Reactions of some *N*-(2,5-dimethoxyaryl)thiobenzamides: *en route* to an analogue of kuanoniamine A

Yvette A. Jackson,*[a] Michael A. Lyon,[a] Norman Townsend,[a] Kettyna Bellabe[b] and Fernando Soltanik[b]

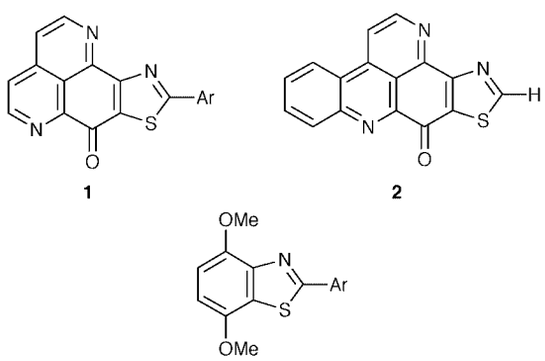
[a] *Department of Chemistry, University of the West Indies, Mona, Kingston 7, Jamaica, West Indies*
[b] *School of Natural and Health Sciences, Barry University, 11300 N.E. 2nd Avenue, Miami Shores, FL 33161-6695, USA*

Received (in Cambridge, UK) 21st September 1999, Accepted 9th November 1999

Nitration of 2-aryl-4,7-dimethoxybenzothiazoles **7a**–**7c** produces a mixture of 5- and 6-nitrobenzothiazoles which were distinguished by synthesis of the 2-aryl-4,7-dimethoxy-6-nitrobenzothiaoles **12a**–**12c** by oxidative cyclization of the corresponding nitrothiobenzanilides. Reaction of *N*-[2,5-dimethoxy-4-(*p*-tolylsulfonylamino)phenyl]thiobenzamide **17d** with base to give 5-methoxy-2-phenyl-6-(*p*-tolylsulfonylamino)benzothiazole **18** with apparent intramolecular replacement of a methoxy group is also described.

Introduction

In our efforts to synthesize analogues **1** of kuanoniamine A **2**,[1] a group of marine alkaloids which show good pharmacobiological activity, we required benzothiazoles of type **3** as starting material.

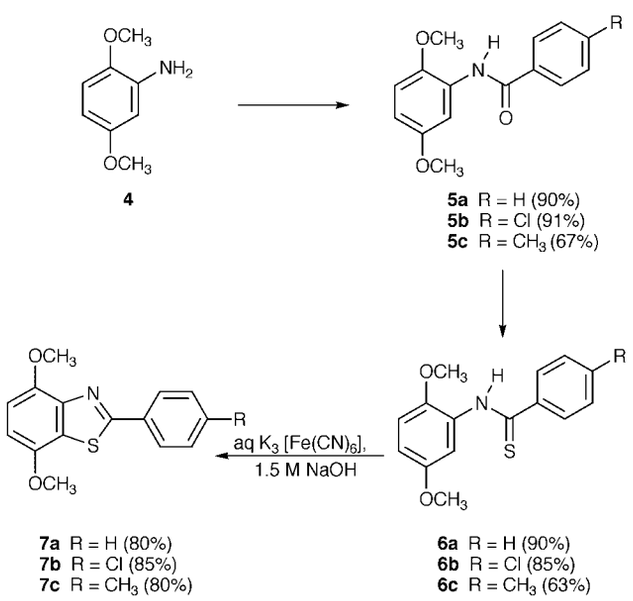


Methods for the preparation of 2-substituted benzothiazoles include reaction of the acid, alkaline or zinc salts of *o*-aminothiophenols with carboxylic acids and their derivatives,[2,3] cyclization of *N*-aryl-thiocarbamates,[4] -thioamides,[4,5] and -thioureas,[6] and base-catalysed intramolecular displacement of the halogen of 2-halogenothioanilides.[5]

The Jacobson method[4] of synthesis of benzothiazoles involves oxidative cyclization of an arylthioanilide on an unsubstituted *ortho*-position, in the presence of potassium ferricyanide in basic medium. We chose this method for synthesis of our dimethoxybenzothiazoles as we could prepare the required arylthioanilides in reasonable yields.

Results and discussion

Treatment of 2,5-dimethoxyaniline **4** with the appropriate aroyl chloride produced the corresponding benzanilides **5a**,[1] **5b** and **5c**, which were then converted to the thiobenzanilides **6a**,[1] **6b** and **6c**, using Lawesson's reagent.[7] The thiobenzanilide was then dissolved in 1.5 M aq. NaOH and treated with potassium ferricyanide [$K_3Fe(CN)_6$] to produce the corresponding dimethoxybenzothiazoles in good yield (Scheme 1).

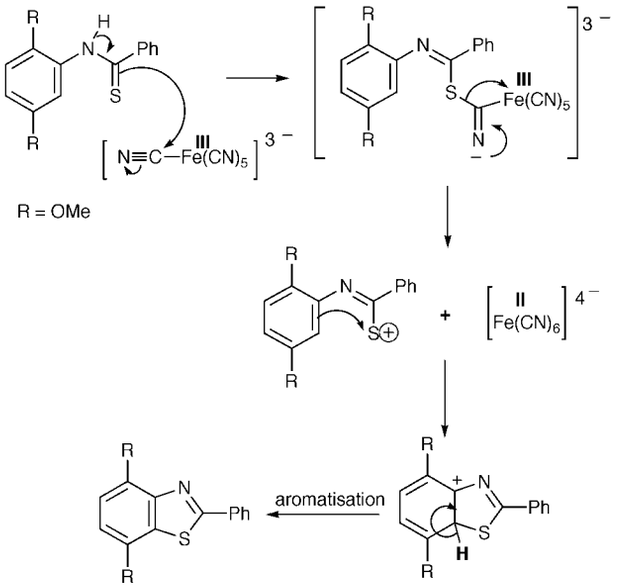


Scheme 1

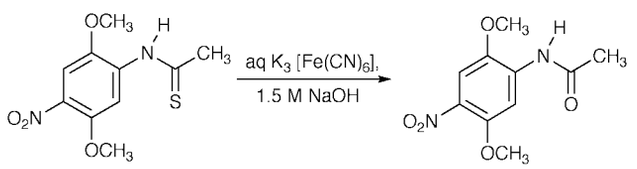
The mechanistic pathway proposed for the Jacobson reaction is shown in Scheme 2.[8] The ease of cyclization of arylthioanilides is influenced by the nature of the ring substituents, and reaction with *p*-nitrothioacetanilide **8** yields 95% desulfurization to *p*-nitroacetanilide **9** by attack of hydroxide on the thiocarbonyl carbon, with subsequent loss of H_2S (Scheme 3).[3c] The *p*-nitro group clearly inhibits the thiol-enolization step (first step) of the Jacobson reaction, and thus ring-closure is affected.

