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Synthesis of benzothiazoles *via ipso* substitution of *ortho*-methoxythiobenzamides

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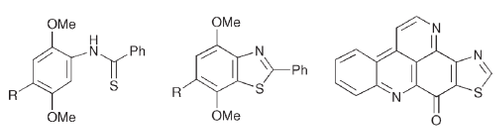
An efficient route to the synthesis of benzothiazoles from *ortho*-methoxythiobenzamides *via* the *ipso* substitution of an aromatic methoxy group is presented, and the mechanism of the Jacobson synthesis of benzothiazoles is further investigated.

Introduction

Benzothiazoles are precursors to natural products, pharmaceutical agents and other compounds that exhibit a wide spectrum of biological activity such as antitumour, immunosuppressive, immunomodulatory and antiviral properties.[1] Various methods of synthesis of benzothiazoles are known.[2] Among these is the Jacobson synthesis—oxidative cyclization of an arylthioamide on an unsubstituted *ortho* position, using potassium ferricyanide in a basic medium.[2b] This method has been well used for the preparation of substituted benzothiazoles.[3–5]

Our previous success with the formation of benzothiazoles **2b–d** by cyclization of thiobenzamides **1b–d** suggested that compound **1a** was a useful precursor to **2a**,[3,4] which was needed in our on-going study of the synthesis of analogues of kuanoniamine A, a pharmacologically active marine alkaloid.[6]



1a R = OMe
1b R = H
1c R = Br
1d R = NO_2

2a R = OMe
2b R = H
2c R = Br
2d R = NO_2

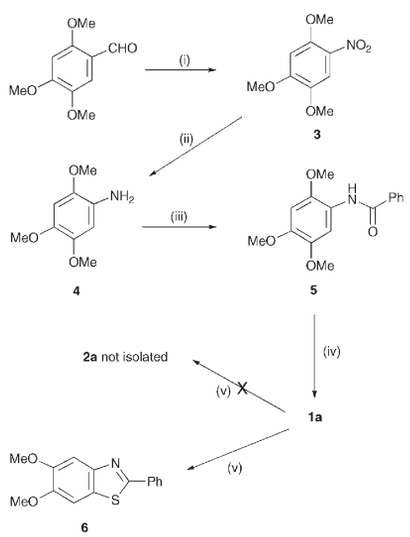
kuanoniamine A

Our previous studies indicated that the presence of electron withdrawing groups on the primary ring significantly reduced the yield of the Jacobson synthesis (compounds **2b–d** were obtained in 80, 54 and 24% respectively after 1, 3 and 7 days at room temperature). It was therefore anticipated that Jacobson cyclization of the highly activated thiobenzamide **1a** would occur at a higher rate and with better yields than those previously carried out. We noted, however, that trisubstituted arylthioanilides are quite unpopular as substrates for the Jacobson synthesis.

Results and discussion

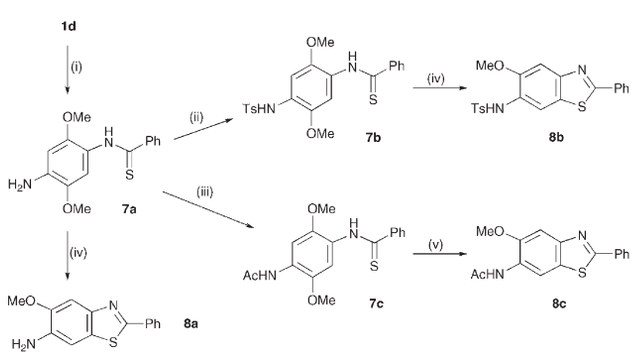
Compound **1a** was easily obtained from commercially available 2,4,5-trimethoxybenzaldehyde by the pathway shown in Scheme 1 (overall yield 50%). Addition of 2,4,5-trimethoxybenzaldehyde to a cold (−5 °C) solution of 50% aqueous nitric acid resulted in *ipso* nitration[7] to produce nitrobenzene **3**. Subsequent reduction, followed by condensation with benzoyl chloride and thionation using Lawesson's reagent, produced thiobenzamide **1a**.

