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SYNTHESIS OF SOME NOVEL BENZOBISTHIAZOLES

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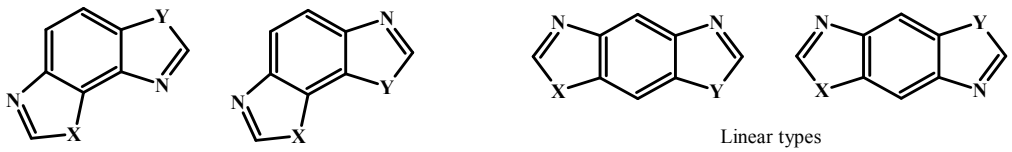
Abstract – The synthesis of angular and linear benzobisthiazoles *via* reaction of *o*-methoxythiobenzanilides with AIBN and basic ferricyanide is described.

INTRODUCTION

The potent and selective antitumour activity of 2-arylbenzothiazoles has been well established.[1] Although benzobisthiazoles have been less researched, a few reports have indicated that these compounds demonstrate potent anti-inflammatory, antibacterial, antifungal and antiprotozoal activity.[2-4] In general, linear benzobisthiazoles (type **B**) have been found to display higher biological activity than their angular counterparts (type **A**).[2, 3] We therefore sought to synthesize benzobisthiazoles in order to evaluate their biological activity.

