The Synthesis of *cis*-6,12-Diaryl-6*H*,12*H*-dibenzo[*b*,*f*][1,5]dithiocin-6,12-imine and *cis*-6,12-Diphenyl-6,12-epoxy-6*H*,12*H*-dibenzo[*b*,*f*][1,5]dithiocin

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When treated with concentrated hydrochloric acid or heated beyond its melting point, the versatile thioimine **2** 2-mercaptobenzhydrylidenamine was unexpectedly converted to the title ring system. Also, this imine can be converted to 3-phenyl-1,2-benzisothiazoles by prolonged exposure to air.

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As part of our program aimed at the discovery of novel inhibitors of the bile acid transport system [1], we were faced with the problem of making large quantities of 2-thiobenzophenone (**3**) as a starting material for a series of 2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazpines. Published literature procedures [2,3] involved diazonium salt formation to give the thiol **3** in poor yields.

Recently, a series of papers [4,5] described the preparation of lithium 2-lithiobenzenethiolate *via* directed *ortho*-lithiation of lithium benzenethiolate. Though these papers dealt with a variety of structure types, the inclusion of electrophiles to prepare substituted benzophenones was omitted.

Our approach was to treat the dilithio salt of thiophenol with benzonitrile to give the thioimine, **2,** which should readily be converted to the corresponding thiobenzophenone, **3** . Initially, we decided to quench the reaction with 6*N* hydrochloric acid at ice-bath temperatures, to give a solid (68%) which was insoluble in both base and acid. Next, we replaced the ice bath, still using 6*N* hydrochloric acid to quench, with a steam bath and allowed the reaction to stir at 70-80°. This change afforded the desired thiol, **3,** in a modest yield of 30%, but we still isolated a sizable amount of the same unknown solid. Using ammonium chloride to quench the reaction afforded a bright red solid, which when heated beyond its melting point, was converted directly to the unknown compound. Also, when this red solid was allowed to stand at ambient conditions, one noticed a gradual change in its color. Analysis of this solid, after 19 days of standing, showed it to be the isothiazole, **5,** which could be reduced with diborane to give the thioamine, **6**. Lastly, when the reaction was quenched with sodium hydroxide instead of hydrochloric acid, compound **3** was isolated in yields up to 85%.

Spectral analysis of the unknown product showed the compound to have a molecular weight of 409 Da and a stretching vibration of a secondary amine NH (3336 cm^{-1}). Its ^1H-nmr showed aromatic protons and an exchangeable proton at 4.70 ppm. An x-ray analysis was performed; the structure of the unknown product was shown to be the novel ring system **4** (see Figure 1). When this chemistry was repeated on other substituted benzonitriles, the corresponding analogs, compounds **4a** and **4b** were isolated and characterized.

