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New Disulfide Route to 3-(1-Piperazinyl)-1,2-benzisothiazole. Nucleus for Atypical Antipsychotic Drugs

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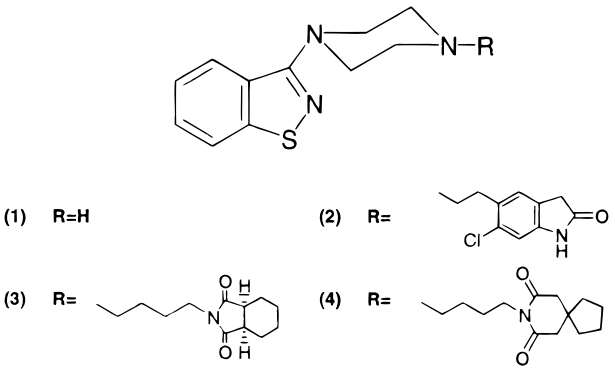
Abstract:

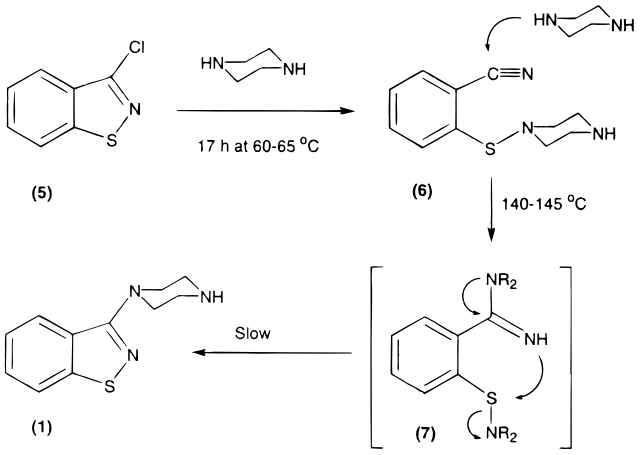
A new, one-step commercial process for the preparation of 3-(1-piperazinyl)-1,2-benzisothiazole hydrochloride, a key intermediate for the syntheses of some new, "atypical antipsychotic" drugs, was developed. Reaction of bis(2-cyanophenyl) disulfide with excess piperazine at 120−140 °C for 3−24 h in the presence of small amounts of DMSO and 2-propanol formed 3-(1-piperazinyl)-1,2-benzisothiazole in 75−80% yields. The DMSO oxidized the liberated 2-mercaptobenzonitrile to regenerate bis-(2-cyanophenyl) disulfide, thereby enabling the utilization of both halves of the symmetrical disulfide to generate product. The reaction mechanism for the conversion of the bis(2-cyanophenyl) disulfide to 3-amino-1,2-benzisothiazole involves the formation of ring-opened sulfenamide and benzamidine intermediates and then their subsequent ring closure to regenerate the 1,2-benzisothiazole nucleus. A safe, efficient, and robust process to prepare 3-(1-piperazinyl)-1,2-benzisothiazole under very concentrated reaction conditions was developed and successfully scaled up in the pilot plant to support the development of ziprasidone.

3-(1-Piperazinyl)-1,2-benzisothiazole (**1**) represents a key intermediate for the synthesis of a new class of "atypical antipsychotic" drugs such as ziprasidone (**2**), Sumitomo's SM-9018 (**3**), and tiospirone (**4**) for the treatment of



schizophrenia. In extensive clinical studies, ziprasidone showed potent 5-HT_2 and dopamine D_2 activity,[1] but it lacked the debilitating, extrapyramidal side effects (EPS) commonly found in first-generation antipsychotics. A new, robust synthetic process for the large-scale preparation of **1** as its hydrochloride salt was developed to support the pharmaceutical development and commercialization of ziprasidone.