Retrosynthetic analysis shows that our desired compound **1** is available from the corresponding 6-nitrobenzothiazole (Scheme 4). Formation of 6-nitrobenzothiazoles by the Jacobson reaction, however, could prove to be challenging, and we explored nitration of the benzothiazole **7a** using 1.1 molar equivalents of conc. HNO_3 in cold glacial acetic acid (Scheme 5). This produced a 6:5 mixture of two mononitrobenzothiazoles in very good yield, and which were indistinguishable by spectroscopic data.

The literature shows that [(arylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones (*e.g.*, **14**) were regioselectively

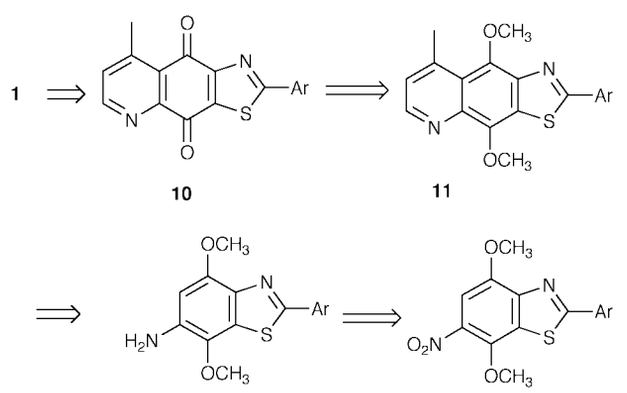


Scheme 2



8 **9** (95%)

Scheme 3

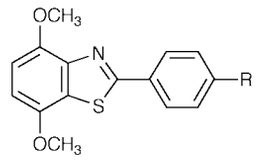


10 **11**

Scheme 4

brominated and nitrated to yield the 4-substituted product, *e.g.* **15a** and **15b**, respectively (Scheme 6).[9] In a previous set of experiments we also noted the bromination of compound **5a** to give *N*-(4-bromo-2,5-dimethoxyphenyl)benzamide as the sole product.[1] We therefore proceeded with nitration of **5a**, and obtained one product, *N*-(2,5-dimethoxy-4-nitrophenyl)benzamide, **16a**, evidenced by the two singlets in the PMR spectrum at δ 7.60 and 8.60 corresponding to H-3 and H-6, respectively. Treatment of **16a** with 0.6 molar equivalents of Lawesson's reagent then produced **17a** in 79% yield (Scheme 7).

Since there are two electron-donating methoxy groups on the thiobenzanilide **17a**, we envisaged that the Jacobson reaction had a better chance at success than with 4′-nitrothiobenzanilide. We therefore proceeded with the cyclization reaction, and obtained the desired 4,7-dimethoxy-6-nitrobenzothiazole **12a** in 24% yield after 7 days. Unchanged starting material (25%), and the corresponding benzanilide (31%) were also recovered from the reaction mixture. Jacobson reaction of compounds **17b** and **17c** also produced the corresponding benzothiazoles **12b** and **12c** after 7–8 days reaction time and



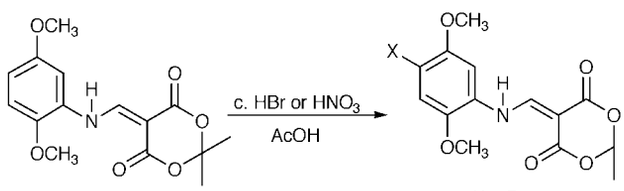
7a R = H
b R = Cl
c R = CH_3

c.HNO_3 or Br_2 in HOAc

12a R = H, R^1 = NO_2
b R = Cl, R^1 = NO_2
c R = CH_3, R^1 = NO_2
d R = H, R^1 = Br
e R = H, R^1 = NH_2

13a R = H, R^1 = NO_2
b R = Cl, R^1 = NO_2
c R = CH_3, R^1 = NO_2
d R = H, R^1 = Br

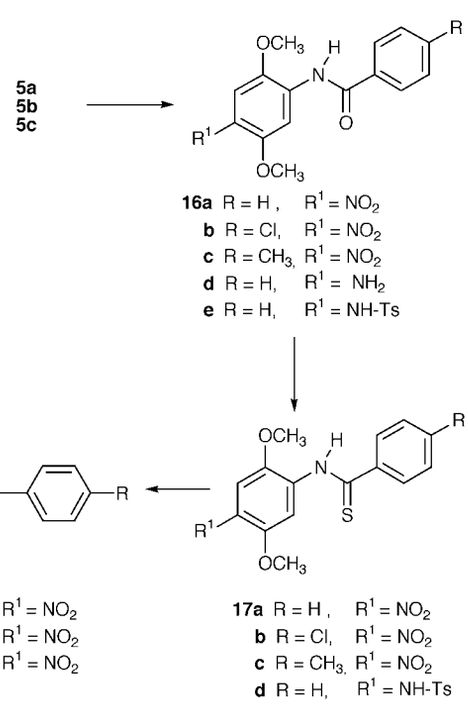
Scheme 5



14

15a X = Br
15b X = NO_2

Scheme 6



16a R = H, R^1 = NO_2
b R = Cl, R^1 = NO_2
c R = CH_3, R^1 = NO_2
d R = H, R^1 = NH_2
e R = H, R^1 = NH-Ts

12a R = H, R^1 = NO_2
b R = Cl, R^1 = NO_2
c R = CH_3, R^1 = NO_2

17a R = H, R^1 = NO_2
b R = Cl, R^1 = NO_2
c R = CH_3, R^1 = NO_2
d R = H, R^1 = NH-Ts

Scheme 7

in 35% and 13% yield respectively. We have thus achieved Jacobson cyclization of nitrothiobenzanilides.