Treatment of compound **1a** with 1.5 M NaOH followed by 20% $K_3Fe(CN)_6$ at room temperature for one day, however, did not produce the expected benzothiazole **2a**, but rather, gave benzothiazole **6**,[5] (entry 4, Table 1), the product of *ipso* substitution of a methoxy group. Not only was an unexpected product obtained, but cyclization had occurred in low yield (15%).



Scheme 1 *Reagents and conditions*: (i) 50% aq. HNO_3, −5 °C, 30 min, 81%; (ii) H_2, Pd/C, MeOH, r.t., 15 psi, 3 h, quant.; (iii) CH_2Cl_2, toluene, pyridine, benzoyl chloride, reflux, 5 h, 86%; (iv) Lawesson's reagent (0.6 molar equiv.), toluene, 80 °C, 2 h, 72%; (v) 20% aq. $K_3Fe(CN)_6$, 1.5 M NaOH, r.t., 15 h, 15%.

The only difference between thiobenzamide **1a** and compounds **1b–d** is that **1a** has three electron donating groups on the primary ring. Other similarly activated thiobenzamides (**7a–c**) were thus prepared and subjected to Jacobson conditions. Compound **7a** was easily obtained from **1d**[4] by reduction. Subsequent tosylation or acylation yielded **7b** or **7c**, respectively (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) Sn, conc. HCl, ethanol, reflux, 3 h, 50%; (ii) TsCl, py, r.t., 12 h, quant.; (iii) Ac_2O, py, r.t., 12 h, quant.; (iv) 20% aq. $K_3Fe(CN)_6$, 1.5 M NaOH, r.t., 24 h, 5–10%.

Under Jacobson reaction conditions, as outlined above, compounds **7a–c** underwent cyclization with substitution of the *ortho* methoxy group, to produce benzothiazoles **8a**, **8b** and

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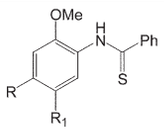
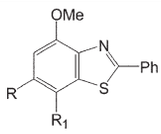
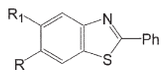
Table 1 Products of the Jacobson and AIBN-induced cyclization of *o*-methoxythiobenzamides

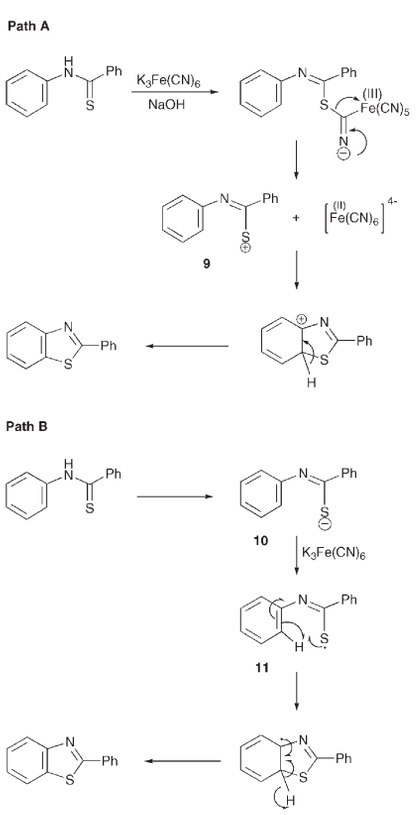
Entry	Substrate	Product of Jacobson synthesis (% yield)	Product of AIBN cyclization (% yield)
			
1	**1b** R_1 = OMe, R = H	**2b** (80)	**12** (84)
2	**1c** R_1 = OMe, R = Br	**2c** (45)	—[a]
3	**1d** R_1 = OMe, R = NO_2	—[a]	—[a]
4	**1a** R_1 = OMe, R = OMe	—[b]	**6** (93)
5	**7a** R_1 = OMe, R = NH_2	—[b]	**8a** (98)[c]
6	**7b** R_1 = OMe, R = NHTs	—[b]	**8b** (81)
7	**7c** R_1 = OMe, R = NHAc	—[b]	**8c** (78)
8	**17** R_1 = H, R = NHTs	—	**18** (82)
9	**19** R_1 = R = H	**20** (74)	—[a]

[a] Starting material recovered. [b] *Ipso* substitution of *ortho*-OMe occurred in 5–15% yield. Major product = benzamide. [c] The product was tosylated for characterization.