Scheme 1. **3-Chloro-1,2-benzisothiazole route**



The pharmaceutical development of ziprasidone required over 2 metric tons of drug substance **2** to evaluate its efficacy and safety and to develop both solid and parenteral dosage forms. Literature methods to prepare 3-piperazinyl-1,2-benzisothiazoles **1** were not suitable for large-scale, commercial processes since the methods involved strong irritants[2] or organometallic reactions,[3] required lengthy protection−deprotection sequences,[4] or utilized neat reactions.[5] To circumvent some of the above process limitations and to develop a robust, practical process to **1**, the reactions of 3-chloro-1,2-benzisothiazole (**5**) with anhydrous piperazine were further investigated as outlined in Scheme 1.

Surprisingly, the reaction of **5** with piperazine is complex involving multiple intermediates, products, and byproducts whose yields depend on reactant stoichiometry, reaction

(1) (a) Howard, H. R.; Prakash, C.; Seeger, T. F. *Drugs Future* **1994**, *19*, 560. (b) Bench, C. J.; Lammertsma, A. A.; Dolan, R. J.; Gasby, P. M.; Warrington, S. J.; Gunn, K.; Cuddigan, M.; Turton, D. J.; Osman, S.; Frackowiak, R. S. *J. Psychopharmacol.* **1993**, *112*, 308. (c) O'Neill, M. F.; Palacios, J. M. *Exp. Opin. Invest. Drugs* **1994**, *3*, 1317.

(2) 3-Chloro-1,2-benzisothiazole (**5**) and 1,2-benzisothiazole-3(2*H*)-one, the synthetic precursor to **5** are strong dermal, ocular, and nasal irritants which require process containment and special handling; whereas, bis(2-cyanophenyl) disulfide did not show any dermal corrosivity or ocular or nasal irritancy. 3-(1-Piperazinyl)-1,2-benzisothiazole hydrochloride and its free base are also strong dermal, ocular, and nasal irritants; therefore, personnel should at least wear double Tyvek suits, gloves, and hood air-supply mask when handling these irritants. The use of a Rosenmund filter/dryer for the isolation of 3-(1-piperazinyl)-1,2-benzisothiazole is highly recommended.

(3) Nakamura, T.; Nagata, H.; Muto, M.; Saji, I. *Synthesis* **1997**, 871.

(4) (a) Cipollina, J. A.; Ruediger, E. H.; New, J. S.; Wire, M. E.; Sheperd, T. A.; Smith, D. W.; Yevich, J. P. *J. Med. Chem.* **1991**, *34*, 3316. (b) Böshagen, H. *Chem. Ber.* **1996**, *99*, 2566. (c) Seeger, W.; Böshagen, H.; Medenuald, H. *Chem. Ber.* **1969**, *102*, 1961.

(5) (a) Yevich, J. P.; New, J. S.; Smith, D. W.; Lobeck, W. G.; Catt, J. D.; Minielli, J. L.; Eison, M. S.; Taylor, D. P.; Riblet, L. A.; Temple, D. L. *J. Med. Chem.* **1986**, *29*, 359. (b) Smith, D. W.; Yevich, J. P. U.S. Patent 4,590,196, May 20, 1986.

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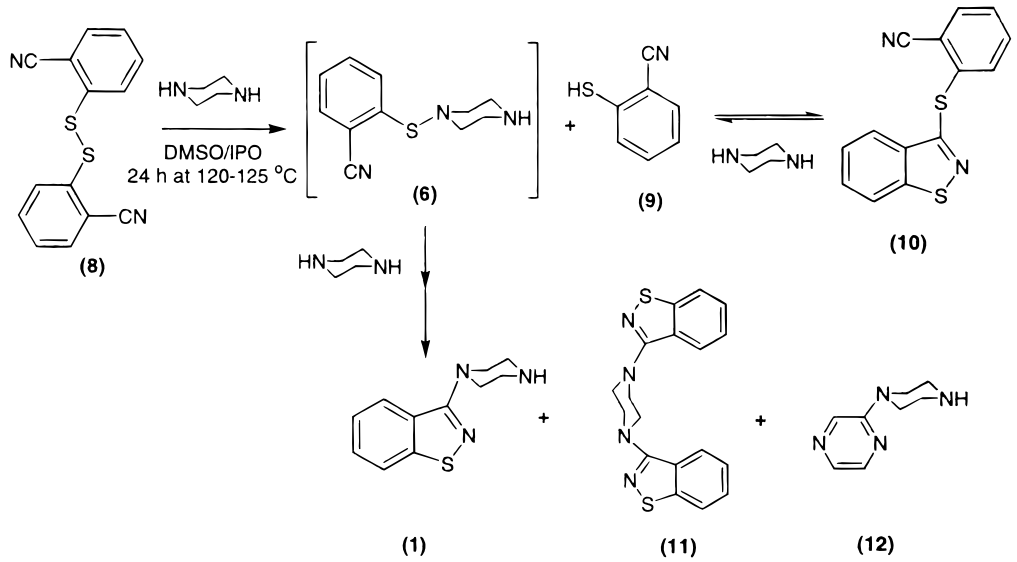
Scheme 2. **Bis(2-cyanophenyl) disulfide route**