Comparison of **12a** with the products of nitration of the benzothiazole **7a** revealed that, contrary to expectation, the major product of this nitration reaction is the 5-nitroanalogue

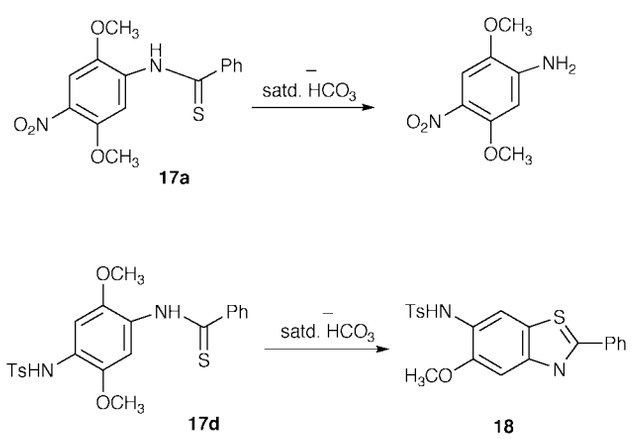
13a. The 6-substituted compound is reported to be the major product of electrophilic aromatic substitution of benzothiazoles,[3b] and, on investigation of mononitration of simple benzothiazoles, the pattern which emerged was 6-NO_2 > 4-/7- > 5-NO_2.[10]

Bromination of **7a** with 1.1 molar equivalents of Br_2 in $CHCl_3$–CCl_4 (1:1) yielded a 9:2 mixture of 6- and 5-bromo-4,7-dimethoxy-2-phenylbenzothiazole **12d** and **13d**, respectively. (Once again the compounds were distinguished by synthesis of the 6-bromo-4,7-dimethoxybenzothiazole *via* the 4-bromobenzanilide.[1])

For the 4,7-dimethoxybenzothiazole **7a** then, bromination proceeds as expected, giving the 6-bromo compound **12d** as the major product, but nitration gives a reversal in yields, with the 5-nitro compound **13a** being the major product. Nitration of compounds **7b** and **7c** produced similar results – a 4:3 and 1.1:1 ratio, respectively, with the 5-nitro analogues **13b** and **13c** being the major product in each case. A look at the 3-dimensional models of the benzothiazole **7a**, the 5- and 6-bromobenzothiazoles **13d** and **12d**, and the 5- and 6-nitrobenzothiazoles **13a** and **12a** indicate that this may be due to steric considerations. The angle made by 7-OMe–C-(7)–C-(7a) in the starting material **7a** is bigger than that made by 4-OMe–C(4)–C(3a). The sulfur atom is larger than the nitrogen atom, causing the 7-methoxy group to be projected toward the 6-position, thus hindering the approach of the incoming larger NO_2^+ (*cf.* Br^+), and resulting in more 5-nitro compound than expected. Comparison of the distance between the substituent and the adjacent methoxy group in these 5- and 6-substituted benzothiazoles (**12a**, **13a**, **12d**, **13d**) showed this distance to be smallest in the 6-nitro compound **12a**.

With the 6-nitrobenzothiazole **12a** in hand, we were able to progress to the desired compound **1** by the pathway referred to in Scheme 4, albeit in low yield. Reduction of **12a** by hydrogen and catalyst produced the amino compound **12e** in 62% yield. The pyridine ring was then formed by Doebner–Miller synthesis[11] using methyl vinyl ketone (11%), and the resultant quinoline **11** was treated with ammonium cerium(IV) nitrate (CAN) to produce quinolinequinone **10** (62%). This compound was identical in all respects to the product of Diels–Alder reaction of 6-bromo-4,7-dioxo-2-phenyl-4,7-dihydrobenzothiazole with crotonaldehyde dimethylhydrazone, and from which we have previously synthesized the desired **1**.[1]

Continuing our studies on reaction of the thioanilides we treated 2,5-dimethoxy-4-nitrothiobenzanilide **17a**, with saturated bicarbonate in refluxing methanol for 24 h and obtained only quantitative conversion to the corresponding amine (Scheme 8).[12] In a similar reaction with the 4-tosylamino-



Scheme 8

thiobenzanilide **17d**, desulfurization to the corresponding benzanilide **16e** was the dominant reaction (60%). We recovered some starting material (25%) and another product which, surprisingly, had only one methoxy group, and had no C=S peak in the ^{13}C NMR spectrum. This product (5%) is 5-methoxy-2-phenyl-6-(tosylamino)benzothiazole **18**. Hydroxide attack at the thiocarbonyl carbon of **17d** generated a nucleophile which attacked the phenyl ring with replacement of a methoxy group. Nucleophilic substitutions on aromatic rings demand the presence of strong deactivating groups. If the tosyl group were acting in that capacity here, then substitution of methoxy by S^- would be expected to occur at position 5. The product of this reaction, however, would be a highly strained 6-membered ring, which is most unlikely to be formed. Substitution then occurred at position 2, resulting in compound **18**. 2-Halogenothioanilides are known to react with base to produce the corresponding benzothiazoles with replacement of halogen.[5] We have, however, encountered no examples of similar intramolecular replacement of methoxy groups.

Experimental

General

All mp are uncorrected. Organic solutions were dried over $MgSO_4$ unless stated otherwise. IR spectra were obtained on a Perkin-Elmer 735B model or a Perkin-Elmer 1600 FT-IR spectrometer and are for KBr discs. NMR spectra (Bruker 200 MHz spectrometer) were determined in $CDCl_3$ solution and the resonances are reported in δ-units downfield from TMS; *J*-Values are given in Hz. Elemental analyses were carried out by MEDAC Ltd., Egham, Surrey, UK.

