction conditions and eliminates benzesulfinic acid. The overall yield for the 4 steps was 50%.

The literature method for the preparation of **11** starts from 3-chloro-4-nitrophenol and involves methylation of the hydroxy group, replacement of the chlorine atom by methylamine, separation of the obtained 4-methoxy-*N*-methyl-2-nitroaniline from the by-product (N^1,N^2-dimethyl-4-nitro-1,3-phenylenediamine) and final cyclocondensation with formic acid [7,8]. The yields were not given.

Scheme 3



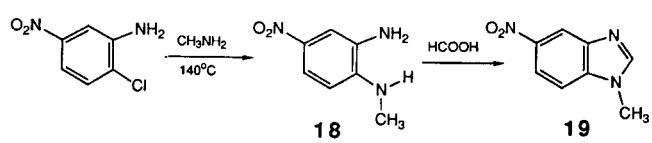
The innovation in our synthesis lies in the last two steps which allow convenient and efficient conversion of 2-(benzenesulfonamido)-5-methoxyaniline (**9**) into 6-methoxy-1-methylbenzimidazole (**11**). Our reaction sequences for **8** and **11** do not require purification of the intermediates. However, the purification of **11** by column chromatography resulted in the separation of two by-products, **16** and **17** (Scheme 3). This indicates the formation of a minor quantity of the bisbenzotriazolylmethylation product **14**. In general, bisbenzotriazolylmethylation is characteristic of aliphatic amines [6] whereas aromatic amines require more stringent conditions [9]; the influence of the electron-donor groups in **9** increases significantly the basicity of the amino group and evidently makes it more susceptible to a second attack by a benzotriazolylmethyl cation [10]. During the reduction step, bisbenzotriazolylmethyl derivative **14** was reduced to dimethylaniline **16**.

By-product **17** had a different origin. Treatment of 4-methoxy-2-nitroaniline with benzenesulfonyl chloride in the presence of a base produced in addition to **6** a small amount of the bisbenzenesulfonyl derivative **12**. Through the further reaction sequence (reduction of the nitro group with tin(II) chloride, benzotriazolylmethylation and reduction with sodium borohydride) this afforded **17**. To prove this hypothesis, derivative **12** was prepared independently by treatment of amine **6** with excess benzenesulfonyl chloride. Reduction of **12** with tin(II) chloride afforded amine **13**. Comparison of the nmr spectra enabled detection of derivatives **12** and **13** in crude products **6** and **9**, respectively.

As is outlined in Scheme 2, 4-methoxy-2-nitroaniline can be converted by a series of simple operations to 5-methoxy- (**8**) or 6-methoxy-1-methylbenzimidazole (**11**). Although only one substituent (the methoxy group) was investigated, we believe that this synthetic method is general allowing the transformation of a variety of 4-substituted-2-nitro anilines to 5- or 6-substituted 1-methylbenzimidazoles **2** or **3**. We expect only a few cases when this method would not work, *i.e.* when necessary reagents would interact with the substituent. In such instances, the substituent would need protection or some steps of our process would have to be modified, *e.g.* use of reducing agents other than tin(II) chloride for reduction of the nitro group.

The preparation of 1-methyl-5- or -6-nitroindoles is a special case, it would be difficult to reduce selectively the *ortho* nitro group leaving the para group unchanged. For this purpose, we developed another procedure. Starting from commercially available 2-chloro-5-nitroaniline, aromatic nucleophilic substitution of the chlorine atom with methylamine afforded diamine **18** which by cycloconden-

Scheme 4



sation with formic acid produced 1-methyl-5-nitrobenzimidazole (**19**) (Scheme 4).

EXPERIMENTAL

The ^1H and ^{13}C nmr spectra were obtained on a Varian VXR-300 spectrometer, and chemical shifts are reported in ppm relative to tetramethylsilane in deuteriochloroform solvent. Melting points (°C) were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

3-Nitro-4-(benzotriazol-1-ylmethyl)aminoanisole (**4**).