concentration, and temperature. For example, reaction of **5** with anhydrous piperazine (4.4 equiv) in THF for 17 h at 60−65 °C cleanly cleaved the 1,2-benzisothiazole ring to produce sulfenamide **6** in 85% yield with <0.1% of the desired 3-amino-1,2-benzisothiazole **1** being formed. However, when anhydrous piperazine (10 equiv) was reacted with **5** at higher temperatures (11 h at 140−145 °C) in diglyme, benzisothiazole **1** was formed in 38% yield. Thin-layer chromatography of the high-temperature piperazine reaction showed the rapid consumption of **5** and **6** to produce a polar intermediate **7**[6] which slowly converted to product. Small amounts of bis(2-cyanophenyl) disulfide (**8**) and 2-(1-piperazinyl)pyrazine (**12**)[7] were also produced as reaction byproducts. Although there are reports in the literature of reactions of 3-chloro-1,2-benzisothiazole with secondary amines to give either sulfenamides[8] or 3-amino-1,2-benzisothiazoles,[5a,9] the intermediacy of sulfenamides **6** and benzamidines **7** in these reactions to generate 3-amino-1,2-benzisothiazoles has not been widely recognized. When the isolated sulfenamide **6** was reacted with excess piperazine (5.0 equiv) in diglyme at 125−130 °C for 40 h, benzisothiazole **1** was produced in 36% yield. However, the thermal rearrangement of **6** at 120−140 °C in solution (diglyme or pyridine), or neat without any added piperazine, produced only trace amounts of 3-amino-1,2-benzisothiazole **1** by TLC analyses. The piperazine-free thermal rearrangement of **6** shows that the conversion of sulfenamide **6** to **1** does not occur by a unimolecular mechanism and that excess piperazine is required to produce **1**.

Yevich and co-workers[5] reported a neat reaction of 3-chloro-1,2-benzisothiazole with molten piperazine (24 h at 125 °C) to give **1** in a 68% isolated yield. The neat reaction was conducted in a sealed, evacuated flask which would be unsuitable at pilot plant scale. Our investigations on 3-chloro-1,2-benzisothiazole reactions have shown that high piperazine concentrations and high reaction temperatures (120−140 °C) are required to efficiently trap sulfenamide intermediate **6** to give benzamidine **7**. The benzamidine intermediate then slowly cyclizes with the elimination of piperazine to produce the isolated benzisothiazole **1**. Since sulfenamide **6** and benzamidine **7** are key intermediates in the ring-opening/ring-closing conversion of **5** to 3-amino-1,2-benzisothiazoles, and since the reaction of **8** with piperazine could potentially form the same intermediates **6** and **7**, the reaction of **8** with excess piperazine was investigated (Scheme 2).