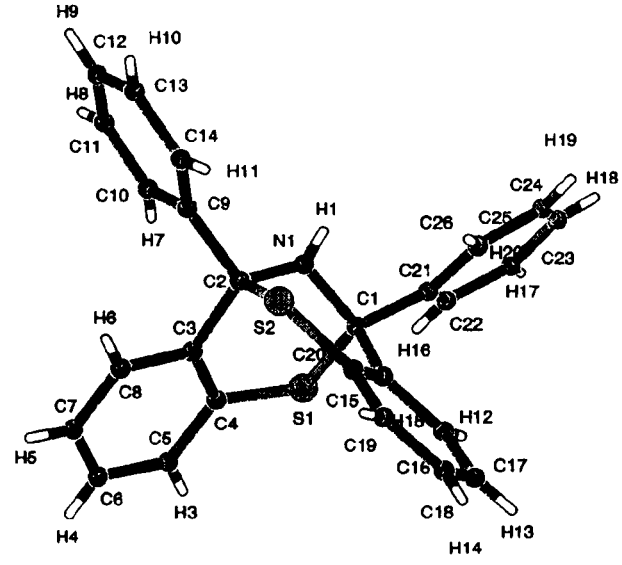
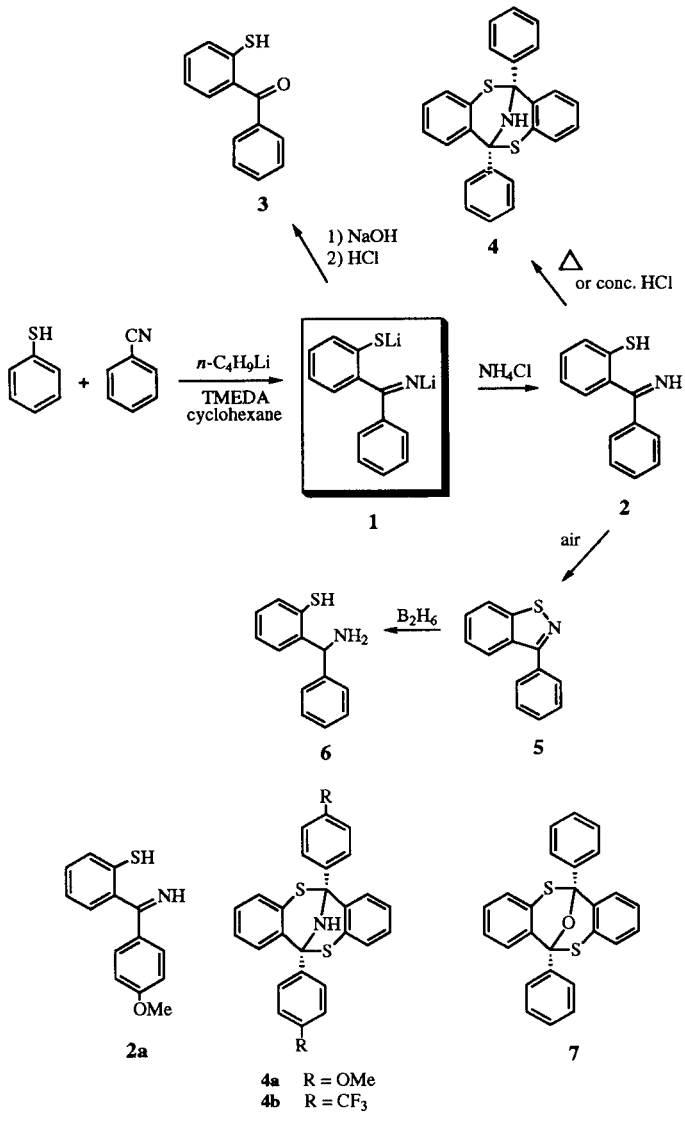


Figure 1.

Scheme 1 summarizes the chemistry that has been discussed above. It is interesting to note that even under basic conditions one still can isolate small amounts of compound **4**. Also, the presence of the isothiazole, **5,** was detected in most of the reaction conditions cited above. Interestingly, the observed coupling of the thioimine was also observed for the thioketone **3**. Treatment of **3** with boron trifluoride etherate in acetonitrile at reflux for 4 hours gave an isolated yield of 27% of the oxo analog, **7**. From this body of data it can be concluded that the thioimine, **2,** is a very reactive substrate which is capable of undergoing a bimolecular reaction with itself under either strong acid conditions or thermally (Scheme 2) to give **4**. Also, compound **2** provides a method for the preparation of substituted 3-phenyl-1,2-benzisothiazoles [6].

Scheme 1



X-Ray Analysis.

X-ray determination of **4** (for details see Tables 1-3) was carried out on samples recrystallized from a mixed solvent system consisting of approximately equal amounts of methylene chloride and hexane. The compound crystallizes in space group Pl, with two independent molecules in the asymmetric unit. The structure was solved by direct methods and expanded using Fourier techniques. The hydrogen atoms were located in Fourier maps computed at an advanced stage of the refinement. Non-hydrogen atoms were refined azeotropically. The N-hydrogen was refined isotropically; all other hydrogens were placed in idealized positions [7].