8c in yields of 5–10%; the major product being the corresponding benzamide. A similar reaction had been observed when, in an attempt at detosylation, **7b** was treated with saturated bicarbonate in refluxing methanol. In this instance, the corresponding benzamide and benzothiazole **8b** were obtained in 60% and 5% yield, respectively.[4] To our knowledge, this is the only other case of cyclization of thiobenzamides with *ipso* substitution of an aromatic methoxy group that has been reported.

The literature provides two likely mechanisms for the Jacobson synthesis. That proposed by Metzger and Planck is illustrated in Scheme 3, Path A, and involves formation of a thioimidic cation (**9**) which then attacks the benzene ring with loss of a proton.[8] The second mechanism proposed by Stevens *et al.* (Scheme 3, Path B),[5] involves reaction of the thiobenzamide with base to form a thiolate ion (**10**), which then undergoes one-electron oxidation to form the thiol radical **11**. Thiol radical **11** then attacks the unoccupied *ortho* position, eliminating a hydrogen radical to form the benzothiazole.

It seemed more probable that the radical mechanism (Path B) was the one operating in the NaOH/potassium ferricyanide



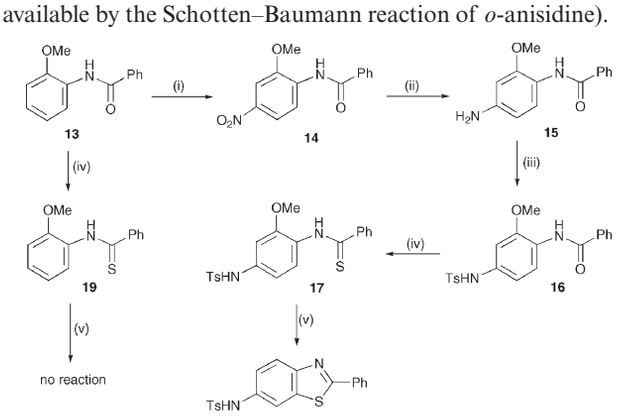
Scheme 3 Proposed mechanisms for the Jacobson synthesis.

cyclization with *ipso* substitution of the methoxy group. The ionic reaction (Path A) would require the unlikely loss of a methoxy cation.

Intramolecular radical *ipso* substitution of an alkoxy group is rare.[9–12] Previously reported *ipso* substitutions of the methoxy group were found to occur on an activated benzene or pyridine ring and involved radical attack at the carbon bearing the methoxy substituent, followed by re-aromatization with loss of the methoxy radical. In these instances, AIBN was used as the radical initiator. The use of AIBN in the synthesis of benzothiazoles from *o*-halogenothiobenzamides is known to occur with the radical abstraction of halide groups.[13] AIBN-induced cyclization with elimination of the methoxy group was thus attempted on the substrates in hand.

Thiobenzamides **1a** and **7a–c** were treated with 1.1–1.5 molar equivalents of AIBN in refluxing benzene, toluene or nitrobenzene for 15 minutes to 12 hours. Analysis of the products revealed that cyclization with elimination of the methoxy group did occur to produce the corresponding benzothiazoles (**6**, **8a**, **8b**, **8c** respectively) in yields of 81–98%. Interestingly, AIBN-induced cyclization of 2,5-dimethoxythiobenzamide **1b** produced, not **2b**, as in the case of the Jacobson reaction, but benzothiazole **12** (84%) from *ipso* substitution of the methoxy group (Table 1, entry 1). This was a clear indication that the Jacobson and AIBN-induced cyclizations were occurring *via* different reaction intermediates.

AIBN-induced cyclization of **17** occurred in good yield, with replacement of the *ortho* methoxy group, whereas attempts at a similar reaction using **19** failed, and only starting material was recovered (thiobenzamides **17** and **19** were prepared as shown in Scheme 4 from the known benzamide **13**, which is itself readily available by the Schotten–Baumann reaction of *o*-anisidine).