Reaction of **8** with anhydrous piperazine (5 equiv) in the presence of a small amount of 2-propanol (IPA, 1.0 mL/g of disulfide) at 120−130 °C for 24 h produced **1** and **9** as the major products in 36% and 37% yields, respectively. Although **9** was easily separated by extraction from **1** and then reoxidized to **8** in quantitative yield using 10% aqueous H_2O_2 in methanol, a simple one-step process to produce 3-piperazinyl-(1,2-benzisothiazole) was desired. When **8** was reacted with anhydrous piperazine (10 equiv) in the presence of DMSO (2.2 equiv) and a small amount of IPA (1.0−1.2 mL/g of disulfide) at 120−130 °C for 24 h, **1**, 3,3′-(1,4-piperazinyl)-1,2-benzisothiazole (**11**), and **12** were formed in 80%, 4.6%, and 4% yields, respectively, as determined by HPLC assays. Product yields are calculated by utilizing both halves of the symmetrical disulfide since DMSO reoxidized the liberated **9** back to the starting disulfide **8**. The starting disulfide **8** and a labile reaction side product, 3-(2-cyanophenylthio)-1,2-benzisothiazole (**10**), were consumed within 1−2 h at 120−130 °C, but product **1** was formed more slowly over 24 h as shown by TLC. The use of other in situ oxidants such as air, cupric acetate, or *n*-butyl sulfoxide to convert **8** to **1** were effective as reported in Table

(6) Although benzamidine **7** was not isolated and characterized due to its polarity and lability, there is good chemical precedent for the benzamidine **7** ring closure to 3-amino-1,2-benzisothiazole. See: Böshagen, H.; Geiger, W. *Phosphorus Sulfur* **1983**, *17*, 325.

(7) 2-(1-Piperazinyl)pyrazine was identified by comparison with an authentic sample prepared by the procedure reported in: Lumma, W. C.; Hartman, R. D., Saari, W. S.; Engelhardt, E. L.; Hirshmann, R. *J. Med. Chem*. **1978**, *21*, 536.

(8) (a) Becke, F.; Hagen, H. *Liebigs Ann. Chem.* **1969**, *729*, 146. (b) Carrington, D. E. L.; Clarke, K.; Scrowston, R. M., *J. Chem. Soc. C* **1971**, 3262.

(9) Knoll, A. G. German Patent 1,174,783, July 30, 1964; *Chem. Abstr*. **1964**, *61*, 12, 008.

Table 1. **Process optimization and synthesis of 3-amino-1,2-benzisothiazoles**

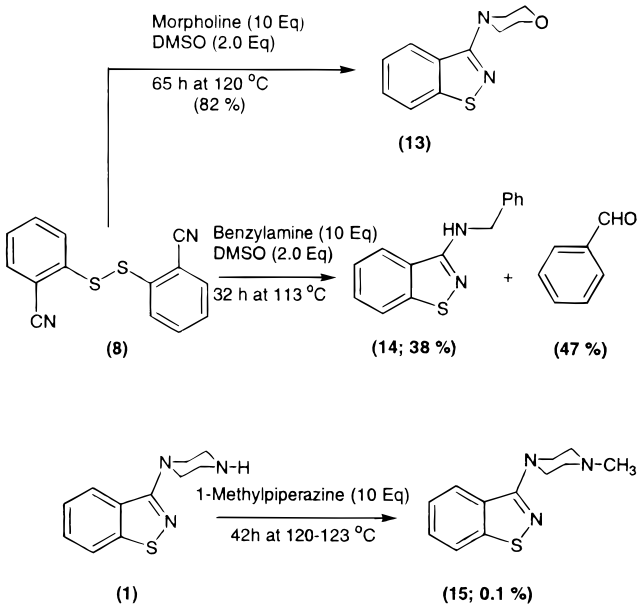
reactants (equiv)			reaction			3-amino-1,2-benzisothiazole yields (%)	byproduct **11** yields (%)
reactant (1.0)	piperazine	oxidant	solvent (mL/g of disulfide)	time (h)	temp (°C)		
8	5.0	DMSO (0)	IPA (1.0)	22	120	36	
8	10.0	DMSO (1.0)	IPA (1.2)	24	118	38	
8	2.5	DMSO (2.2)	IPA (0.6)	48	122	61	19.1
8	6.0	DMSO (2.2)	IPA (1.2)	24	118	65	6.3
8	10.0	DMSO (2.2)	IPA (1.2)	3	140 (61 psi)	73	4.5
8	15.0	DMSO (2.2)	IPA (1.2)	24	118	78	2.4
8	4.4		diglyme (8.5)	12	140	28	
6	5.0		diglyme (8.7)	40	125	36	
8	10.0	DMSO (2)	pyridine (1.0)	24	122	73	
6	0		pyridine (1.0)	24	120	0	
8	10.0	air	IPA (1.2)	66	108	74	
8	10.0	$Cu(OAc)_2$ (2.0)	IPA (1.2)	24	121	49	
8	10.0	*n*-butyl sulfoxide (2.2)	IPA (1.2)	24	120	73	
8	morpholine (10)	DMSO (2)	Neat	65	113	82	
9	10.0	DMSO (2)	IPA (1.0)	25	120	70	