Formaldehyde (37%, 33.7 ml, 0.45 mole) was added in one portion to a stirred solution of 4-amino-3-nitroanisole (67.26 g, 0.40 mole), benzotriazole (53.60 g, 0.45 mole) and acetic acid (50 ml) in ethanol (600 ml) at 50°. After a few minutes, the whole mixture suddenly solidified and was set aside at 22° overnight. The precipitate was collected, washed with ether (200 ml) and dried in a vacuum oven at 60° to give pure 4-(benzotriazol-1-ylmethyl)amino-3-nitroanisole (115.9 g, 97%) as orange needles, mp 188°; ^1H nmr: δ 3.74 (s, 3H, OCH_3), 6.34 (d, J = 6.8 Hz, 2H, CH_2), 7.16 (dd, J = 3.0 and 9.3 Hz, 1H, H-6), 7.39 (dd, J = 7.0 and 8.0 Hz, 1H, H-5'), 7.42 (d, J = 9.3 Hz, 1H, H-5), 7.52 (dd, J = 7.0 and 8.3 Hz, 1H, H-6'), 7.61 (d, J = 2.9 Hz, 1H, H-2), 7.70 (d, J = 8.3 Hz, 1H, H-7'), 8.06 (d, J = 8.4 Hz, 1H, H-4'), 8.77 (t, J = 6.8 Hz, N-H); ^{13}C nmr: δ 55.5 (OCH_3), 56.0 (CH_2), 107.7 (C-2), 111.1 (C-7'), 116.2 (C-5), 119.1 (C-4'), 124.0 (C-5'), 125.6 (C-6), 127.3 (C-6'), 132.2 (C-3), 132.3 (C-7a'), 137.7 (C-4), 145.6 (C-3a'), 150.6 (C-1).

Anal. Calcd. for $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.38; N, 23.40. Found: C, 56.13; H, 4.34; N, 23.70.

4-Methoxy-*N*-methyl-2-nitroaniline (**5**).

Sodium borohydride (13.88 g, 367 mmoles) was added portionwise over 1 hour to a stirred suspension of *N*-(benzotriazol-1-yl)-methyl-4-methoxy-2-nitroaniline (110.0 g, 367 mmoles in absolute ethanol (1000 ml) heated to 70°. After the addition was complete, the mixture was refluxed for an additional 1 hour. The product was poured onto crushed ice (1500 g), the precipitate collected, washed with water and dried in a vacuum oven at 60° to give pure *N*-methyl-4-methoxy-2-nitroaniline (65.4 g, 98%) as red needles, mp 99°, lit [11] mp 97-98°; ^1H nmr: δ 3.01 (d, J = 5.3 Hz, 3H, $N-CH_3$), 3.79 (s, 3H, OCH_3), 6.81 (d, J = 9.5 Hz, 1H, H-6), 7.17 (dd, J = 3.1 and 9.3 Hz, 1H, H-5), 7.59 (d, J = 2.9 Hz, 1H, H-3), 7.96 (bs, 1H, NH); ^{13}C nmr: δ 29.9 ($N-CH_3$), 55.8 ($O-CH_3$), 106.9 (C-3), 114.8 (C-6), 127.4 (C-5), 130.8 (C-2), 142.4 (C-1), 149.5 (C-4).

3-Amino-4-methylaminoanisole (**7**).

