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A General and Efficient Synthesis of 2-Phenylbenzothiazoles From Diphenyl Disulfides

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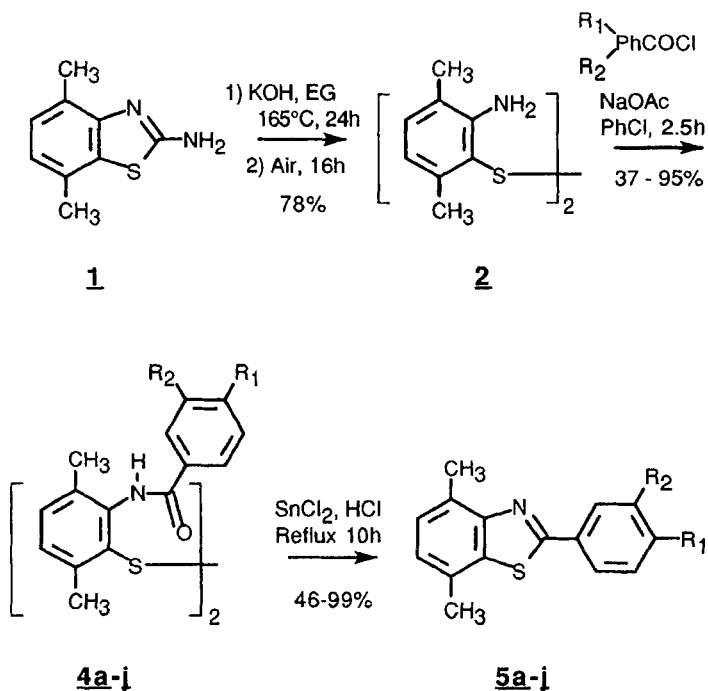
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Abstract Benzothiazoles containing a substituted-phenyl at the 2 position can be synthesized cleanly and efficiently from the corresponding bis(2-aminophenyl) disulfide. Bis(2-aminophenyl) disulfides represent a stable source of 2-aminobenzenethiols.

Ortho-aminobenzenethiols are an important class of starting materials for the synthesis of heterocyclic systems such as phenothiazines and benzothiazines¹ as well as polybenzothiazoles² and their corresponding benzothiazole model compounds. The synthesis of ortho-aminobenzenethiol derivatives^{3, 4, 5} is complicated by the fact that the thiols are easily oxidized to the corresponding disulfides. Immediate use or storage in a stable form such as the hydrochloride or zinc thiolate is generally required. As part of our program to generate substituted polybenzothiazoles,⁶ we have prepared a series of 2-(substituted-phenyl)-4,7-dimethylbenzothiazoles using bis(2-amino-3,6-dimethyl-phenyl) disulfide (2) as a precursor.⁷ It is not anticipated that the methyl substituents,

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necessary in our case for subsequent monomer formation, present a significant electronic or steric influence relative to the unsubstituted system.



| Cmpd | R ₁ | R ₂ | Cmpd | R ₁ | R ₂ |
|--------|-----------------|-----------------|--------|----------------------------------|------------------|
| 4a, 5a | H | H | 4f, 5f | Cl | H |
| 4b, 5b | H | CH ₃ | 4g, 5g | H | OCH ₃ |
| 4c, 5c | CH ₃ | H | 4h, 5h | OCH ₃ | H |
| 4d, 5d | Br | H | 4i, 5i | N(CH ₃) ₂ | H |
| 4e, 5e | H | Cl | 4j, 5j | NO ₂ | H |

The preparation of 2-amino-4,7-dimethylbenzothiazole (**1**) from N-(2,5-dimethylphenyl)thiourea was carried out in thionyl chloride.⁸ Hydrolytic cleavage of 2-amino-4,7-dimethylbenzothiazole (**1**) with potassium hydroxide in ethylene glycol, followed by oxidation of the

potassium salt with air provided bis(2-amino-3,6-dimethylphenyl) disulfide (**2**) in 78% yield

The reaction of (**2**) with a series of substituted benzoyl chlorides **3a-j** yielded the corresponding bisamide disulfides **4a-j** in good yields and high purity. The dimethylamino derivative **4j** was prepared by a modified procedure in which pyridine was used as base and solvent. The bisamides were characterized by infrared absorptions indicative of N-H ($3291\text{--}3227\text{ cm}^{-1}$) and amide C=O ($1659\text{--}1645\text{ cm}^{-1}$) and by the ^1H and ^{13}C NMR absorptions listed in Table 1.

Reduction of bisamides **4a-j** with stannous chloride in ethanol in the presence of small amount of water provided the corresponding 2-phenylbenzothiazoles **5a-j**. Reduction of **4j** with stannous chloride was unsuccessful in that the major product was 2-(4-aminophenyl)-4,7-dimethylbenzothiazole. An 8% yield of 2-(4-nitrophenyl)benzothiazole (**5j**) was isolated. The benzothiazoles were characterized by the ^1H and ^{13}C NMR absorptions listed in Table 2.