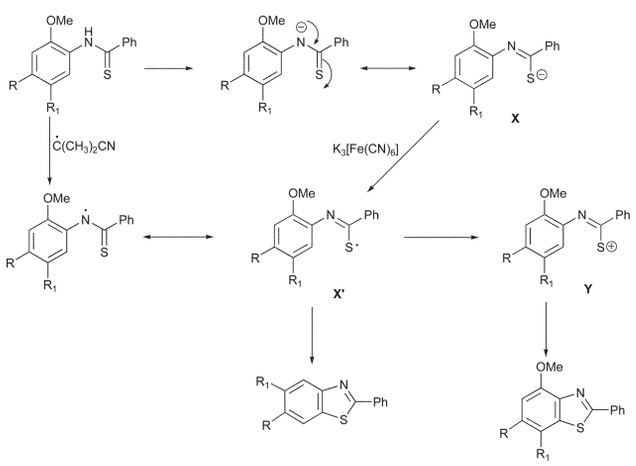


Scheme 4 *Reagents and conditions*: (i) conc. HNO_3, AcOH, r.t., 1 day, 60%; (ii) H_2, 10% Pd/C, r.t., 15 psi, 1 h, 96%; (iii) TsCl, py, r.t., 12 h, quant.; (iv) Lawesson's reagent, toluene, reflux, 2 h; (v) 1.1 equiv. AIBN, nitrobenzene, reflux, 15 min.

The AIBN-induced cyclization of *ortho*-methoxythiobenzamides clearly requires a benzene ring with high electron density. When there are two or more electron donating groups on the primary ring, AIBN-induced cyclization is accomplished with *ipso* substitution of the methoxy group (Table 1, entries 1 and 4–8). When there is only one electron donating group on the primary ring, or two electron donating groups and one electron withdrawing group, there is no reaction (Table 1, entries 2, 3 and 9).

Jacobson cyclization of *ortho*-methoxythiobenzamides bearing one or two electron donating groups on the primary ring occurs with replacement of the *ortho* hydrogen.[3–5] When there are three electron donating groups on the primary ring, however, cyclization occurs in very low yield, and with *ipso* substitution of the *ortho* methoxy group (Table 1, entries 3–7).

We suggest that the AIBN-induced cyclization and the Jacobson reaction of these compounds may be linked, as shown in Scheme 5. Under Jacobson reaction conditions the mechanism of cyclization of these arylthiobenzamides seems to depend on the electron density of the primary aromatic ring, and on the stability of ions **X** and **Y** (Scheme 5). For R_1 = R = H or R_1 = OMe, R = H (Table 1, entries 9 and 1, respectively), the reaction proceeds *via* cation **Y** with replacement of *ortho* H^+, and yields are good. As R becomes more electron withdrawing, *i.e.* H to Br to NO_2 (Table 1, entries 1–3), the reaction goes more and more slowly (80, 45 and 0% yield respectively after one day, with compound **1d** undergoing cyclization with loss of H^+ in 24% yield after 7 days). Anion **X** is stabilized by the delocalization of negative charge onto the R groups, leading to formation of only small amounts of **X′** or **Y**, and these need greater electron density on the primary ring for effective cyclization.



Scheme 5 Likely mechanistic link between AIBN-induced and Jacobson cyclizations.

When R is an electron donating group, the Jacobson reaction with replacement of H^+ does not occur. Here the thiomidic cation **Y** which is formed is stabilized and thus made less reactive by electron donating groups *para* to the thioamide substituent. The radical **X′**, which is formed *en route* from **X** to **Y**, may then be the effective reacting species, leading to substitution of the *ortho* methoxy group in low yield. Further studies in this area are in progress.

Experimental

General

IR spectra were obtained on a Perkin-Elmer 735B model and are for KBr discs. NMR spectra (Bruker 200 and 500 MHz) were determined in $CDCl_3$ solution and the resonances are reported in ppm downfield from TMS; *J* values are given in Hz. Elemental analyses were carried out by MEDAC Ltd., Egham, Surrey, UK.