Anhydrous tin(II) chloride (265.44 g, 1.40 moles) was added to a stirred solution of 4-methylamino-3-nitroanisole (63.90 g, 350 mmoles) in 37% hydrochloric acid (300 ml) at a rate which raised the temperature of the mixture to 80°. After the addition was complete, stirring was continued at 25° for 1 hour and the product poured onto crushed ice (1500 g). Sodium hydroxide, 50% solution (600 g) was added and the mixture was extracted with chloroform (2 x 500 ml). The combined extracts were dried over anhydrous sodium carbonate, filtered and the solvent evaporated to give pure 3-amino-4-methylaminoanisole (42.38 g, 80%) as colorless prisms, mp 77-78°, lit [11] mp 78-79°; ^1H nmr: δ 2.79 (s, 3H, NCH_3), 3.48 (bs, 3H, NH_2, NH), 3.72 (s, 3H, OCH_3), 6.33 (d, J = 2.3 Hz, 1H, H-2), 6.36 (dd, J = 2.7 and 8.3 Hz, 1H, H-6), 6.58 (d, J = 8.3 Hz, 1H, H-5); ^{13}C nmr: δ 31.8 ($N-CH_3$), 55.5 ($O-CH_3$), 103.2 (C-2), 103.7 (C-6), 112.7 (C-5), 132.2 (C-4), 136.6 (C-3), 153.2 (C-1).

1-Methyl-5-methoxybenzimidazole (**8**).

A solution of 3-amino-4-(methylamino)anisole (46.60 g, 0.27 mole) in 96% formic acid (50 ml, 1.27 moles) was refluxed for 2 hours. Toluene (200 ml) and water (50 ml) were added and all the volatile liquids were evaporated under reduced pressure. The residue was poured into water (300 ml) and extracted with ethyl acetate (2 x 200 ml). The combined extracts were washed with water (200 ml), dried over magnesium sulfate and evaporated to give 5-methoxy-1-methylbenzimidazole (35.59 g, 81%) of purity 95% (according to nmr). Because the product was brownish, it was further purified by filtration of its solution in dichloromethane through silica gel. A concentrated solution of the product (15 g) in dichloromethane (50 ml) was added dropwise to stirred hexane (400 ml). The obtained precipitate was collected and dried in a vacuum oven to give analytically pure 5-methoxy-1-methylbenzimidazole as plates, mp 112°, lit [11] mp 112-113°; ^1H nmr: δ 3.78 (s, 3H, $N-CH_3$), 3.86 (s, 3H, $O-CH_3$), 6.96 (dd, J = 2.4 and 8.8 Hz, 1H, H-6), 7.24 (d, J = 8.8 Hz, 1H, H-7), 7.27 (d, J = 2.4 Hz, 1H, H-4), 7.78 (s, 1H, H-2); ^{13}C nmr: δ 31.1 ($N-CH_3$), 55.8 ($O-CH_3$), 102.3 (C-4), 109.7 (C-6), 113.1 (C-7), 129.2 (C-7a), 143.7 (C-2), 144.6 (C-3a), 156.1 (C-5).

N-(4-Methoxy-2-nitrophenyl)benzenesulfonamide (**6**).

To a stirred solution of 4-methoxy-2-nitroaniline (101.51 g, 0.604 mole) in pyridine (300 ml) was added benzenesulfonyl chloride (92.5 ml, 0.725 mole) in small portions in over 30 minutes. The temperature of the mixture rose from 22 to 45°. The mixture was stirred at this temperature for 3 hours and poured into ice-water (1500 g) and ethanol (300 ml). Acetic acid (200 ml) was added. The oil phase which separated on the bottom was triturated with a spatula until the oil turned into solid lumps. The solid was separated by decantation, powdered in a mortar and triturated with water (1000 ml). The product was collected, washed with water (1000 ml) and dried in a vacuum oven at 60° to give crude **6** (197 g) of purity 79% (nmr), yield 84%. An analytical sample was obtained by recrystallization from ethanol to give *N*-(4-methoxy-2-nitrophenyl)benzenesulfonamide as orange prisms, mp 82-83°, lit [12] mp 84°; ^1H nmr: δ 3.82 (s, 3H, Me), 7.18 (dd, J = 2.9 and 8.8 Hz, 1H, H-5), 7.43 (dd, J = 7.8 and 8.0 Hz, 2H, H-3', 5'), 7.48 (d, J = 2.9 Hz, 1H, H-3), 7.55 (t, J = 7.8 Hz, 1H, H-4'), 7.72 (d, J = 7.8 Hz, 2H, H-2', 6'), 7.79 (d, J = 9.1 Hz, 1H, H-6), 9.23 (bs, 1H, N-H); ^{13}C nmr: δ 56.0 (OCH_3), 109.1 (C-3), 123.0 (C-5), 125.0 (C-6), 126.2 (C-1), 127.1 (2C, 2', 6'), 129.3 (2C, 3', 5'), 133.5 (C-4'), 138.5 (C-2), 139.2 (C-1'), 156.4 (C-4).