4′-Chloro-*N*-(2,5-dimethoxyphenyl)benzamide 5b

To a solution of 2,5-dimethoxyaniline **4** (2.0 g, 13.2 mmol) in a mixture of dry toluene (16 mL) and pyridine (12 mL) was added 4-chlorobenzoyl chloride (1.6 mL, 12.26 mmol). The solution was heated on an oil-bath at 80–90 °C for 1 h. The mixture was cooled to room temperature and poured into water (200 mL). The two layers were separated and the aqueous layer extracted with toluene (3 × 20 mL). The combined toluene solutions were washed with 1 M HCl (3 × 10 mL) followed by brine (3 × 10 mL), dried ($MgSO_4$), and the solvent removed *in vacuo*. Recrystallization from MeOH gave **5b** as an off-white solid (3.45 g, 91%), mp 90–93 °C (Found: C, 61.94; H, 4.97; N, 4.68. Calc. for $C_{15}H_{14}ClNO_3$: C, 61.84; H, 4.85; N, 4.81%); ν_{max}/cm^{-1} 3340, 1663; δ_H 3.81 and 3.88 (each 3H, s, OCH_3), 6.62 (1H, dd, *J* 3.4 and 9, 4-H), 6.82 (1H, d, *J* 9, 3-H), 7.46 (2H, d, *J* 9, 2′-, 6′-H), 7.83 (2H, d, *J* 9, 3′-, 5′-H), 8.23 (1H, d, *J* 3.4, 6-H), 8.50 (1H, br s, NH); δ_C 55.71, 56.18, 105.86, 108.86, 110.55, 128.36, 128.41, 128.95, 142.22, 153.76, 164.02.

N-(2,5-Dimethoxyphenyl)-4′-methylbenzamide 5c

To a solution of *p*-toluic acid (3.0 g, 22.06 mmol) in methylene dichloride (30 mL) were added pyridine (5.2 mL, 64.3 mmol) and thionyl dichloride (1.8 mL, 24 mmol) and the mixture stirred at room temperature for 90 min.[13] After this time, pyridine (13 mL) and toluene (10 mL) were added to the mixture, followed by 2,5-dimethoxyaniline **4** (3.0 g, 22.06 mmol), and the whole heated at reflux overnight. The reaction mixture was then concentrated *in vacuo* and the residue was triturated with hexane to give **5c** as a tan-coloured solid (4.0 g, 67%), mp 62–65 °C (from MeOH) (Found: C, 70.64; H, 6.27; N, 5.11. Calc. for $C_{16}H_{17}NO_3$: C, 70.82; H, 6.32; N, 5.16%); ν_{max}/cm^{-1} 3400, 1653; δ_H 2.45 (3H, s, CH_3), 3.80 and 3.88 (each 3H, s, OCH_3), 6.60 (1H, dd, *J* 3.5 and 9, 4-H), 6.83 (1H, d, *J* 9, 3-H), 7.28 (2H, d, *J* 9, 3′-, 5′-H), 7.79 (2H, d, *J* 9, 2′-, 6′-H), 8.28 (1H, d, *J* 3.5, 6-H), 8.58 (1H, br s, NH); δ_C 21.4, 55.69, 56.2, 105.67, 108.59, 110.57, 126.91, 128.41, 129.34, 132.19, 142.21, 142.27, 153.8, 165.10.

Nitration of benzamides 5

To a cold solution of a benzamide (1.0 g) in glacial acetic acid

(10 mL) was added a solution of conc. nitric acid (69%) (1.1 molar equiv.) in glacial acetic acid (5 mL) and the resulting mixture stirred at ambient temperature for 1.5 h. The mixture was then poured into water (50 mL) and the precipitate which formed was collected by filtration and washed throughly with cold water.

***N*-(2,5-Dimethoxy-4-nitrophenyl)benzamide 16a.** Yellow-green crystals (1.05 g, 89%), mp 169–171 °C (from CH_2Cl_2–hexane) (Found: C, 59.39; H, 4.62; N, 9.20. Calc. for $C_{15}H_{14}N_2O_5$: C, 59.58; H, 4.67; N, 9.27%); ν_{max}/cm^{-1} 3415, 1680; δ_H 4.0 and 4.05 (each 3H, s, OCH_3), 7.55 (3H, m, 3′-, 4′-, 5′-H), 7.60 (1H, s, 3-H), 7.91 (2H, m, 2′-, 6′-H), 8.60 (1H, s, 6-H), 8.90 (1H, br s, NH); δ_C 56.60, 56.97, 104.58, 107.46, 127.11, 129.02, 132.58, 134.15, 140.86, 149.81, 165.62.

4′-Chloro-*N*-(2,5-dimethoxy-4-nitrophenyl)benzamide 16b. Yellow solid (854 mg, 81%), mp 188–192 °C (from acetone–MeOH) (Found: C, 53.33; H, 3.89; N, 8.25. Calc. for $C_{15}H_{13}ClN_2O_5$: C, 53.50; H, 3.89; N, 8.32%); ν_{max}/cm^{-1} 3405, 1686, 1594, 1539; δ_H 3.98 and 4.01 (each 3H, s, OCH_3), 7.51 (2H, d, *J* 8, 3′-, 5′-H), 7.60 (1H, s, 3-H), 7.82 (2H, d, *J* 8, 2′-, 6′-H), 8.56 (1H, s, 6-H) and 8.72 (1H, br s, NH); δ_C 56.69, 57.03, 104.69, 107.54, 128.52, 129.35, 132.47, 139.02, 140.77, 149.62, 164.56.

***N*-(2,5-Dimethoxy-4-nitrophenyl)-4′-methylbenzamide 16c.** Pale yellow solid (992 mg, 85%), mp 163–165 °C (from MeOH) (Found: C, 60.72; H, 5.06; N, 8.62. Calc. for $C_{16}H_{16}N_2O_5$: C, 60.74; H, 5.10; N, 8.86%); ν_{max}/cm^{-1} 3400, 1602, 1529; δ_H 2.45 (3H, s, CH_3), 3.98 and 4.02 (each 3H, s, OCH_3), 7.34 (2H, d, *J* 8, 3′-, 5′-H), 7.61 (1H, s, 3-H), 7.80 (2H, d, *J* 8, 2′-, 6′-H), 8.62 (1H, s, 6-H) and 8.77 (1H, br s, NH); δ_C 21.56, 56.61, 57.00, 104.47, 107.49, 127.13, 129.69, 131.24, 134.31, 140.74, 143.33, 149.97, 165.60.

Thionation of benzamides 5b,c, 16a–c

To a solution of the benzamide (1.0 g) in dry toluene (40 mL) was added Lawesson's reagent (0.6 mol. equiv.). The mixture was heated under an atmosphere of nitrogen at 80 °C for 2 h, after which time it was cooled and filtered. The solvent was evaporated *in vacuo* and the thiobenzamide product (yellow crystalline solid) was purified by recrystallization from ethanol or by column chromatography (CH_2Cl_2–hexane 3 : 2).