1, but these oxidants were not as practical or as cost-effective as DMSO. Volatile dimethyl sulfide (DMS), which was produced in the disulfide reaction, was removed overhead and bubbled through either a 15% NaOCl solution or an aqueous potassium permanganate slurry to eliminate odor and volatile emissions. Excess piperazine (10 equiv) was required in the disulfide reaction to efficiently trap sulfenamide **6**, to accelerate a sluggish reaction, and to maximize mono- versus bis(1,2-benzisothiazole) substitution on piperazine (**1** versus **11**) since no N-protecting groups were used. When **6** or **10** were reacted with excess piperazine under the disulfide reaction conditions, comparable reaction rates, product yields, and byproducts were obtained. Reaction of **5** with excess piperazine under the disulfide reaction conditions but without any added DMSO produced **1** in a 68% isolated yield. Again, this supported the importance of using very concentrated reaction conditions with excess piperazine to trap the sulfenamide intermediate.

Small volumes of IPA (1.0−1.2 mL/g of disulfide) were added to the disulfide reaction to fluidize the molten piperazine reaction, to help prevent solidification of the reaction mixture upon cooling, and finally to rinse crystallized piperazine from the reactor's headspaces and condenser lines during the reaction. Small volumes of pyridine, *tert*-butyl alcohol, and 1-butanol have also been used successfully as fluidizing agents in the disulfide process, but IPA is the preferred "solvent". After the reaction was quenched with water, residual DMS was removed overhead by distillation, byproduct **11** was removed by filtration, and finally **1** was isolated by an extractive acid−base workup to remove excess piperazine and other byproducts. Compound **1** of excellent quality (98% by HPLC) was crystallized from IPA−toluene as its hydrochloride salt. Both **1** and its HCl salt are very strong dermal, nasal, and ocular irritants; therefore, in the pilot plant, the HCl salt of **1** (73.1 kg scale) was isolated by filtration and dried on a Rosenmund filter to provide containment and to minimize worker exposure.

To test the generality of the disulfide process, **8** was also reacted with excess morpholine or benzylamine under neat reaction conditions to give good yields of 3-amino-1,2-benzisothiazoles **13** and **14** as shown in Scheme 3. The morpholine and benzylamine reactions were conducted neat to achieve higher reaction temperatures. In the benzylamine reaction, 50% of the primary amine was oxidized to benzaldehyde, which was isolated after an aqueous workup. Benzaldehyde is most likely formed from benzaldimine which may result from an E_2 elimination of 2-mercaptobenzonitrile from the sulfenamide. In addition, benzisothiazole **1** was shown to be stable to prolonged heating (42 h at 120−123 °C) with 1-methylpiperazine, indicating that ring-opening of **1** to give the 1-methylpiperazine analogue of **6** does not occur to any significant extent in the presence of secondary amines.

Scheme 3. **Additional examples**



Summary

Understanding of an unexpected ring-opening/ring-closing reaction mechanism involving sulfenamide and benzamidine intermediates for the conversion of 3-chloro-1,2-benzisothi-

azole to 3-(1-piperazinyl)-1,2-benzisothiazole has led to the development of a new, robust commercial process to **1**. Reaction of **8** with excess piperazine in the presence of small amounts of DMSO and IPA at 120−125 °C for 24 h affords **1** in 75−80% yield. DMSO is added to the reaction to reoxidize the reaction-liberated 2-mercaptobenzonitrile to **8**, thereby utilizing both halves of the symmetrical disulfide to generate product. A small volume of IPA is added to the reaction mixture to fluidize a nearly neat reaction mixture and to rinse solid condensed piperazine from the reactor's headspaces. Compound **8** is readily available and possesses a major advantage of being a fairly innocuous starting material that is easy to handle. The new disulfide route represents a high-yielding, one-step process to **1**, a nucleus for exciting new antipsychotic drugs.