N-(2-Amino-4-methoxyphenyl)benzenesulfonamide (**9**).

A mixture of compound **6** (27.75 g, 90 mmoles), 37% hydrochloric acid (100 ml) and tin(II) chloride dihydrate (90.25 g, 400 mmoles) was stirred at 22° for 12 hours. The reaction mixture was poured into ice-water (500 g), alkalized with 40% sodium hydroxide and finally neutralized with acetic acid. The mixture was stirred at 22° for 3 hours, the precipitate separated by filtration, washed with water, transferred to an Erlenmayer flask and triturated with a mixture of ethyl acetate (500 ml) and 2-propanol (100 ml). The obtained suspension was stirred at 22° for 2 hours. The precipitate was filtrated off and washed with ethyl acetate. The combined filtrate and washings were dried over magnesium sulfate and evaporated to give **9** (19.70 g, 79%) of purity above

90% (nmr) as colorless prisms, mp 115°, lit [12] mp 123-125°; ^{1}H nmr: δ 3.64 (s, 3H, MeO), 4.24 (bs, 2H, NH_2), 6.00 (dd, J = 8.8 and 2.4 Hz, 1H, H-5), 6.20 (d, J = 2.7 Hz, 1H, H-3), 6.37 (d, J = 8.5 Hz, 1H, H-6), 7.41 (t, J = 8.1 Hz, 2H, Ph), 7.52 (t, J = 7.7 Hz, 1H, Ph), 7.73 (d, J = 7.1 Hz, 2H, Ph), 7.90 (bs, 1H, NH). ^{13}C nmr: δ 55.1 (MeO), 101.2 (C-3), 103.7 (C-5), 114.1 (C-1), 127.4 (2C, Ph), 128.7 (2C, Ph), 129.8 (C-6), 132.6 (Ph), 139.4 (Ph), 146.1 (C-2), 159.7 (C-4).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06. Found: C, 56.00; H, 5.00; N, 9.83.

6-Methoxy-1-methylbenzimidazole (**11**).

To a solution of the crude sulfonamide **9** (42.00 g, 136 mmoles) and benzotriazole (16.18 g, 136 mmoles) in ethanol (300 ml) stirred at 60° was added 37% formaldehyde (25.5 ml, 340 mmoles). The stirring at 60° was continued for an additional 1 hour and then the mixture was stored at 0° overnight. The obtained precipitate **10** was separated by filtration, washed with ethanol (50 ml) and dried in a vacuum oven at 60°.

A suspension of this product and sodium borohydride (5.14 g, 136 mmoles) in dioxane (200 ml) was stirred and heated at reflux for 5 hours. The reaction mixture was poured into ice-water (800 g) and extracted with methylene chloride (3 x 200 ml). The combined extracts were washed with 10% sodium hydroxide (100 ml) followed by water (100 ml), dried and evaporated to give crude 6-methoxy-1-methylbenzimidazole. Column chromatography (silica gel/chloroform) afforded pure **11** (16.50 g, 75%) as a hygroscopic solid mp 60-62°, lit [13] mp 66-67°; ^{1}H nmr: δ 3.73 (s, 3H, N-CH_3), 3.86 (s, 3H, O-CH_3), 6.78 (d, J = 2.3 Hz, 1H, H-7), 6.91 (dd, J = 2.4 and 8.8 Hz, 1H, H-5), 7.66 (d, J = 8.8 Hz, 1H, H-4), 7.71 (s, 1H, H-2); ^{13}C nmr: δ 30.8 (N-CH_3), 55.7 (OCH_3), 92.6 (C-7), 111.5 (C-5), 120.4 (C-4), 135.1 (C-7a), 138.0 (C-3a), 142.7 (C-2), 156.7 (C-6).