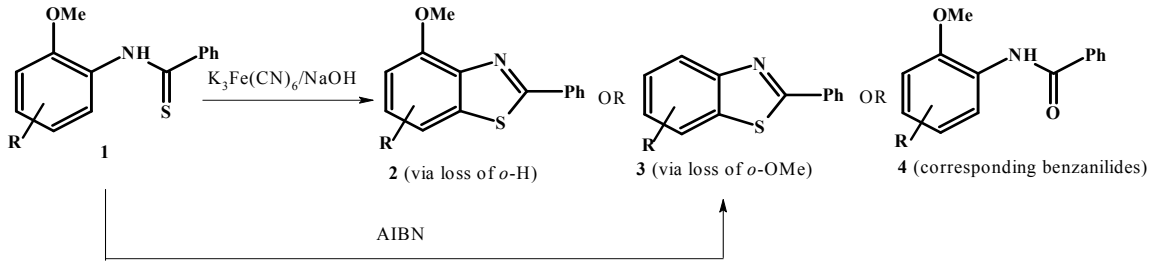


A: Angular Benzobisthiazoles: X = Y = S

B: Linear Benzobisthiazoles: X = Y = S

Figure 1. Examples of structural types

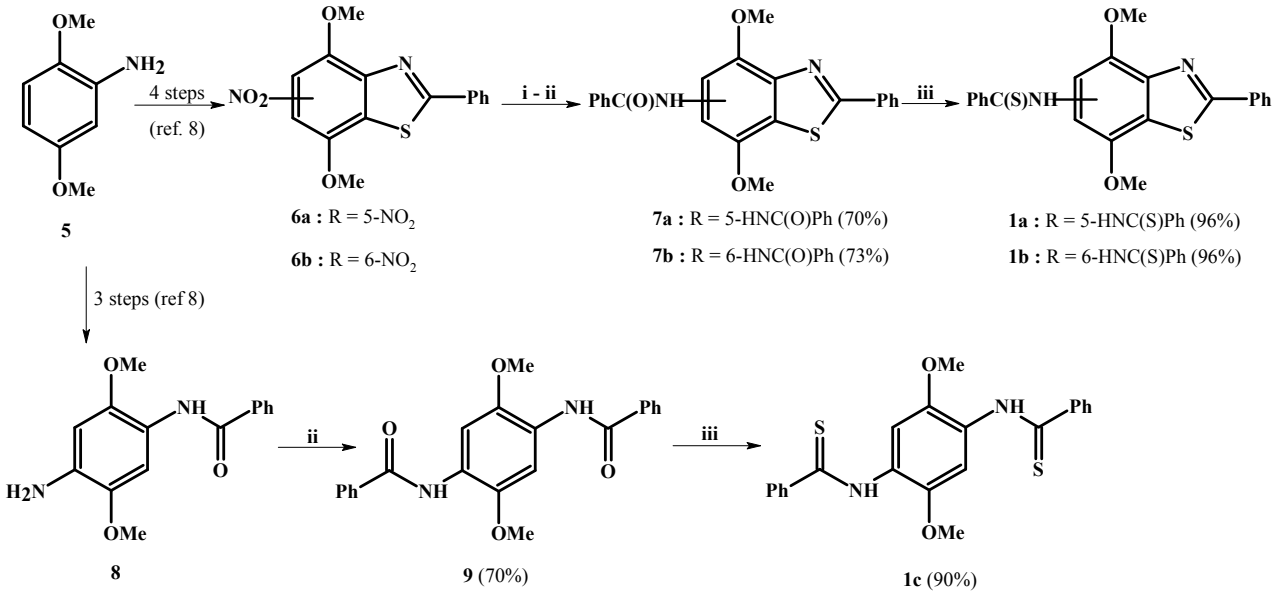
Benzobisthiazoles have previously been synthesized by oxidative cyclization of phenyldithiourea[5] or condensation of *p*-phenylenediaminedithiols with substituted nitriles, aldehydes or carboxylic acids.[6] In addition, we have demonstrated that a common *ortho*-methoxythiobenzanilide may serve as a precursor to either of two benzothiazoles depending on the conditions used (Scheme 1).[7] Subjecting *o*-methoxythiobenzanilides to radical conditions may yield benzothiazoles with loss of the *ortho* methoxy group unlike the more traditional methods such as the Jacobson synthesis (potassium ferricyanide and base), which commonly yield benzothiazole from loss of the *ortho* hydrogen. In this paper, we report the extension of our previous work to effect synthesis of both angular and linear benzobisthiazoles.



Scheme 1

RESULTS AND DISCUSSION

Compounds **1a-c** were chosen as substrates and were obtained from commercially available 2,5-dimethoxyaniline *via* the corresponding benzanilides as shown in Scheme 2. 4,7-Dimethoxy-5-nitro-2-phenylbenzothiazole (**6a**) and 4,7-dimethoxy-6-nitro-2-phenylbenzothiazole (**6b**) were synthesized from 2,5-dimethoxyaniline (**5**) in four steps with an overall yield of 50%.[8]



Scheme 2. Reagents and conditions: (i) 10% Pd/C, MeOH, H_2 atm; (ii) PhCOCl, toluene, pyridine, reflux (iii) Lawesson's reagent, toluene, N_2, reflux.

Palladium catalyzed reduction of nitrophenylbenzothiazoles **6a** and **6b** in the presence of hydrogen gave the corresponding aminophenylbenzothiazoles in almost quantitative yield. Upon treatment of aminophenylbenzothiazoles with benzoyl chloride in pyridine followed by thionation of the resulting benzanilides, thiobenzanilides **1a** and **1b** were obtained in 65% and 70% respectively over the 3 steps. 2,5-Dimethoxy-1,4-dithiobenzanilide **1c** was also synthesized as shown in Scheme 2. 6-Amino-4,7-

dimethoxybenzanilide **8** was obtained from compound **5** in three steps.[8] Treatment of compound **8** with benzoyl chloride in pyridine followed by thionation of the resulting dibenzanilide **9** with Lawesson's reagent furnished dithiobenzanilide **1c**.