2,4,5-Trimethoxynitrobenzene (3)

To a cold aqueous solution of 50% nitric acid (100 mL) was added over a 5 min period, with stirring, 2,4,5-trimethoxybenzaldehyde (5.1 g, 26.2 mmol). The resulting mixture was stirred for a further 30 min with cooling in an ice bath, after which water was added to form a slurry. The precipitate was filtered and rinsed with water to yield **3** as a yellow powder (5.0 g, 90%), mp 123–124 °C (acetone) (lit.,[14] 87–89 °C); ν_{max}/cm^{-1} 3009, 1588, 1277; δ_H 4.04 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 4.13 (3H, s, OCH_3), 6.70 (1H, s, 3-H), 7.73 (1H, s, 6-H); δ_C 56.8, 56. 9, 57.6, 98.0, 109.4, 131.2, 142.8, 150.8, 155.2.

2,4,5-Trimethoxyaniline (4)

To a solution of 2,4,5-trimethoxynitrobenzene **3** (1.1 g, 5.2 mmol) in methanol (200 mL) was added 5% Pd/C (0.1 g). The mixture was shaken under hydrogen (Parr apparatus) at a pressure of 15 psi for 3 h, after which it was filtered through Celite and concentrated to yield **4** as a purple crystalline solid (0.95 g, quant.), mp 89.5–90.5 °C (dichloromethane–hexanes) (lit.,[15] 92–93 °C); ν_{max}/cm^{-1} 3391, 2841; δ_H 3.22 (2H, s, N–H), 3.71 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 6.31 (1H, s, 3-H), 7.45 (1H, s, 6-H); δ_C 57.0, 57.7, 100.7, 102.4, 130.2, 141.3, 141.9, 144.3.

N-(2,4,5-Trimethoxyphenyl)benzamide (5)

To a solution of 2,4,5-trimethoxyaniline **4** (11.5 g, 62.6 mmol) in dichloromethane (100 mL) was added benzoyl chloride (8 mL, 68.9 mmol), toluene (30 mL) and pyridine (40 mL). The mixture was heated at reflux for 5 h, after which time it was concentrated, extracted with dichloromethane and rinsed with 1 M HCl (200 mL) followed by a saturated aqueous solution of sodium bicarbonate (100 mL). The organic layer was then dried (Na_2SO_4) and concentrated to produce **5** as a purple crystalline solid (15.3 g, 86%), mp 134–135 °C (dichloromethane–hexanes) (Found: C, 66.70; H, 6.01; N, 4.92%. Calc. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87%); ν_{max}/cm^{-1} 3201, 1651, 1539, 1209; δ_H 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 6.52 (1H, s, 3-H), 7.45 (3H, m, 3′,4′,5′-H), 7.78 (2H, m, 2′,6′-H), 8.22 (1H, s, 6-H), 8.34 (1H, s, N–H); δ_C 56.9, 58.0, 57.0, 98.0, 105.8, 121.3, 127.3, 128.8, 129.2, 129.9, 130.5, 132.1, 142.7, 143.3, 145.5, 165.4.

Thionation of benzamides

To a solution of the benzamide (1.0 g) in dry toluene (40 mL) was added Lawesson's reagent (0.6 molar equiv.). The mixture was heated under an atmosphere of nitrogen at reflux for 2 h, after which it was concentrated and purified by column chromatography or recrystallized from methanol or ethyl acetate–hexanes to give yellow crystals.

***N*-(2,4,5-Trimethoxyphenyl)thiobenzamide (1a).** (72%), mp 104–105 °C (methanol) (Found: C, 63.25; H, 5.78; N, 4.67%. Calc. for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62%); ν_{max}/cm^{-1} 3359, 1530, 1197; δ_H 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 6.64 (1H, s, 3-H), 7.50 (3H, m, 3′,4′,5′-H), 7.88 (2H, m, 2′,6′-H), 9.07 (1H, s, 6-H), 9.60 (1H, s, N–H); δ_C 56.8, 57.0, 57.1, 97.3, 107.0, 122.1, 127.1, 129.0, 131.3, 142.3, 144.4, 144.7, 195.0.