N-(4-Methoxy-2-nitrophenyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**12**).

To a solution of 4-methoxy-2-nitroaniline (1.68 g, 10 mmoles) in pyridine (25 ml) was added benzenesulfonyl chloride (3.83 ml, 30 mmoles) and the obtained mixture stirred at 60° for 20 hours. The reaction mixture was poured onto ice (100 g). The obtained precipitate was collected, dried in air and recrystallized from ethanol to give pure *N*-(4-methoxy-2-nitrophenyl)-*N*-(benzenesulfonyl)benzenesulfonamide (4.12 g, 92%). Final recrystallization of the product from toluene afforded an analytical sample, mp 192°; ^{1}H nmr: δ 3.87 (s, 3H, Me), 7.02 (d, J = 8.6 Hz, 1H, H-6), 7.03 (dd, J = 2.5 and 8.6 Hz, 1H, H-5), 7.49 (d, J = 2.5 Hz, 1H, H-3), 7.53 (t, J = 8.0 Hz, 4H, Ph), 7.68 (t, J = 7.3 Hz, 2H, Ph), 7.95 (d, J = 7.4 Hz, 4H, Ph); ^{13}C nmr: δ 56.2 (Me), 111.2 (C-3), 118.7 (C-5), 119.4 (C-1), 128.9 (4C, Ph), 129.2 (4C, Ph), 134.3 (2C, Ph), 135.5 (C-6), 138.5 (2C, Ph), 148.9 (C-2), 161.1 (C-4).

Anal. Calcd. for $C_{19}H_{16}N_2O_7S_2$: C, 50.89; H, 3.60; N, 6.25. Found: C, 51.22; H, 3.52; N, 6.16.

N-(2-Amino-4-methoxyphenyl)-*N*-(benzenesulfonyl)benzenesulfonamide (**13**).

To a suspension of **12** (2.24 g, 5 mmoles) in 37% hydrochloric acid (20 ml) was added stannous chloride monohydrate (5.41 g, 24 mmoles) and the obtained mixture was stirred at 22° for 20 hours. The mixture was poured onto ice (100 g) and alkalized with 25% sodium hydroxide. The obtained precipitate was collected, dried in a vacuum oven and extracted with chloroform (2 x 50 ml). The solvent was evaporated and the residue recrystallized from toluene to give analytically pure amine (1.62 g, 77%), mp 108°; ^{1}H nmr: δ 3.67 (s, 3H, Me), 4.00 (bs, 2H, NH_2), 6.10 (dd, J = 2.8 and 8.8 Hz, 1H, H-5), 6.24 (d, J = 2.8 Hz, 1H, H-3), 6.37 (d, J = 8.8 Hz, 1H, H-6), 7.48 (t, J = 8.0 Hz, 4H, Ph), 7.63 (tt, J = 1.3 and 7.5 Hz, 2H, Ph), 7.95 (dd, J = 1.3 and 8.0 Hz, 4H, Ph); ^{13}C nmr: δ 55.2 (Me), 101.2 (C-3), 104.7 (C-5), 111.9 (C-1), 128.8 (4C, Ph), 128.9 (4C, Ph), 133.2 (C-6), 134.1 (2C, Ph), 139.0 (2C, Ph), 148.3 (C-2), 161.9 (C-4).

Anal. Calcd. for $C_{19}H_{18}N_2O_5S_2$: C, 54.53; H, 4.34; N, 6.69. Found: C, 54.48; H, 4.28; H, 6.60.

N-(2-Dimethylamino-4-methoxyphenyl)benzenesulfonamide (**16**) and *N*-(Phenylsulfonamido)-*N*-(4-methoxy-2-methylaminophenyl)-benzenesulfonamide (**17**).