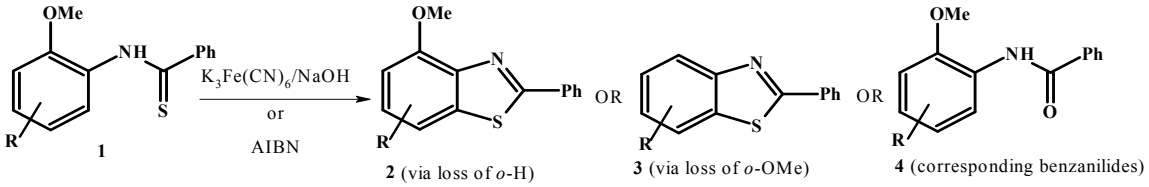
The Jacobson reaction is known to induce cyclization of thiobenzamides with loss of the *ortho* hydrogen.[9] We have reported, however, that under these conditions (potassium ferricyanide and base), cyclization of highly activated *o*-methoxythiobenzanilides may proceed with loss of the *ortho* methoxy group.[7] Subjecting compound **1a** to Jacobson conditions yielded no linear benzobisthiazole from loss of the *ortho* hydrogen, and **1b** yielded only minor amounts of the corresponding **2b** (Table 1). Not surprisingly, benzobisthiazoles **3a** and **3b**, formed by loss of the *ortho* methoxy group, were the dominant products. As was expected too,[7] the reaction of 2-methoxythiobenzanilides **1a** and **1b** with 2,2′-azobisisobutyronitrile (AIBN), proceeded with loss of methoxy radical to give benzobisthiazoles **3a** and **3b** as the only products.

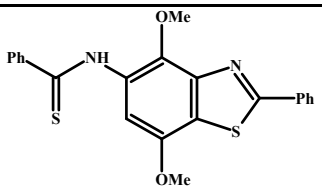
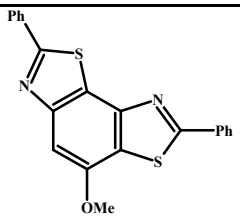
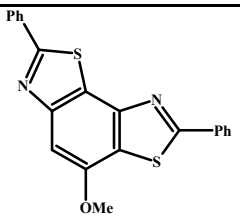
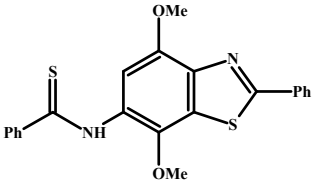
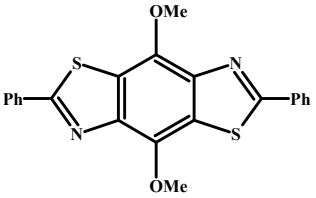
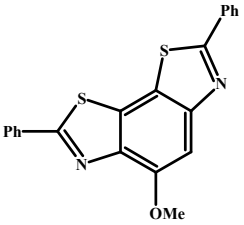
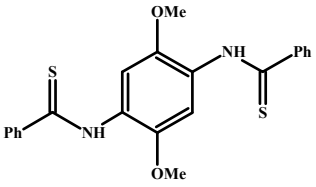
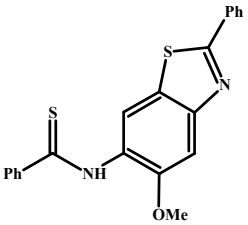
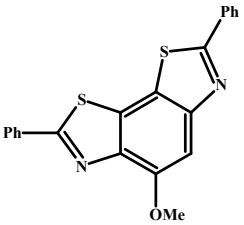
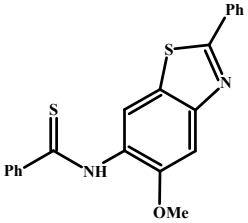
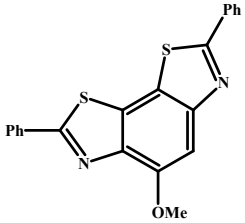
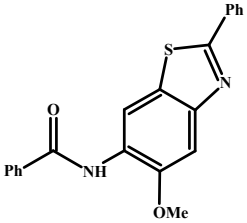
Under these (Jacobson and AIBN) conditions, however, thiobenzanilide **1c** did not produce linear benzobisthiazole **3c** by double *ipso* substitution of the methoxy groups. Under both sets of reaction conditions, benzobisthiazole **3b** was obtained showing cyclization with loss of *ortho* methoxy group at one thiobenzanilide moiety and loss of *ortho* hydrogen at the other. Compound **1d**, the product of cyclization with loss of one methoxy group, was also isolated from these reactions (Table 2, entry 3).