***N*-[2-Methoxy-4-(*p*-tolylsulfonylamino)phenyl]thiobenzamide (17).** (76%), mp 149–150 °C (ethyl acetate–hexanes) (Found: C, 61.17; H, 4.80; N, 6.79%. Calc. for $C_{21}H_{20}N_2O_3S_2$: C, 61.14; H, 4.89; N, 6.79%); ν_{max}/cm^{-1} 3361, 1531; δ_H 2.32 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 6.63 (1H, m, 5-H), 6.89 (1H, m, 3-H), 7.21 (2H, d, *J* 8, tosyl), 7.39 (4H, m, 3′,4′,5′-H and N–H), 7.70 (2H, d, *J* 8, tosyl), 7.76 (2H, m, 2′,6′-H), 8.90 (1H, m, 6-H), 9.54 (1H, s, N–H); δ_C 21.5, 56.1, 104.5, 112.4, 121.9, 125.7, 126.7, 128.6, 129.7, 131.0, 135.1, 135.8, 144.0, 150.5, 195.5.

***N*-(2-Methoxyphenyl)thiobenzamide (19).** (80%), mp 78–79 °C (ethyl acetate–hexanes) (lit.,[5] 121–122 °C); δ_H 3.91 (3H, s, OCH_3), 6.99 (2H, m, 3,5-H), 7.21 (1H, m, 4-H), 7.46 (3H, m, 3′,4′,5′-H), 7.83 (2H, m, 2′,6′-H), 9.13 (1H, d, *J* 7, 6-H), 9.64 (1H, s, N–H); δ_C 56.4, 110.7, 120.8, 121.9, 126.9, 127.2, 129.0, 131.4, 144.5, 150.3, 196.5.

General procedure for the Jacobson synthesis

To the thiobenzamide (0.1 g) in ethanol (0.5 mL) was added 1.5 M sodium hydroxide (7 mL). The solution was cooled in an ice–water bath and freshly prepared (20%) aq. potassium ferricyanide (2–3 molar equiv.) added. The mixture was stirred at room temperature for 1 day, the mixture neutralized with 1 M HCl and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), the solvent removed *in vacuo* and the residue purified by column chromatography or recrystallization from ethanol or ethyl acetate–hexanes to give white needles.

General procedure for the AIBN-induced cyclization of thiobenzamides

To a solution of the thiobenzamide (0.1 g) in benzene, toluene or nitrobenzene (10 mL) was added AIBN (1.1 molar equiv.) and the mixture was stirred at reflux for the appropriate time. The solvent was removed *in vacuo*, the crude product eluted through a neutral alumina column and recrystallized from ethyl acetate–hexanes or ethanol. When nitrobenzene was used as solvent, this was removed by eluting the reaction mixture through a silica column with hexanes followed by ethyl acetate. The ethyl acetate fraction was concentrated and recrystallized from ethyl acetate–hexanes or ethanol.

5,6-Dimethoxy-2-phenylbenzothiazole (6). (Jacobson synthesis: 15%; AIBN cyclization: nitrobenzene, 15 min, 93%), mp 145–146 °C (ethanol) (lit.,[5] 142–144 °C); δ_H 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 7.58 (3H, m, 3′,4′,5′-H), 7.66 (1H, s, 7-H), 7.73 (1H, s, 4-H), 8.07 (2H, m, 2′,6′-H); δ_C 56.1, 56.3, 103.7, 105.8, 126.7, 126.9, 129.7, 131.0, 133.6, 148.2, 148.9, 165.2.

6-Amino-5-methoxy-2-phenylbenzothiazole (8a). (Jacobson synthesis: <10%; AIBN cyclization: nitrobenzene, 15 min, 98%), mp 150–151 °C (ethyl acetate–hexanes); ν_{max}/cm^{-1} 3461, 1474, 1327; δ_H 3.87 (3H, s, OCH_3), 7.03 (1H, s, 7-H), 7.39 (4H, m, 3′,4′,5′-H and 4-H), 7.91 (2H, m, 2′,6′-H); δ_C 54.7, 102.9, 103.6, 125.8, 127.9, 129.0, 133.1, 134.9, 146.4, 146.9, 164.5.

5-Methoxy-2-phenyl-6-(*p*-tolylsulfonylamino)benzothiazole (8b). (Jacobson synthesis: <10%; AIBN cyclization: toluene, 12 h, 81%), mp 184–186 °C (lit.,[4] 184–186 °C).