Experimental: Starting materials were purchased from Aldrich Chemical Company and used without further purification. Melting points were obtained on an Electrothermal capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained by using a Varian EM-360-A spectrometer (^1H) and IBM AF-100 spectrometer (^1H and ^{13}C). All samples were run in deuterated chloroform or deuterated dimethyl sulfoxide (DMSO-d_6) at approximately 10% w/v concentration using tetramethylsilane as an internal standard. Infrared spectra were recorded with a Nicolet 5-DX FTIR spectrometer using KBr discs. Mass spectra were obtained from Finnigan MAT INCOS

Table 1. Physical and Spectral Properties of Bisamides 4a-j

| Cmp | Yield % | Mp (°C) | ¹ H NMR δ ^a | | | ¹³ C NMR ppm | | | |
|-----------|---------|---------|-----------------------------------|------|--------------|-------------------------|---|--|----------------|
| | | | Ar / Ar' | N-H | Me-3/6 | C-2 | Ar-C | Ar-CH | Me-3/6 |
| 4a | 76 | 217-8.5 | 6.95 7.45 | 7.91 | 2.17 2.40 | 165.81 | 141.49, 137.86, 134.56, 133.64, 133.35 | 132.14, 131.54, 129.33, 128.28, 127.18 | 18.86 21.58 |
| 4b | 59 | 188-9 | 7.05 7.33 | 9.42 | 2.17 2.32 | 165.45 | 140.37, 138.45, 137.34, 134.45, 134.31, 133.80 | 131.62, 131.44, 128.80, 127.95, 127.67, 124.20 | 20.87 21.25 |
| 4c | 64 | 227-8 | 6.98 7.27 | 7.88 | 2.17 2.40 | 165.70 | 141.78, 141.28, 137.98, 134.42, 133.24, 130.76 | 131.92, 129.06, 128.78, 127.13, | 18.75 21.42 |
| 4d | 62 | 257-8 | 7.12 7.60 | 9.63 | 2.18 2.32 | 164.43 | 140.45, 138.18, 134.35, 132.91, 125.09 | 131.52, 131.13, 129.19, 128.99 | 18.09 21.16 |
| 4e | 73 | 208-9 | 7.11 7.61 | 9.68 | 2.18 2.33 | 163.99 | 140.43, 137.93, 135.68, 134.30, 133.09 | 131.61, 131.21, 130.15, 129.02, 126.91, 125.77 | 18.10 21.16 |
| 4f | 95 | 265 | 7.12 7.53 | 9.67 | 2.17 2.40 | 164.29 | 140.46, 138.18, 137.69, 136.20, 134.37, 132.51 | 131.52, 131.04, 128.89, 128.67 | 18.09 21.16 |
| 4g | 74 | 194 | 6.93 7.19 | 7.82 | 2.18 2.42 | 165.60 | 159.63, 141.36, 137.74, 135.04, 134.40, 133.26 | 132.03, 129.31, 129.24, 129.03, 117.82, 112.38 | 18.72 21.46 |
| 4h | 37 | 208-9 | 7.00 7.17 | 7.85 | 2.20 2.42 | 162.29 | 141.34, 138.15, 134.46, 133.27, 126.02 | 132.04, 129.09, 113.47 | 18.86 21.52 |
| 4i | 75 | 198-9 | 7.10 7.08 | 9.13 | 2.18 2.30 | 165.04 | 152.17, 140.06, 139.20, 134.33, 120.48 | 131.31, 128.66, 128.42, 110.58 | 18.28 21.53 |
| 4j | 88 | 286-7 | 7.13 8.10 | 9.93 | 2.20 2.30 | 163.72 | 149.11, 140.57, 139.51, 137.93, 134.28 | 131.65, 129.19, 128.64, 123.35 | 18.06 21.10 |

^a Ar = two proton benzothiazole AB absorption midpoint, Ar' = four proton substituted 2-phenyl absorption (AB for para substituted systems).

50 mass spectrometer. All new compounds gave acceptable elemental analyses which were performed by Midwest Micro Laboratories, Indianapolis, Indiana.

Bis(2-amino-3,6-dimethylphenyl)disulfide (2) To a solution of potassium hydroxide (10 g) in ethylene glycol (20 mL) was added, at 90°C, 2-amino-4,7-dimethylbenzothiazole (2 g, 0.0112 mol). The temperature was brought to 165°C and maintained for 24 h. The solution was then cooled and poured into water (400 mL). Air was drawn through the stirred aqueous solution overnight. A yellow-green precipitate was filtered and recrystallized from 45 mL of 85% aqueous ethanol (1.2 g, 78%): m.p. 90-91°C; IR(KBr, cm⁻¹) 3437, 3352 (N-H), 1609, 1468 (C=C); ¹H NMR (CDCl₃) δ 6.98-6.41 (m, 4H, aromatic), 4.29 (s, 4H, N-H), 2.15, 2.10 (s, 12H, methyl); ¹³C NMR (CDCl₃) ppm 147.86, 141.49, 119.51, 118.12, 131.60, 118.97, 21.10 (C-3 Me), 17.85 (C-6 Me); MS m/e (ion) 304 (M⁺), 152 (M⁺/2). Anal. calcd. for C₁₆H₁₆N₂S₂: C, 63.20; H, 6.62; N, 9.20; S, 21.06. Found: C, 62.93; H, 6.79; N, 8.98; S, 21.31.