Treatment of thiobenzanilide **1d** with AIBN or basic $K_3Fe(CN)_6$ resulted in cyclization with loss of the *ortho* hydrogen yielding **3b** in 45% and 35% respectively, and indicating that **1d** was an intermediate in the conversion of **1c** to **3b**. Complete conversion of **1c** to **3b** was not observed even with extended reaction time or addition of excess reagents.

We have thus successfully synthesized the novel benzobisthiazoles **2b**, **3a**, and **3b**.We will continue work in this area to gain a better understanding of the factors which give rise to the selectivity in the cyclization reaction. Initial screening of these compounds against common bacterial pathogens such as *B. subtilis*, *P. aeruginosa*, *E. coli*, and *S. aureus* indicated no antibacterial activity.

Table 1. Cyclization of thiobenzanilides 1a-c using the basic ferricyanide and AIBN



Entry	Thiobenzanilides	Basic ferricyanide	$AIBN/PhNO_2$
1	 **1a**	 **3a** (73%)	 **3a** (86%)
2	 **1b**	 **2b** (10%) **3b** (64%)	 **3b** (74%)
3	 **1c**	 **1d** (23%) **4d** (23%) **3b** (15%)	 **3b** (25%) **1d** (23%) **S.M.** (43%)
4	 **1d**	 **3b** (35%) **4d** (27%)	 **4d** (5%) **3b** (45%) **S.M.** (12%)

EXPERIMENTAL

1. General

IR spectra were obtained on a Perkin-Elmer 735B FT-IR spectrometer as KBr discs. NMR spectra (Bruker 200 and 500 MHz) were obtained in $CDCl_3$ solution and the resonances are reported in δ units downfield from TMS as an internal standard; *J* values are given in Hz. The ^{1}H NMR spectroscopic data for all known compounds were identical to that reported in the literature. Column chromatography was carried out using silica gel as the adsorbent. All elemental analyses were done by MEDAC Ltd, Egham, Surrey, UK.

1.1. General procedure for the benzoylation of anilines

To a solution of an aniline (6.0 g) in dry toluene (35 mL) and pyridine (25 mL), benzoyl chloride (1.2 molar equiv.) was added. The solution was heated at reflux for 2 - 6 h, cooled to room temperature and poured into water (200 mL). The two layers were separated and the aqueous layer extracted with EtOAc (3 x 25 mL). The organic fractions were combined, washed with 1M HCl (3 x 25 mL) followed by saturated aqueous sodium hydrogen carbonate (3 x 25 mL) and then dried over magnesium sulfate. The solution was filtered and the solvent removed in vacuo to yield the corresponding benzanilide, which was recrystallized from MeOH or CH_2Cl_2 –hexanes.

1.1.1. *N*-(2-Phenyl-4,7-dimethoxybenzothiazol-5-yl)benzamide (7a).

Off-white crystals (70%); mp 185-186 °C (MeOH); Anal. Calcd for $C_{22}H_{18}N_2O_3S$: C, 67.67; H, 4.65; N, 7.17%. Found: C, 67.97; H, 4.72; N, 7.23%; IR ν_{max}/cm^{-1} 3437, 2818, 1684, 1525; ^{1}H NMR 3.95 (3H, s, OCH_3), 4.36 (3H, s, OCH_3), 7.53 (6H, m, H-3′,4′,5′ and H-3″,4″,5″), 7.91 (2H, d, *J* = 7 Hz, H-2′, 6′), 8.12 (2H, d, *J* = 3 Hz, H-2″, 6″), 8.36 (1H, s, H-6), 8.87 (1H, s, N-H); ^{13}C NMR δ 56.0, 56.6, 99.1, 99.3, 119.9, 127.5, 128.0, 128.9, 129.0, 131.0, 132.0, 133.6, 135.1, 136.2, 146.3, 149.2, 165.4, 168.1.

1.1.2. *N*-(2-Phenyl-4,7-dimethoxybenzothiazol-6-yl)benzamide (7b).