Experimental Section

Commercial quantities of bis(2-cyanophenyl) disulfide can be obtained from Zambon, Sumitomo Seika, or SEAC or is easily prepared from *S*-benzyl-*o*-cyanothiophenol,[8b] 2-nitrobenzonitrile,[10a] or 2,2′-dithiobenzoic acid.[10b] Anhydrous, flake piperazine was obtained from Texaco or Berol Nobel. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on a Brucker WM 300 (300 MHz) spectrometer in deuteriochloroform or dimethyl sulfoxide-d_6. Mass spectra were determined with a Finnigan 4510 mass spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY. Thin-layer chromatography was conducted on Merck Kieselgel 60 F_{254} plates (5 × 10 cm) using 1:1 hexanes−EtOAc, 10:10:1 hexanes−EtOAc−triethylamine (TEA), or 15:5:1 CH_2Cl_2−IPA−TEA eluants. The TLC plates were visualized with UV light (254 nm). High-pressure liquid chromatography was performed on an LDC Analytical ConstaMetric 3200 HPLC pump using a Zorbax C8 column (4.6 × 150 mm) and a mobile phase containing 40% acetonitrile, 15% methanol, and 45% 0.05 M KH_2PO_4 which was adjusted to pH 6.0 with KOH; flow rate 1 mL/min; injection volume (10 μL); UV detector (229 nm); retention times **13**, 1.23 min; **9**, 1.25 min; **12**, 2.00 min; **6**, 2.81 min; **1**, 3.03 min; **8**, 9.86 min; **10**, 10.89 min; and **11**, 22.75 min.

1-(2-Cyanophenylthio)piperazine (6). Anhydrous piperazine (22.5 g, 261 mmol) and THF (100 mL) were combined under a nitrogen atmosphere and then the mixture was heated to 60−65 °C to afford a colorless solution. 3-Chloro-1,2-benzisothiazole (10.0 g, 59.0 mmol) was slowly added over 1 h to the warm piperazine solution, and the resulting amber solution was heated an additional 17 h at 60−65 °C. Thin-layer chromatography (SiO_2, EtOAc−hexanes−TEA, 10:10:1) showed that the reaction was complete. The thin slurry was cooled to 30 °C and filtered. Toluene (100 mL) was added to the filtrate and the resultant mixture was concentrated at reduced pressure (40 °C) to half of its volume. The concentrate was washed with water (100 mL) and then further concentrated at reduced pressure to 30 mL. The solution was cooled to 0−5 °C; hexanes (50 mL) was added over 0.5 h, producing yellow crystals. After granulating for 1 h at 0−5 °C, the product was filtered; the cake washed with hexanes (15 mL) and then dried for 18 h at 20−25 °C affording 11.51 g (89% yield) of finely divided yellow crystals: mp 67−71 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (m, 1H), 7.56 (m, 3H), 7.21 (m, 1H), 2.96 (m, 4H), 2.87 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 142.69, 133.55, 132.67, 128.14, 126.69, 116.80, 110.24, 57.34, 47.06; HR MS found 220.0878; $C_{11}H_{13}N_3S$ requires (FAB P + 1) 220.0908.

Not unexpectedly, sulfenamide **6** is both thermally and hydrolytically labile. When **6** was stored at room temperature, it slowly converted to 1,4-bis-(2-cyanophenylthio)piperazine. The isolated sulfenamide **6** contained ∼5% of the bissulfenamide by ^{1}H NMR. Attempts to purify **6** by recrystallization or chromatography were unsuccessful in completely removing the bissulfenamide.