4′-Chloro-*N*-(2,5-dimethoxyphenyl)thiobenzamide 6b. (0.89 g, 85%), mp 120–123 °C (Found: C, 58.36; H, 4.61; N, 4.46. Calc. for $C_{15}H_{14}ClNO_2S$: C, 58.62; H, 4.60; N, 4.56%); ν_{max}/cm^{-1} 3350, 1605, 1235; δ_H 3.79 and 3.88 (each 3H, s, OCH_3), 6.75 (1H, dd, *J* 3.8 and 9, 4-H), 6.88 (1H, d, *J* 9, 3-H), 7.39 (2H, d, *J* 9, 2′-, 6′-H), 7.79 (2H, d, *J* 9, 3′-, 5′-H), 9.0 (1H, br s, 6-H), 9.68 (1H, br s, NH); δ_C 55.79, 56.31, 106.85, 110.84, 111.36, 127.98, 128.7, 128.97, 137.16, 143.63, 152.97, 193.99.

***N*-(2,5-Dimethoxyphenyl)-4′-methylthiobenzamide 6c.** (670 mg, 63%), mp 115–117 °C (Found: C, 66.97; H, 5.99; N, 4.78. Calc. for $C_{16}H_{17}NO_2S$: C, 66.88; H, 5.97; N, 4.88%); ν_{max}/cm^{-1} 3342, 1534, 1233; δ_H 2.38 (3H, s, CH_3), 3.80 and 3.86 (each 3H, s, OCH_3), 6.72 (1H, dd, *J* 3 and 9, 4-H), 6.87 (1H, d, *J* 9, 3-H), 7.22 (2H, d, *J* 8, 3′-, 5′-H), 7.75 (2H, d, *J* 8, 2′-, 6′-H), 9.08 (1H, br s, 6-H), 9.70 (1H, br s, NH); δ_C 21.39, 55.76, 56.31, 106.96, 110.85, 111.06, 126.61, 127.45, 128.55, 128.68, 141.49, 143.69, 152.96, 195.54.

***N*-(2,5-Dimethoxy-4-nitrophenyl)thiobenzamide 17a.** Reaction time: 12 h (830 mg, 79%), mp 162–164 °C (from CH_2Cl_2–MeOH) (Found: C, 56.64; H, 4.43; N, 8.77. Calc. for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.44; N, 8.81%); ν_{max}/cm^{-1} 3357, 1542, 1223; δ_H 4.0 (6H, s, 2 × OCH_3), 7.49 (3H, m, 3′-, 4′-, 5′-H), 7.60 (1H, s, 3-H), 7.84 (2H, m, 2′-, 6′-H), 9.65 (1H, s, 6-H), 9.92 (1H, br s, NH); δ_C 56.72, 57.16, 105.08, 107.36, 126.58, 128.82, 131.61, 134.44, 141.82, 143.73, 149.0, 197.4.

4′-Chloro-*N*-(2,5-dimethoxy-4-nitrophenyl)thiobenzamide 17b. Reaction time: 12 h (993 mg, 98%), mp 189–191 °C (Found: C, 50.94; H, 3.83; N, 7.64. Calc. for $C_{15}H_{13}ClN_2O_4S$: C, 51.07; H, 3.71; N, 7.94%); ν_{max}/cm^{-1} 3315, 1592, 1543, 1313; δ_H 3.98 and 3.99 (each 3H, s, OCH_3), 7.43 (2H, d, *J* 8, 3′-, 5′-H), 7.62 (1H, s, 3-H), 7.78 (2H, d, *J* 8, 2′-, 6′-H), 9.59 (1H, s, 6-H) and 9.86 (1H, br s, NH); δ_C 56.78, 57.18, 105.16, 107.43, 127.94, 129.08, 134.25, 138.01, 141.81, 141.97, 148.98, 195.69.

***N*-(2,5-Dimethoxy-4-nitrophenyl)-4′-methylthiobenzamide 17c.** Reaction time: 12 h, yellow solid (895 mg, 85%), mp 167–170 °C (Found: C, 57.78; H, 4.98; N, 8.20. Calc. for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43%); ν_{max}/cm^{-1} 3363, 1589, 1524; δ_H 2.41 (3H, s, CH_3), 3.97 (6H, s, 2 × OCH_3), 7.26 (2H, d, *J* 8, 3′-, 5′-H), 7.61 (1H, s, 3-H), 7.75 (2H, d, *J* 8, 2′-, 6′-H), 9.65 (1H, s, 6-H) and 9.89 (1H, br s, NH); δ_C 21.36, 56.74, 57.17, 105.16, 107.37, 126.62, 129.45, 133.33, 134.61, 141.06, 141.83, 142.44, 149.06, 197.20.

Preparation of benzothiazoles 7b,c, 12a–c

The thiobenzamide (2.0 g) was dissolved in 1.5 M aq. sodium hydroxide (150 mL) and the solution cooled in an ice–water-bath. To this was added freshly prepared (20%) aq. potassium ferricyanide (15 mL g^{-1} of thiobenzamide). The mixture was stirred at room temperature for the appropriate time and the benzothiazole was collected by filtration, washed with cold water and recrystallized.

2-(4′-Chlorophenyl)-4,7-dimethoxybenzothiazole 7b. Reaction time: 24 h. White needles (1.7 g, 85%), mp 182–184 °C (from MeOH) (Found: C, 58.64; H, 3.91; N, 4.42. Calc. for $C_{15}H_{12}ClNO_2S$: C, 58.92; H, 3.96; N, 4.58%); ν_{max}/cm^{-1} 1495, 1445, 1267; δ_H 3.92 and 4.05 (each 3H, s, OCH_3), 6.72 (1H, d, *J* 8, 5- or 6-H), 6.82 (1H, d, *J* 8, 6- or 5-H), 7.42 (2H, d, *J* 10, 2′-, 6′-H), 8.06 (2H, d, *J* 10, 3′-, 5′-H); δ_C 56.05, 56.34, 105.51, 107.14, 125.5, 128.8, 129.1, 132.01, 136.62, 141.75, 145.25, 149.04, 166.23.