Green finely divided crystals (73%); mp 153-155 °C (MeOH); Anal. Calcd for $C_{22}H_{18}N_2O_3S$: C, 67.67; H, 4.65; N, 7.17%. Found: C, 67.48; H, 4.63; N, 7.36%; IR ν_{max}/cm^{-1} 3419, 2820, 1671, 1522; ^{1}H NMR 4.07 (3H, s, OCH_3), 4.18 (3H, s, OCH_3), 7.53 (6H, m, H-3′,4′,5′ and H-3″,4″,5″), 7.91 (2H, dd, *J* = 8, 2 Hz, H-2′, 6′), 8.12 (2H, m, H-2″, 6″), 8.32 (1H, s, H-6), 8.67 (1H, s, N-H); ^{13}C NMR δ 56.5, 59.9, 100.9, 127.0, 127.3, 127.6, 128.7, 128.9, 129.0, 130.8, 132.1, 133.2, 134.8, 135.9, 141.4, 150.0, 165.4, 165.5.

1.1.3. *N,N′*-[2,5-Dimethoxylphenyl]-1,4-dibenzamide (9).

Light brown needles (70%); mp 218-220 °C (MeOH); Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N,

7.44%. Found: C, 70.60; H, 5.56; N, 7.63%; IR ν_{max}/cm^{-1} 3326, 2824, 1660, 1540; ^1H NMR 3.95 (6H, s, 2 x OCH_3), 7.51 (6H, m, H-3′,4′,5′ and H-3″,4″,5″), 7.89 (4H, d, *J* = 8 Hz, H-2′, 6′ and H-2″, 6″), 8.43 (2H, s, H-3, 6), 8.63 (2H, s, 2 x N-H); ^{13}C NMR δ 56.5, 103.2, 123.4, 127.0, 128.9, 131.8, 135.1, 141.9, 165.1.

1.2. General procedure for the thionation of benzanilides

To a solution of the benzanilide (1.0 g) in dry toluene (40 mL) was added Lawesson's reagent (0.6 molar equiv.). The mixture was heated at reflux under an atmosphere of nitrogen for 2-6 h, after which it was concentrated and purified by column chromatography or recrystallized from MeOH or EtOAc-hexanes to give finely divided yellow crystals.

1.2.1. *N*-(2-Phenyl-4,7-dimethoxybenzothiazol-5-yl)thiobenzamide (1a).

(96% from **7a**); mp. 160-161 °C (MeOH); Anal. Calcd for $C_{22}H_{18}N_2O_2S_2$: C, 65.00; H, 4.46; N, 6.89%. Found: C, 65.17; H, 4.43, N, 6.78%; IR ν_{max}/cm^{-1} 3361, 2927, 1607, 1522, 1362; ^1H NMR 4.02 (3H, s, OCH_3), 4.36 (3H, s, OCH_3), 7.45 (6H, m, H-3′,4′,5′ and H-3″,4″,5″), 7.91 (2H, d, *J* = 8 Hz, H-2′, 6′), 8.15 (2H, m, H-2″, 6″), 8.96 (1H, s, H-6), 9.96 (1H, s, N-H); ^{13}C NMR δ 55.5, 62.6, 100.3, 122.4, 126.8, 127.6, 128.8, 129.1, 129.7, 129.9, 131.2, 133.4, 138.4, 144.0, 146.2, 148.3, 168.2, 196.2.

1.2.2. *N*-(2-Phenyl-4,7-dimethoxybenzothiazol-6-yl)thiobenzamide (1b).

(96% from **7b**); mp. 165-167 °C (MeOH); Anal. Calcd for $C_{22}H_{18}N_2O_2S_2$: C, 65.00; H, 4.46; N, 6.89%. Found: C, 65.13; H, 4.49; N, 7.13%; IR ν_{max}/cm^{-1} 3369, 3005, 1592, 1341; ^1H NMR 4.03 (3H, s, OCH_3), 4.16 (3H, s, OCH_3), 7.51 (6H, m, H-3′,4′,5′ and H-3″,4″,5″), 7.89 (2H, s, H-2′, 6'), 8.15 (2H, m, H-2″, 6″), 8.86 (1H, s, H-5), 9.71 (1H, s, N-H); ^{13}C NMR δ 55.5, 62.6, 100.3, 122.4, 126.8, 127.6, 128.8, 129.7, 129.9, 131.2, 131.2, 133.4, 138.4, 144.0, 146.2, 148.3, 168.2, 196.2.