6-Acetylamino-5-methoxy-2-phenylbenzothiazole (8c). (Jacobson synthesis: <5%; AIBN cyclization: toluene, 12 h, 78%), mp 169–170 °C (ethyl acetate–hexanes) (Found: C, 64.02; H, 4.68; N, 9.26%. Calc. for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39%); ν_{max}/cm^{-1} 3422, 3055, 1690, 1262; δ_H 2.26 (3H, s, CH_3), 3.99 (3H, s, OCH_3), 7.47 (3H, m, 3′,4′,5′-H), 7.54 (1H, s, 4-H), 7.96 (1H, s, N–H), 8.04 (2H, m, 2′,6′-H), 8.97 (1H, s, 7-H); δ_C 25.4, 56.4, 103.9, 111.6, 127.0, 127.5, 128.0, 129.3, 131.0, 134.1, 148.2, 150.5, 168.7.

6-(*p*-Tolylsulfonylamino)-2-phenylbenzothiazole (18). (AIBN cyclization: nitrobenzene, 15 min, 82%), mp 209–210 °C (ethyl acetate–hexanes) (Found: C, 62.96; H, 4.16; N, 7.30%. Calc. for $C_{20}H_{16}N_2O_2S_2$: C, 63.13; H, 4.24; N, 7.36%); ν_{max}/cm^{-1} 3433, 1647; δ_H 2.40 (3H, s, CH_3), 6.74 (1H, s, N–H), 7.25 (3H, m, 7-H and tosyl), 7.52 (3H, m, 3′,4′,5′-H), 7.70 (2H, d, *J* 8, tosyl), 7.72 (1H, m, 5-H), 7.80 (1H, d, *J* 9, 4-H), 8.07 (2H, m, 2′,6′-H); δ_C 21.9, 116.6, 120.7, 122.5, 127.7, 127.9, 129.5, 130.2, 131.6, 132.7, 133.8, 135.7, 136.5, 144.4, 155.2, 170.1.

5-Methoxy-2-phenylbenzothiazole (12). (AIBN cyclization: benzene, 1.5 h, 84%), mp 75–77 °C (ethyl acetate–hexanes) (Found: C, 69.49; H, 4.78; N, 5.80%. Calc. for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80%); ν_{max}/cm^{-1} 1597, 1462, 1256; δ_H 3.87 (3H, s, OCH_3), 7.04 (1H, dd, *J* 3 and 9, 6-H), 7.45 (3H, m, 3′,4′,5′-H), 7.55 (1H, d, *J* 2, 4-H), 7.68 (1H, d, *J* 9, 7-H), 8.05 (2H, m, 2′,6′-H); δ_C 56.0, 106.1, 115.9, 122.2, 127.4, 127.8, 129.4, 131.2, 134.2, 155.9, 159.6, 169.6.

N-(4-Amino-2,5-dimethoxyphenyl)thiobenzamide (7a)

To a solution of *N*-(2,5-dimethoxy-4-nitrophenyl)thiobenzamide (**1d**) (2.6 g, 8.6 mmol) in ethanol (40 mL) was added tin pellets (3 g, 25.3 mmol) and conc. hydrochloric acid (10 mL). The mixture was heated at reflux for 3 h, cooled to room temperature, poured into water (100 mL) and the pH adjusted to 7 with 10% aq. sodium hydroxide. The resultant yellow precipitate was collected by filtration, purified by column chromatography and recrystallized from ethyl acetate–hexanes as fine orange crystals (1.2 g, 50%), mp 104–106 °C (ethyl acetate–hexanes); ν_{max}/cm^{-1} 3361, 1535, 1266; δ_H 3.79 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 6.35 (1H, s, 3-H), 7.43 (3H, m, 3′,4′,5′-H), 7.80 (2H, m, 2′,6′-H), 8.89 (1H, s, 6-H), 9.58 (1H, s, N–H); δ_C 56.7, 56.8, 99.0, 106.3, 119.8, 127.1, 129.0, 131.1, 135.2, 140.0, 144.5, 145.4, 193.5.

Tosylation of 7a and 15

To a solution of the amino compound (200 mg) in dry pyridine (5 mL) was added toluene-*p*-sulfonyl chloride (1.2 equiv.). The resulting mixture was stirred at room temperature for 12 h, toluene (15 mL) added and the solvent removed *in vacuo.* The product was then recrystallized from ethyl acetate–hexanes.