4,7-Dimethoxy-2-(4′-methylphenyl)benzothiazole 7c. Reaction time: 24 h. White needles (1.60 g, 80%), mp 151–152.5 °C (from CH_2Cl_2–MeOH) (Found: C, 67.37; H, 5.29; N, 4.89. Calc. for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91%); ν_{max}/cm^{-1} 1503, 1495, 1267; δ_H 2.50 (3H, s, CH_3), 4.0 and 4.10 (each 3H, s, OCH_3), 6.69 (1H, d, *J* 8, 5- or 6-H), 6.81 (1H, d, *J* 8, 6- or 5-H), 7.28 (2H, d, *J* 8, 3′-, 5′-H), 8.03 (2H, d, *J* 8, 2′-, 6′-H); δ_C 21.48, 56.01, 56.3, 105.14, 106.97, 127.59, 129.53, 130.85, 141.19, 147.91, 148.06, 167.75.

4,7-Dimethoxy-6-nitro-2-phenylbenzothiazole 12a. Reaction time: 7 days. Bright yellow crystals (470 mg, 24%), mp 186–187 °C (from CH_2Cl_2–MeOH) (Found: C, 56.80; H, 3.82; N, 8.79. Calc. for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.83; N, 8.86%); ν_{max}/cm^{-1} 1518, 1472, 1354; δ_H 4.10 and 4.15 (each 3H, s, OCH_3), 7.53 (4H, m, 5-, 3′-, 4′-, 5′-H), 8.13 (2H, m, 2′-, 6′-H); δ_C 56.60, 61.64, 104.07, 127.93, 129.15, 131.98, 132.59, 143.19, 148.31, 149.16, 172.11.

2-(4′-Chlorophenyl)-4,7-dimethoxy-6-nitrobenzothiazole 12b. Reaction time: 8 days. Bright yellow crystals (691 mg, 35%), mp 229–230.5 °C (from EtOH) (Found: C, 51.17; H, 3.14, N, 7.89. Calc. for $C_{15}H_{11}ClN_2O_4S$: C, 51.36; H, 3.16; N, 7.98%); ν_{max}/cm^{-1} 1579, 1526, 1336; δ_H 4.10 and 4.12 (each 3H, s, OCH_3), 7.46 (2H, d, *J* 8, 3′-, 5′-H), 7.48 (1H, s, 5-H), 8.04 (2H, d, *J* 8, 2′-, 6′-H); δ_C 56.83, 61.89, 104.18, 129.08, 129.46, 131.06, 138.23, 143.13, 148.18, 149.19, 170.60.

4,7-Dimethoxy-2-(4′-methylphenyl)-6-nitrobenzothiazole 12c. Reaction time: 7 days. Pale yellow crystals (260 mg, 13%), mp 223–226 °C (from MeOH) (Found: C, 57.20; H, 4.19; N, 8.28. Calc. for $C_{16}H_{14}N_2O_4S·1/4H_2O$: C, 57.39; H, 4.36; N, 8.36%); ν_{max}/cm^{-1} 1582, 1531, 1481, 1339; δ_H 2.44 (3H, s, CH_3), 4.10 and 4.11 (each 3H, s, OCH_3), 7.31 (2H, d, *J* 8, 3′-, 5′-H), 7.47 (1H, s, 5-H), 8.02 (2H, d, *J* 8, 2′-, 6′-H); δ_C 21.59, 56.78, 61.80, 104.02, 127.87, 129.84, 142.72, 143.21, 148.99.

General method for nitration of benzothiazoles 7

A solution of the benzothiazole (2.0 g) in glacial acetic acid (50 mL) was cooled in an ice–water-bath, with stirring. To this cold solution was added conc. nitric acid (69%) (1.1 mol equiv.) in glacial acetic acid (2.5 mL) and the mixture was stirred at ambient temperature for 1 h. The mixture was then poured into water (300 mL) and the precipitate which formed was collected by filtration, washed with water, and oven-dried (temp. ~80 °C). Column chromatography (dichloromethane–hexane 1.5 : 2) yielded the 5- and 6-nitrobenzothiazoles as yellow crystalline solids.

(i) Reaction with **7a** yielded 4,7-dimethoxy-6-nitro-2-phenylbenzothiazole **12a** (1.01 g, 43%), and 4,7-dimethoxy-5-nitro-2-phenylbenzothiazole **13a** (1.18 g, 51%), mp 162–163 °C (from CH_2Cl_2–MeOH) (Found: C, 56.57; H, 3.87; N, 8.84. Calc. for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.86%); ν_{max}/cm^{-1} 1580, 1529, 1479; δ_H 4.0 and 4.39 (each 3H, s, OCH_3), 7.25 (1H, s, 6-H), 7.53 (3H, m, 3′-, 4′-, 5′-H), 8.12 (2H, m, 2′-, 6′-H); δ_C 56.54, 63.33, 102.02, 127.67, 129.15, 131.69, 132.75, 140.57, 148.45.

(ii) Reaction with **7b** yielded 2-(4′-chlorophenyl)-4,7-dimethoxy-6-nitrobenzothiazole **12b** (740 mg, 32%), and 2-(4′-chlorophenyl)-4,7-dimethoxy-5-nitrobenzothiazole **13b** (1.05 g, 46%), mp 248–249 °C (from MeOH) (Found: C, 51.11; H, 3.13, N, 7.89. Calc. for $C_{15}H_{11}ClN_2O_4S$: C, 51.36; H, 3.16; N, 7.98%); ν_{max}/cm^{-1} 1530, 1338, 1129, 1090; δ_H 4.03 and 4.38 (each 3H, s, OCH_3), 7.27 (1H, s, 6-H), 7.49 (2H, d, *J* 8, 3′-, 5′-H), 8.05 (2H, d, *J* 8, 2′-, 6′-H); δ_C 56.60, 63.37, 101.25, 128.86, 129.47, 130.94, 131.29, 137.89, 148.52.