1.2.3. *N,N′*-(2,5-Dimethoxyphenyl)-1,4-dithiobenzamide (1c).

(90% from **9**); mp. 223-225 °C (MeOH); Anal. Calcd for $C_{22}H_{20}N_2O_2S_2$: C, 64.68; H, 4.93; N, 6.86%. Found: C, 64.82; H, 4.97; N, 7.00%; IR ν_{max}/cm^{-1} 3327, 2994, 1538, 1357; ^1H NMR 3.95 (6H, s, 2 x OCH_3), 7.45 (6H, m, H-3′,4′,5′ and H-3″,4″,5″), 7.86 (4H, d, *J* = 8 Hz, H-2′, 6′ and H-2″, 6″), 9.43 (2H, s, H-3, 6), 9.87 (2H, s, 2 x N-H); ^{13}C NMR δ 56.8, 103.8, 126.1, 126.7, 128.8, 131.2, 142.6, 144.2, 195.0.

1.3. General procedure for the Jacobson Synthesis

To the thiobenzanilide (0.4 g) in EtOH (0.5 mL) was added 30% aqueous NaOH solution (8 molar equiv.). The mixture was diluted with water to provide a final solution / suspension in 10% aqueous NaOH.

Aliquots (0.5 mL) of this mixture were added at 1 minute intervals to a stirred solution of $K_3Fe(CN)_6$ (4 molar equiv.) in water at 90 °C. The reaction mixture was then heated at reflux for a further 2 h and allowed to cool to room temperature. The product was collected by filtration, washed with water and recrystallized from MeOH or CH_2Cl_2-hexanes to give the corresponding benzothiazoles. Column chromatography was done when necessary using CH_2Cl_2: hexanes – 3:1 as eluent.

1.3.1. 5-Methoxy-2,7-diphenylbenzo[1,2-*d*; 3,4-*d*]bisthiazole (3a).

Off-white crystals (73% from **1a**); mp. 235-236 °C (MeOH); Anal. Calcd for $C_{21}H_{14}N_2OS_2$: C, 67.35; H, 3.77; N, 7.48%. Found: C, 67.54; H, 3.93; N, 7.43%; IR ν_{max}/cm^{-1} 3006, 1556, 1329; ^{1}H NMR 4.03 (3H, s, OCH_3), 7.51 (7H, m, H-6, H-3′,4′,5′ and H-3″,4″,5″), 8.15 (4H, m, H-2′, 6′ and H-2″, 6″); ^{13}C NMR δ 56.3, 100.2, 121.2, 122.6, 127.3, 127.5, 129.1, 130.8, 131.2, 133.5, 133.8, 147.8, 153.6, 154.6, 168.3, 170.1.

1.3.2. 4-Methoxy-2,7-diphenylbenzo[1,2-*d*; 4,3-*d*]bisthiazole (3b).

Yellow-green needles (64% from **1b** and 15% from **1c**); mp. 225-227 °C (EtOH); Anal. Calcd for $C_{21}H_{14}N_2OS_2$: C, 67.35; H, 3.77; N, 7.48%. Found: C, 67.32; H, 4.05; N, 7.30%; IR ν_{max}/cm^{-1} 3000, 1554, 1346; ^{1}H NMR 4.16 (3H, s, OCH_3), 7.48 (m, 6H, H-3′,4′,5′ and H-3″,4″,5″), 7.57 (1H, s, H-5), 8.14 (4H, m, H-2′, 6′ and H-2″, 6″); ^{13}C NMR δ 56.4, 101.8, 119.3, 127.3, 127.6, 129.0, 129.1, 131.0, 133.2, 133.4, 143.6, 153.0, 153.1, 166.4, 167.8.

1.3.3. 4,8-Dimethoxy-2,6-diphenylbenzo[1,2-*d*; 4,5-*d*]bisthiazole (2b).