The first fraction obtained from column chromatography of crude 6-methoxy-1-methylbenzimidazole **11** (prepared from 136 mmoles of **9**) was recrystallized from ethanol/toluene (80 + 20 ml) to give pure **17** (0.68 g, 1%) as colorless needles, mp 178°; ^{1}H nmr: δ 2.61 (s, 3H, NCH_3), 3.29 (bs, 1H, NH), 3.77 (s, 3H, OCH_3), 6.05 (dd, J = 2.8 and 8.6 Hz, 1H, H-5), 6.10 (d, J = 2.7 Hz, 1H, H-3), 6.37 (d, J = 8.67 Hz, 1H, H-6), 7.59 (t, J = 8.0 Hz, 4H, H-3'), 7.74 (t, J = 7.3 Hz, 2H, H-4'), 7.51 (d, J = 7.3 Hz, 4H, H-2'); ^{13}C nmr: δ 29.9 (NCH_3), 55.1 (OCH_3), 96.9 (C-3), 101.6 (C-5), 111.6 (C-1), 128.5 (4C, C-2'), 128.9 (4C, C-3'), 132.9 (C-6), 134.2 (2C, C-4'), 138.9 (2C, C-1'), 149.6 (C-2), 162.3 (C-4).

Anal. Calcd. for $C_{20}H_{20}N_2O_5S_2$: C, 55.54; H, 4.66; N, 6.48. Found: C, 55.38; H, 4.61; N, 6.40.

After separation of **17**, the filtrate was stored at −5° for 24 hours to give **16** (1.89 g, 4.5%) as colorless needles, mp 106°; ^{1}H nmr: δ 2.31 (s, 6H, NMe_2), 3.73 (s, 3H, OMe), 6.63 (dd, J = 2.8 and 9.4 Hz, 1H, H-5), 6.64 (d, J = 2.8 Hz, 1H, H-3), 7.40 (t, J = 7.7 Hz, 2H, Ph), 7.49 (m, 1H, Ph), 7.53 (d, J = 9.4 Hz, 1H, H-6), 7.78 (d, J = 8.2 Hz, 2H, Ph); ^{13}C nmr: δ 45.0 (2C, NMe_2), 55.4 (OMe), 108.0 (C-3), 110.0 (C-5), 120.2 (C-6), 126.1 (C-1), 127.1 (2C, Ph), 128.9 (2C, Ph), 132.8 (Ph), 139.4 (Ph), 145.2 (C-2).

Anal. Calcd. for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.69; H, 5.75; N, 8.82.

1-Methyl-5-nitrobenzimidazole (**19**).

A mixture of 2-chloro-5-nitroaniline (25.78 g, 0.15 mole) and anhydrous methylamine (30 ml, at −50°) was heated in a pressure vessel at 140° for 40 hours. After cooling to room temperature, the vessel was opened and the excess of methylamine was allowed to evaporate. The residue was transferred to a 500 ml flask, 96% formic acid (50 ml) added and the mixture heated at reflux for 3 hours. The reaction mixture was poured into ice-water (300 g), neutralized with 10% sodium hydroxide and extracted with chloroform (4 x 300 ml). The combined chloroform extracts were dried (sodium sulfate), concentrated and subjected to column chromatography (silica gel-chloroform). The first fraction obtained appeared to be 3-nitroformanilide (2.08 g, 8%) and was rejected. The second fraction was the desired 1-methyl-5-nitrobenzimidazole. The product was recrystallized from ethanol to give pure **19** (10.99 g, 41%) as yellow needles, mp 210°, lit [14] mp 209-210°; ^{1}H nmr: δ 3.95 (s, 3H, CH_3), 7.71 (d, J = 9.0 Hz, 1H, H-7), 8.18 (dd, J = 2.2 and 9.0 Hz, 1H, H-6), 8.41 (s, 1H, H-2), 8.53 (d, J = 2.0 Hz, H-4); ^{13}C nmr: δ 31.2 (CH_3), 110.4 (C-7), 115.7 (C-4), 117.9 (C-6), 138.8 (C-7a), 142.6 (C-5), 142.8 (C-3a), 148.3 (C-2).

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