(iii) Reaction with **7c** yielded 4,7-dimethoxy-2-(4′-methylphenyl)-6-nitrobenzothiazole **12c** (864 mg, 37%), and 4,7-dimethoxy-2-(4′-methylphenyl)-5-nitrobenzothiazole **13c** (932 mg, 40%), mp 172–174 °C (from MeOH) (Found: C, 58.47; H, 4.33; N, 8.48. Calc. for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48%); ν_{max}/cm^{-1} 1581, 1522, 1513, 1356, 1330; δ_H 2.44 (3H, s, CH_3), 4.01 and 4.35 (each 3H, s, OCH_3), 7.27 (3H, m, 6-, 3′-, 5′-H), 7.99 (2H, d, *J* 8, 2′-, 6′-H); δ_C 21.52, 56.44, 63.18, 100.61, 127.51, 129.78, 130.06, 140.50, 142.24, 142.57, 148.20, 148.37.

6-Amino-4,7-dimethoxy-2-phenylbenzothiazole 12e

4,7-Dimethoxy-6-nitro-2-phenylbenzothiazole **12a** (1.68 g, 5.3 mmol) was stirred in methanol (210 mL) containing pH 7 buffer solution (55 mL). To this suspension was added 10% Pd/C (187 mg) with stirring and the mixture was stirred at room temperature under hydrogen gas (15 psi) for 2.5 h. The mixture was then filtered through Celite to remove the catalyst, and the solvent was removed *in vacuo*. The residue was diluted with H_2O (140 mL), extracted with $CHCl_3$ (3 × 70 mL), the extract was dried, and the solvent removed to give **12e** as a green solid (948 mg, 62%), mp 100–102 °C (from MeOH) (Found: C, 63.22; H, 4.98; N, 9.69. Calc. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.79%); ν_{max}/cm^{-1} 3464, 3366, 1611, 1497; δ_H 3.85 and 3.91 (each 3H, s, OCH_3), 6.33 (1H, s, 5-H), 7.39 (3H, m, 3′-, 4′-, 5′-H), 8.04 (2H, m, 2′-, 6′-H); δ_C 55.93, 58.59, 97.88, 126.92, 128.58, 129.89, 132.91, 133.48, 137.54, 150.04, 162.23.

4,9-Dimethoxy-8-methyl-2-phenylthiazolo[4,5-*g*]quinoline 11

6-Amino-4,7-dimethoxy-2-phenylbenzothiazole **12f** (246 mg, 0.86 mmol), $FeCl_3$ (370 mg, 1.38 mmol) and $ZnCl_2$ (50 mg, 0.36 mmol) were stirred in 95% ethanol (20 mL). To this mixture was added ethanolic conc. HCl (25%; 20 mL). The resulting solution was warmed to 60–65 °C and methyl vinyl ketone (1 mL, 12 mmol) was added slowly over 2 h. After this time, the mixture was heated at reflux for a further 5 h and then stirred at room temperature for 10 h. The solvent was removed *in vacuo*, and the residue was basified with 1.5 M aq. NaOH (16 mL). The mixture was extracted exhaustively with ethyl acetate, dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2; CH_2Cl_2) to give **11** as a green solid (32 mg, 11%), mp 167–169 °C (MeOH): ν_{max}/cm^{-1} 1679, 1578, 1433; δ_H 3.01 (3H, s, CH_3), 4.26 and 4.39 (each 3H, s, OCH_3), 7.17 (1H, d, *J* 4, 7-H), 7.54 (3H, m, 3′-, 4′-, 5′-H), 8.20 (2H, m, 2′-, 6′-H) and 8.76 (1H, d, *J* 4, 6-H); δ_C 24.13, 61.43, 62.86, 122.11, 123.03, 127.97, 129.05, 131.49, 133.34, 145.44, 146.14, 149.28.

This compound was then oxidized using CAN to give the known quinone **10**.

8-Methyl-2-phenylthiazolo[4,5-*g*]quinoline-4,9-dione 10

4,9-Dimethoxy-8-methyl-2-phenylthiazolo[4,5-*g*]quinoline **11** (25 mg, 0.08 mmol) was stirred in acetonitrile (2.5 mL) on an ice–water-bath. To this cold solution was added, over 5 min, a cold solution of CAN (82 mg, 0.15 mmol) in 2.5 mL of H_2O. The mixture was then stirred at room temperature for 30 min, diluted with water (5 mL), and the resulting solid was collected by filtration, washed with water, and dried at the pump. The solid was chromatographed (methylene dichloride) to yield **10** as a yellow powder (14 mg, 62%), mp 277 °C (decomp.).[1]

N-(4-Amino-2,5-dimethoxyphenyl)benzamide 16d

To a solution of *N*-(2,5-dimethoxy-4-nitrophenyl)benzamide **16a** (10 g, 33 mmol) in ethanol (200 mL) were added finely divided tin (16 g, 132 mmol) and conc. hydrochloric acid (50 mL). The mixture was heated at reflux for 3 h, cooled to room temperature, poured into water (200 mL) and the pH adjusted to 7 with 10% aq. sodium hydroxide. The resultant cream precipitate was collected by filtration, washed with cold water, and dried in the oven. Recrystallization from CH_2Cl_2–hexane produced **16d** as tan coloured crystals (7.79 g, 89%), mp 167–169 °C (Found: C, 66.11; H, 5.96; N, 10.25. Calc. for $C_{15}H_{16}N_2O_3$: C, 66.15; H, 5.93; N, 10.29%); ν_{max}/cm^{-1} 3436, 3357, 1646; δ_H 3.81 (5H, s, OCH_3 and 4-NH_2), 3.88 (3H, s, OCH_3), 6.38 (1H, s, 3-H), 7.49 (3H, m, 3′-, 4′-, 5′-H), 7.85 (2H, m, 2′-, 6′-H), 8.18 (1H, s, 6-H), 8.83 (1H, br s, NH); δ_C 56.21, 56.31, 99.17, 104.73, 118.8, 128.88, 129.68, 131.43, 132.19, 135.42, 140.76, 142.88, 164.65.