Scheme 2

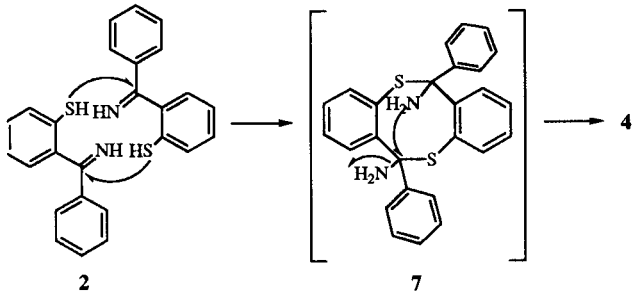


Table 1

Crystal and Empirical Data for **3**

Empirical Formula	$C_{26}H_{19}NS_2$
Formula weight	409.56
Crystal size	0.350 x 0.150 x 0.100 mm
$F_{(000)}$	856
Crystal system	triclinic
Space group	Pl (#2) [note line above l]
a	14.655(2) angstroms
b	19.040(2) angstroms
c	7.9750(8) angstroms
α	101.880(8) degrees
β	105.630(8) degrees
γ	102.371(8) degrees
V	2009.4(4) angstroms^3
D_{calcd}	1.354 g/cm^3
$\mu_{(CuK\alpha)}$	24.32 cm^{-1}
Radiation	CuKα (λ = 1.54178)
Diffractometer	Rigaku AFC5R
Temperature	23° Cent.
$2\theta_{max}$	120.1°
No. Observations(I>3.00σ(I))	3520
No. Variables	532
Reflection/Parameter Ratio	6.62
Residuals: R; R_w	0.052; 0.060
Goodness of Fit Indicator	1.55
Max Shift/Error in Final Cycle	0.00
Maximum Peak in Final Diff. Map	0.57 e$^-$/angstrom^{-3}
Minimum Peak in Final Diff. Map	-0.25 e$^-$/angstrom^{-3}

Table 2

Intramolecular Distances Involving the Non-hydrogen Atoms in **3**

atom	atom	distance	atom	atom	distance
S(1)	C(1)	1.854(5)	C(21)	C(22)	1.362(7)
S(1)	C(4)	1.765(5)	C(21)	C(26)	1.386(7)
S(2)	C(2)	1.866(5)	C(22)	C(23)	1.390(8)
S(2)	C(20)	1.765(5)	C(23)	C(24)	1.358(8)
S(3)	C(33)	1.869(5)	C(24)	C(25)	1.360(8)
S(3)	C(42)	1.763(5)	C(25)	C(26)	1.387(8)
S(4)	C(27)	1.758(6)	C(27)	C(28)	1.401(7)
S(4)	C(34)	1.850(5)	C(27)	C(32)	1.403(7)
N(1)	C(1)	1.452(6)	C(28)	C(29)	1.365(8)
N(1)	C(2)	1.438(6)	C(29)	C(30)	1.395(8)
N(2)	C(33)	1.429(6)	C(30)	C(31)	1.371(8)
N(2)	C(34)	1.451(6)	C(31)	C(32)	1.394(7)
C(1)	C(15)	1.528(7)	C(32)	C(33)	1.528(7)
C(1)	C(21)	1.536(7)	C(33)	C(35)	1.530(7)
C(2)	C(3)	1.529(7)	C(34)	C(41)	1.534(7)
C(2)	C(9)	1.529(7)	C(34)	C(47)	1.516(7)
C(3)	C(4)	1.390(7)	C(35)	C(36)	1.393(7)
C(3)	C(8)	1.396(7)	C(35)	C(40)	1.390(7)