3-[(2-Cyanophenyl)thio]-1,2-benzisothiazole (10). 8 (1.25 g, 4.66 mmol), anhydrous piperazine (4.01 g, 46.6 mmol), and DMSO (0.80 g, 10.3 mmol) in 15 mL of THF were added to a 50-mL round-bottom flask equipped with a magnetic stirring bar, thermometer, and condenser topped with a nitrogen inlet. After the flask was purged with nitrogen, the mixture was heated at reflux (75 °C) for 25 h. The reaction mixture was cooled to 25 °C, and THF was removed at reduced pressure. The resulting solid was dissolved in a 40 mL of a CH_2Cl_2−water (1:1), the layers were separated, and the organic layer was washed with water (20 mL). The CH_2Cl_2 solution was evaporated to afford a crude solid (0.85 g) which was recrystallized from IPA (17 mL) to give light yellow crystals. After filtration, the product was dried in vacuo at 40 °C to give 0.39 g (31% yield) of **10**: mp 115.5−117 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (m, 1H), 7.92 (m, 1H), 7.77 (m, 1H), 7.70 (m, 1H), 7.57 (m, 2H), 7.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 154.99, 152.30, 134.83, 134.56, 134.06, 133.24, 129.07, 128.51, 125.33, 123.29, 120.13, 117.13, 116.95. Anal. Calcd for $C_{14}H_8N_2S_2$ C, 62.66; H, 3.00; N, 10.44; S, 23.90. Found: C, 62.43; H, 3.01; N, 10.68; S, 24.05.

3-(1-Piperazinyl)-1,2-benzisothiazole (1) from (5). A mixture of anhydrous piperazine (76.2 g, 884 mmol) and 23 mL of pyridine was heated to 115 °C under a nitrogen atmosphere. A solution of 3-chloro-1,2-benzisothiazole (30.0 g, 17.7 mmol) in 15 mL of pyridine was slowly added over 1 h to the piperazine solution to moderate an exothermic reaction. Once the addition was complete, the amber solution was heated for 24 h at 119 °C when thin-layer chromatography (SiO_2, CH_2Cl_2−IPA−TEA, 15:5:1) showed that the reaction was complete. The solution was cooled to 90 °C and water (154 mL) was added. The brownish slurry was stirred for 1 h at 25 °C and filtered through Celite to remove **11**, and then the cake was washed with 35 mL of pyridine−water (1:4) solution. The wash and filtrate were combined and the pH adjusted to 12.0−12.5 with 50% (w/w) aqueous NaOH (10.2 mL). The solution was concentrated at reduced pressure (60 mmHg at 45−50 °C) to 170 mL. Water (240 mL) and toluene (308 mL) were added to the concentrate

(10) (a) Beck, J. R., Yahner, J. A. *J. Org. Chem.* **1978**, *34*, 1604. (b) Saji, K.; Nagata, H.; Muto, M.; Nakamua, T. Japanese Patent Appl. 93-27357, January 22, 1993; *Chem. Abstr.* **1995**, *122*, 31512.

and then the aqueous layer was separated and washed with fresh toluene (77 mL). The combined toluene layers were washed with water (116 mL), the layers were separated, and the toluene solution was concentrated at reduced pressure (60 mmHg at 45−50 °C) to 120 mL. After addition of IPA (320 mL), the pH was adjusted to 4.5−5.5 with concentrated HCl. The slurry was cooled to 0−5 °C, granulated for 1 h, and then filtered. The cake was washed with cold IPA (80 mL) and then dried in vacuo at 35 °C to give 30.5 g (67% yield) of 3-(1-piperazinyl)-1,2-benzisothiazole hydrochloride. CAUTION: 3-(1-piperazinyl)-1,2-benzisothiazole is a strong eye, skin and nasal irritant! The spectroscopic and physical properties of the solid were identical to an authentic sample,[5a] and the product was 98% pure by HPLC versus a reference standard: ^{1}H NMR (D_2O) δ 7.80 (m, 2H), 7.49 (m, 1H), 7.35 (m, 1H), 3.58 (m, 4H), 3.42 (m, 4H); ^{13}C NMR (DMSO) δ 162.72, 152.10, 128.15, 127.09, 124.63, 124.12, 121.21, 46.48, 42.49.