General Procedures for the Synthesis of Bisamides. A solution of **2** (1 g, 3.29 mmol) in chlorobenzene (20 mL) and water (2 mL) with sodium acetate (0.8 g) was treated with the appropriate benzoyl chloride (8.23 mmol) in 2 mL of chlorobenzene dropwise at 85°C. After heating at 95-100°C for 2.5 h, the solution was cooled to room temperature and poured into 400 mL water with stirring and the precipitate was filtered. The crude material was recrystallized from ethanol to give the product. The general synthesis was modified in the preparation of **4b** in that the organic layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was recrystallized from

Table 2. Physical and Spectral Properties of Benzothiazoles 5a-i

| Cmp | Yield % | Mp (°C) | ¹ H NMR δ ^a Ar / Ar' | Me-4/7 | ¹³ C NMR ppm | | | Ar-CH | Me-4/7 |
|-----|---------|---------|---|--------------|-------------------------|--------|---|--|----------------|
| | | | | | C-2 | C-3 | Ar-C | | |
| 5a | 99 | 54-5 | 7.13 / 7.84 | 2.55 2.78 | 166.15 | 153.24 | 135.46, 134.19 | 130.55, 128.90, 127.47, 126.93, 125.24 | 18.00 21.11 |
| 5b | 46 | 46-7 | 7.13/7.62 | 2.52 2.78 | 166.51 | 153.34 | 138.75, 135.53, 134.21, 130.58 | 131.49, 128.89, 128.05, 126.98, 125.25, 124.85 | 18.17 21.28 |
| 5c | 70 | 71 | 7.05/7.53 | 2.42 2.73 | 166.17 | 153.12 | 140.72, 135.18, 131.38, 130.17, 128.56 | 129.45, 127.28, 126.78, 124.97 | 18.06 b |
| 5d | 74 | 93 | 7.10/7.71 | 2.45 2.72 | 164.29 | 153.07 | 135.80, 135.48, 130.79, 128.79 | 130.37, 130.05, 127.27, 127.09, 125.57 | 18.00 21.11 |
| 5e | 80 | 118-9 | 7.13/7.72 | 2.53 2.77 | 164.63 | 153.12 | 136.53, 135.42, 132.60, 130.60, 128.75 | 129.05, 128.53, 127.04, 125.42 | 18.02 21.14 |
| 5f | 66 | 115.5 | 7.10/7.69 | 2.52 2.78 | 164.60 | 153.10 | 135.37, 132.99, 130.58, 124.85 | 131.95, 128.68, 127.01, 125.42 | 17.99 21.10 |
| 5g | 67 | 70 | 7.12/7.45 | 2.50 2.76 | 164.86 | 153.06 | 159.93, 135.35, 130.44, 128.63 | 129.87, 126.92, 125.27, 120.09, 116.62, 112.24 | 18.01 21.07 |
| 5h | 61 | 97 | 7.13/7.56 | 2.55 2.78 | 165.91 | 153.27 | 161.64, 135.20, 130.08, 128.61, 127.05 | 128.94, 126.83, 124.85, 114.23 | 18.04 21.18 |
| 5i | 99 | 137.5-8 | 7.08/7.36 | 2.52 2.76 | 166.94 | 153.46 | 134.91, 129.59, 128.52, 124.33 | 128.79, 126.72, 111.81 | 18.12 21.28 |

^a Ar = two proton benzothiazole AB absorption midpoint, Ar' = four proton substituted 2-phenyl absorption (AB for para substituted systems).

^b Only one methyl absorption is observed.

ethanol. The general synthesis was modified in the preparation of 4i in that pyridine was used as solvent. The hot reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was recrystallized from ethanol.

General Procedure for the Synthesis of 2-Phenylbenzothiazoles. To a solution of concentrated hydrochloric acid (30 mL), ethanol (30 mL) and water (6 mL), at room temperature, was added the appropriate bisamide 3a-i (4.9 mmol) and stannous chloride (6.16 mmol). The solution was refluxed at 100°C for 10 h and then cooled to room temperature and poured into water (200 mL) with vigorous stirring. Excess tin was dissolved with NaOH (4.8 g, 45 min). After the solution was acidified with acetic acid (22 mL), the precipitate was filtered, washed with water (30 mL), and recrystallized from ethanol.

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