Yellow crystals (10% from **1b**) mp. 274-276 °C (MeOH); Anal. Calcd for $C_{22}H_{16}N_2O_2S_2 \cdot ½H_2O$: C, 63.92; H, 4.12; N, 6.78%. Found: C, 64.24; H, 3.93; N, 6.73%. IR ν_{max}/cm^{-1} 2820, 1481, 1349, 1261; ^{1}H NMR 4.51 (6H, s, OCH_3), 7.51 (6H, m, H-3′,4′,5′ and H-3″,4″,5″), 8.14 (4H, dd, J = 7, 3 Hz, H-2′, 6′ and H-2″, 6″); ^{13}C NMR δ 61.7, 126.7, 127.6, 129.0, 130.1, 133.7, 142.4, 142.9, 166.9.

1.3.4. *N*-(5-Methoxy-2-phenylbenzothiazol-6-yl)thiobenzamide (1d)

Yellow needles (23% from **1c**); mp. 137-140 °C (EtOH); Anal. Calcd for $C_{21}H_{16}N_2OS_2$: C, 66.99; H, 4.28; N, 7.44%. Found: C, 67.27; H, 4.01; N, 7.41%; IR ν_{max}/cm^{-1} 3350, 2944, 1573, 1510; ^{1}H NMR 4.04 (3H, s, OCH_3), 7.50 (7H, m, H-4, H-3′4′,5′ and H-3″,4″,5″), 7.88 (2H, dd, J = 8, 2 Hz, H-2′, 6′), 8.07 (2H, m, H-2″, 6″), 9.93 (1H, s, H-7), 10.06 (1H, s, N-H); ^{13}C NMR δ 56.4, 103.8, 112.6, 115.4, 126.7, 127.3, 127.7, 128.8, 129.1, 130.9, 131.1, 133.6, 144.1, 149.4, 151.8, 169.5, 195.6.

1.3.5. *N*-(5-Methoxy-2-phenylbenzothiazol-6-yl)benzamide (4d)

Finely divided yellow crystals (23% from **1c**); mp. 182-184 ^{o}C (MeOH); Anal. Calcd for $C_{21}H_{16}N_2O_2S$: C, 69.98; H, 4.47; N, 7.77%. Found: C, 69.77; H, 4.38; N, 7.69; IR ν_{max}/cm^{-1} 3452, 2949, 2848, 1668, 1571; ^{1}H NMR 4.04 (3H, s, OCH_3), 7.50 (7H, m, H-4, H-3′,4′,5′ and H-3″,4″,5″), 7.88 (2H, dd, *J* = 8, 2 Hz, H-2′, 6′), 8.07 (2H, m, H-2″, 6″), 8.76 (1H, s, H-7), 9.22 (1H, s, N-H); ^{13}C NMR δ 56.3, 103.6, 111.3, 126.7, 127.0, 127.2, 127.7, 128.8, 129.0, 130.7, 131.9, 133.7, 135.0, 148.3, 150.3, 165.3, 168.2.

1.4. General procedure for the AIBN-induced Cyclizaton of thiobenzanilides

To a solution of the thiobenzanilide (0.1 g) in nitrobenzene (5 mL) was added AIBN (1.2 molar equiv.) and the mixture stirred at reflux for 30 min. The crude product was eluted through a silica column, first with hexanes to remove the nitrobenzene followed by EtOAc. The EtOAc fraction was concentrated and recrystallized from EtOAc-hexanes or EtOH.

1.4.1. 8-Methoxy-2,7-diphenylbenzo[2,3-d: 4,5-d]bisthiazole (3a).

Off-white crystals (86% from **1a**).

1.4.2. 4-Methoxy-2,7-diphenylbenzo[2,3-d: 4,5-d]bisthiazole (3b).

Yellow-green needles (74 % from **1b**, 25% from **1c**; and 45% from **1d**).

1.4.3. 5-Methoxy-6-thiobenzamidobenzothiazole (1d)

Yellow needles (23% from **1c**).

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