3-(1-Piperazinyl)-1,2-benzisothiazole hydrochloride 1 from (8). 8 (53.3 kg, 198.7 mol), anhydrous piperazine (171 kg, 1987 mol), DMSO (34 kg, 435 mol), and IPA (64 L) were melted (∼80 °C) under a nitrogen atmosphere and then the mixture was heated to reflux (120−125 °C). Vapors from the reflux condenser were vented through a scrubber solution containing 15% (w/w) NaOCl (320 L). After 24 h at reflux, thin-layer chromatography (SiO_2, CH_2Cl_2−IPA−TEA, 15:5:1) of the reddish reaction mixture showed that the reaction was complete. The solution was cooled to 85−90 °C, water (350 L) was added, and the resulting slurry was cooled to 30−35 °C. The mixture was concentrated at 50−60 °C under reduced pressure (25−30 mmHg) by pulling vacuum through the scrubber to remove residual dimethyl sulfide. The reaction mixture was concentrated to ∼580 L. Drager tubes showed that the reactor's headspace contained ≥1 ppm of residual dimethyl sulfide vapors. Water (190 L) and IPA (75 L) were added, and the resulting slurry was granulated for 0.5 h at 25−30 °C. The slurry was filtered through an 18-in. Sparkler coated with Celite on cotton filter cloths and then through Fulflo filters. The reactor and filters were then rinsed with a water (75 L)−IPA (75 L) wash. The combined wash and filtrate was extracted with toluene (800 L), and then the aqueous layer was separated and washed with fresh toluene (400 L). The combined toluene layers were washed with water (320 L), separated, and then treated with Darco KB-B (5.3 kg). After filtration through an 18-in. Sparkler coated with Celite and then through Fluflo filters, the toluene solution was concentrated (240 L). The solution was cooled to 20 °C and IPA (580 L) was added. The pH of the solution was slowly adjusted to 4−5 using concentrated HCl. The slurry was granulated for 0.5 h at 20−25 °C and then an additional hour at 0−5 °C. The solids were isolated and dried (40−50 °C at 25 mmHg) for 48 h on a Rosenmund filter. 3-(1-Piperazinyl)-1,2-benzisothiazole hydrochloride (73.1 kg) was isolated in 72.0% overall yield.

4-(1,2-Benzisothiazol-3-yl)morpholine (13). 13 was prepared by the disulfide method used for the preparation of **1**: mp 52−53 °C (crystallized from methanol−water, 2:3) (lit.[11] mp 65 °C); ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 1H), 7.84 (m, 1H), 7.46 (m, 1H), 7.35 (m, 1H), 3.91 (m, 4H), 3.52 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 163.82, 152.87, 127.84, 127.65, 124.01, 123.74, 120.65, 66.78, 50.60. Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72; S, 14.56. Found: C, 59.76; H, 5.52; N, 12.83; S, 14.64.

***N*-(1,2-Benzisothiazol-3-yl)benzylamine (14). 14** was prepared by the disulfide method used for the preparation of **1**: mp 75−77 °C (crystallized from methanol) (lit.[12] mp 85 °C); ^{1}H NMR ($CDCl_3$) δ 7.78 (m, 1H), 7.63 (m, 1H), 7.45 (m, 3H), 7.32 (m, 4H), 5.28 (s, 1H), 4.78 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 158.82, 151.60, 138.99, 128.73, 128.17, 128.06, 127.56, 126.36, 123.96, 121.17, 120.45, 47.35; HR MS found 241.0796; $C_{14}H_{12}N_2S$ requires (FAB P + 1) 241.0799.

Amine Exchange in 3-(1-Piperazinyl)-1,2-benzisothiazole. 3-(1-Piperazinyl)-1,2-benzisothiazole (0.5 g, 2.3 mmol) and 1-methylpiperazine (2.3 g, 23.0 mmol) in 0.5 mL of IPA were heated at 120−123 °C for 42 h under nitrogen. The yellow solution was then cooled to 25 °C and analyzed by HPLC. 1-(1,2-Benzisothiazol-3-yl)-4-methylpiperazine (**15**) was formed in only 0.1% and 3-(1-piperazinyl)-1,2-benzisothiazole was recovered essentially unchanged.

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