N-[2,5-Dimethoxy-4-(*p*-tolylsulfonylamino)phenyl]benzamide 16e

N-(4-Amino-2,5-dimethoxyphenyl)benzamide **16d** (853 mg, 3.13 mmol) was stirred in dry pyridine (10 mL). To this solution was added toluene-*p*-sulfonyl chloride (84 mg, 4.69 mmol) and the resulting mixture was stirred at room temperature for 24 h. The mixture was poured into water (50 mL), and then extracted with ethyl acetate (3 × 50 mL). The extract was washed successively with 2 M HCl (3 × 50 mL), brine (3 × 50 mL) and water (3 × 50 mL), dried and evaporated. Compound **16e** was obtained as a cream coloured solid (1.2 g, 90%), mp 169–171 °C (from MeOH–hexane) (Found: C, 62.10; H, 5.24; N, 6.58. Calc for $C_{22}H_{22}N_2O_5S$: C, 61.95; H, 5.20; N, 6.57%); ν_{max}/cm^{-1} 3443, 3259, 1668; δ_H 2.40 (3H, s, CH_3), 3.60 and 3.93 (each 3H, s, OCH_3), 6.90 (1H, s, 3-H), 7.20 (3H, m, 3′-, 4′-, 5′-H), 7.53 (4H, m, 2′-, 6′-H and 2″-, 6″-H), 7.76 (2H, m, 3″-, 5″-H), 8.18 (1H, s, 6-H) and 8.53 (1H, br s, NH); δ_C 21.48, 56.16, 56.52, 103.65, 105.74, 120.65, 125.35, 126.90, 127.17, 128.62, 129.32, 131.91, 134.92, 135.95, 142.11, 143.69, 144.18, 165.18.

N-[2,5-Dimethoxy-4-(*p*-tolylsulfonylamino)phenyl]thiobenzamide 17d

The benzamide **16e** (950 mg, 2.23 mmol) was stirred in dry toluene (20 mL). To this solution was added Lawesson's reagent (0.95 g, 2.34 mmol) and the resulting suspension was heated at 80 °C under an atmosphere of nitrogen for 2 h. The suspension was filtered and the filter cake washed with toluene. The combined filtrate was concentrated to afford a green oil. Column chromatography with hexane–chloroform (1.2 : 1) as eluent, and recrystallization from hexane–methanol, produced **17d** as orange crystals (909 mg, 92%), mp 146–148 °C (Found: C, 59.72; H, 5.00; N, 6.30. Calc. for $C_{22}H_{22}N_2O_4S_2$: C, 59.71; H, 5.02; N, 6.33%); ν_{max}/cm^{-1} 3389, 3259, 1524, 1327; δ_H 2.40 (3H, s, *p*-CH_3), 3.63 and 3.90 (each 3H, s, OCH_3), 7.0 (1H, s, 3-H), 7.25 (2H, m, tosyl), 7.43 (3H, m, 3′-, 4′-, 5′-H), 7.64 (2H, m, 2′-, 6′-H), 7.78 (2H, m, tosyl), 9.19 (1H, s, 6-H), 9.70 (1H, br s, NH); δ_C 21.51, 56.38, 56.63, 104.53, 122.94, 125.79, 126.59, 127.13, 128.68, 129.49, 131.06, 135.96, 142.67, 143.66, 143.99, 195.0.

5-Methoxy-2-phenyl-6-(*p*-tolylsulfonylamino)benzothiazole 18

To a saturated aq. solution of potassium bicarbonate (8 mL) was added a suspension of *N*-[2,5-dimethoxy-4-(*p*-tolylsulfonylamino)phenyl]thiobenzamide **17d** (110 mg, 0.25 mmol) in methanol (20 mL) and the mixture refluxed for 24 h. The solvent was removed, and water added (100 mL) to the residue, which was then extracted with chloroform (3 × 50 mL), and the extract dried over sodium sulfate and evaporated. Purification by column chromatography (CH_2Cl_2) yielded unchanged starting material **17d** (38 mg, 35% recovery), the corresponding benzamide **16e** (63 mg, 60%), and compound **18** (5 mg, 5%) as cream crystals, mp 184–186 °C (CH_2Cl_2–MeOH) (Found: C, 61.17; H, 4.41; N, 6.76. Calc. for $C_{21}H_{18}N_2O_3S_2$: C, 61.45; H, 4.42; N, 6.83%); ν_{max}/cm^{-1} 3287, 1465, 1336; δ_H 2.32 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 7.15 (3H, m, 7-H and 2 × tosyl), 7.40 (1H, s, 4-H), 7.45 (3H, m, 3′-, 4′-, 5′-H), 7.65 (2H, m, 2′-, 6′-H), 8.02 (2H, m, tosyl); δ_C 21.46, 55.94, 104.18, 113.18, 124.93, 127.18, 127.35, 129.0, 129.44, 130.85, 133.43, 135.98, 143.86, 149.43, 151.56, 168.66.

References

1 M. A. Lyon, S. Lawrence, D. J. Williams and Y. A. Jackson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 437.
2 C. M. Orlando, J. G. Wirth and D. R. Heath, *J. Org. Chem.*, 1970, **35**, 3147.
3 (*a*) D. L. Boger, *J. Org. Chem.*, 1978, **43**, 2296; (*b*) J. M. Sprague and A. H. Long, in *Heterocyclic Compounds*, ed. R. C. Elderfield, John Wiley & Sons, Inc., New York, 1957, vol. 5, ch. 8; (*c*) R. N. Hurd and G. De La Mater, *Chem. Rev.*, 1961, **61**, 45.
4 P. Jacobson, *Ber. Dtsch. Chem. Ges.*, 1886, **19**, 1067.
5 M. J. Spitulnik, *Synthesis*, 1976, 730.
6 A. Hugershoff, *Ber. Dtsch. Chem. Ges.*, 1903, **36**, 3121.
7 (*a*) I. Thomsen, K. Clausen, S. Scheibye and S. O. Lawesson, *Org. Synth.*, 1984, **62**, 158: (*b*) M. P. Cava and M. I. Levinson, *Tetrahedron*, 1985, **41**, 5061.
8 J. Metzger and H. Planck, *Chim. Ind.* (*Paris*), 1956, **75**, 930.
9 E. Gómez-Bengoa and A. M. Echavarren, *J. Org. Chem.*, 1991, **56**, 3497.
10 E. R. Ward and W. H. Poesche, *J. Chem. Soc.*, 1961, 2825.
11 J. Jones in *Quinolines*, ed. G. Jones, Wiley-Interscience, London, 1997, p. 1.
12 G. Heller and T. Hemmer, *J. Prakt. Chem.*, 1931, **129**, 207.
13 F. Matsuda, M. Yanagiya and T. Matsumoto, *Tetrahedron Lett.*, 1982, **23**, 4043.

Paper a907633f