***N*-[2,5-Dimethoxy-4-(*p*-tolylsulfonylamino)phenyl]thiobenzamide (7b).** Orange crystals (quant.), mp 145–146 °C (lit.,[4] 146–149 °C).

***N*-[2-Methoxy-4-(*p*-tolylsulfonylamino)phenyl]benzamide (16).** Orange-brown crystals (quant.), mp 172–173 °C (Found: C, 63.28; H, 4.87; N, 7.07%. Calc. for $C_{21}H_{20}N_2O_4S$: C, 63.62; H, 5.03; N, 7.07%); ν_{max}/cm^{-1} 3427, 1531, 1203; δ_H 2.37 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 6.85 (2H, m, 3,5-H), 7.22 (2H, d, *J* 8, tosyl), 7.50 (3H, m, 3′,4′,5′-H), 7.69 (2H, d, *J* 8, tosyl), 7.88 (2H, m, 2′,6′-H), 8.16 (1H, s, 6-H), 8.51 (1H, s, N–H); δ_C 21.9, 56.5, 114.9, 118.4,127.4, 127.5,127.7, 127.8, 129.2, 130.0, 132.3, 144.0, 146.4, 166.0.

***N*-(4-Acetylamino-2,5-dimethoxyphenyl)thiobenzamide (7c).** To a solution of *N*-(4-amino-2,5-dimethoxyphenyl)thiobenzamide **7a** (0.20 g, 0.7 mmol) in dry pyridine (5 mL) was added acetic anhydride (0.06 mL, 0.8 mmol). The resulting mixture was stirred at room temperature for 12 h, toluene (15 mL) added and the solvent removed *in vacuo*. The product was then recrystallized from ethyl acetate–hexanes as yellow crystals (quant., 0.23 g), mp 174–175 °C (Found: C, 61.58; H, 5.54; N, 8.56%. Calc. for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.47%); ν_{max}/cm^{-1} 3419, 1587, 1542, 1210; δ_H 2.21 (3H, s, CH_3), 3.90 (6H, s, 2 × OCH_3), 7.46 (3H, m, 3′,4′,5′-H), 7.86 (3H, m, 2′,6′-H and N–H), 8.25 (1H, s, 3-H), 9.21 (1H, s, 6-H), 9.75 (1H, s, N–H); δ_C 25.4, 56.8, 56.9, 103.3, 104.5, 124.3, 125.7, 127.1, 129.1, 131.4, 140.7, 144.0, 144.5, 168.8, 194.9.

***N*-(2-Methoxy-4-nitrophenyl)benzamide (14).** A solution of the benzamide **13** (3.0 g, 13.2 mmol) in glacial acetic acid (65 mL) was cooled in an ice–water bath, with stirring. To this cold solution was added conc. nitric acid (1.2 mL, 26.8 mmol) in glacial acetic acid (5 mL) and the mixture stirred at ambient temperature overnight. The mixture was poured into water (500 mL) and the white precipitate collected by filtration, purified by column chromatography and obtained as white crystals (2.16 g, 60%), mp 147–148 °C (lit.,[16] 149–150 °C).

***N*-(4-Amino-2-methoxyphenyl)benzamide (15).** To a suspension of the nitrobenzamide **14** (3.0 g, 11.1 mmol) in methanol (200 mL) was added 10% Pd/C (0.4 g). The mixture was shaken under hydrogen (Parr apparatus) at a pressure of 15 psi for 1 h, after which it was filtered through Celite, concentrated *in vacuo* and recrystallized from ethyl acetate–hexanes. Compound **15** was obtained as light brown crystals (2.7 g, 99%), mp 112–113 °C; ν_{max}/cm^{-1} 3430, 1265; δ_H 3.84 (3H, s, OCH_3), 6.30 (2H, m, 3,5-H), 7.50 (3H, m, 3′,4′,5′-H), 7.88 (2H, m, 2′,6′-H), 8.21 (1H, d, *J* 8, 6-H), 8.25 (1 H, br s, N–H); δ_C 56.1, 98.8, 107.4, 119.8, 121.8, 127.3, 129.1, 131.8, 135.9, 143.9, 149.9, 165.2.

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