Table 2 (continued)

atom	atom	distance	atom	atom	distance
C(4)	C(5)	1.397(7)	C(36)	C(37)	1.368(8)
C(5)	C(6)	1.371(8)	C(37)	C(38)	1.373(9)
C(6)	C(7)	1.382(8)	C(38)	C(39)	1.359(9)
C(7)	C(8)	1.372(8)	C(39)	C(40)	1.384(8)
C(9)	C(10)	1.386(7)	C(41)	C(42)	1.390(7)
C(9)	C(14)	1.384(7)	C(41)	C(46)	1.392(7)
C(10)	C(11)	1.372(8)	C(42)	C(43)	1.400(7)
C(11)	C(12)	1.360(8)	C(43)	C(44)	1.369(8)
C(12)	C(13)	1.362(9)	C(44)	C(45)	1.393(8)
C(13)	C(14)	1.397(9)	C(45)	C(46)	1.364(7)
C(15)	C(16)	1.400(7)	C(47)	C(48)	1.393(7)
C(15)	C(20)	1.383(7)	C(47)	C(52)	1.376(7)
C(16)	C(17)	1.376(8)	C(48)	C(49)	1.382(8)
C(17)	C(18)	1.369(8)	C(49)	C(50)	1.374(8)
C(18)	C(19)	1.376(8)	C(50)	C(51)	1.366(8)
C(19)	C(20)	1.388(7)	C(51)	C(52)	1.388(8)

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Table 3

Intramolecular Distances Involving the Hydrogen Atoms

atom	atom	distance	atom	atom	distance
N(1)	H(1)	0.80(5)	C(26)	H(20)	0.950
N(2)	H(2)	0.84(4)	C(28)	H(21)	0.950
C(5)	H(3)	0.950	C(29)	H(22)	0.950
C(6)	H(4)	0.950	C(30)	H(23)	0.950
C(7)	H(5)	0.950	C(31)	H(24)	0.950
C(8)	H(6)	0.950	C(36)	H(25)	0.950
C(10)	H(7)	0.950	C(37)	H(26)	0.950
C(11)	H(8)	0.950	C(38)	H(27)	0.950
C(12)	H(9)	0.950	C(39)	H(28)	0.950
C(13)	H(10)	0.950	C(40)	H(29)	0.950
C(14)	H(11)	0.950	C(43)	H(30)	0.950
C(16)	H(12)	0.950	C(44)	H(31)	0.950
C(17)	H(13)	0.950	C(45)	H(32)	0.950
C(18)	H(14)	0.950	C(46)	H(33)	0.950
C(19)	H(15)	0.950	C(49)	H(34)	0.950
C(22)	H(16)	0.950	C(49)	H(35)	0.950
C(23)	H(17)	0.950	C(50)	H(36)	0.950
C(24)	H(18)	0.950	C(51)	H(37)	0.950
C(25)	H(19)	0.950	C(52)	H(38)	0.950

EXPERIMENTAL

Unless otherwise noted all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as dichloromethane, tetrahydrofuran (THF) and cyclohexane were obtained from Aldrich Chemical Co. in Sure/Seal bottles. Chromatography was performed using EM Science silica gel 60 (230-400 mesh ASTM). Thin-layer chromatography was performed with EM Science silica gel 60 F_{254} plates. Infrared spectra were taken in potassium bromide pellets on a Analect FX 6260 FTIR spectrometer. Mass spectra were performed on a Finnegan 4500 spectrometer operating in the chemical ionization mode with methane as the reagent gas. The ^{1}H nmr spectra were recorded using Varian Gemini 200 and Unity 300 spectrometers operating in the fourier transform mode. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H nmr data are reported in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and number of protons. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected.

2-Thiobenzophenone (**3**).

A solution of TMEDA (104.6 g, 0.90 mole) in cyclohexane (500 ml) was cooled to 0° and 2.5*M* *n*-butyllithium (360 ml, 0.90 mole) was added. To this solution, thiophenol (50 g, 0.45 mole) in cyclohexane (100 ml) was slowly added and the reaction was allowed to warm and was then stirred at room temperature for 17 hours. To the resulting slurry, benzonitrile (46.4 g, 0.45 mole) in cyclohexane (100 ml) was added and stirred for 4 hours, then water (500 ml) was added and stirred for an additional 30 minutes. The aqueous layer was separated, basified with solid sodium hydroxide to a *p*H of 14, and then warmed for a period of 60 minutes. The mixture was cooled to room temperature, acidified with concentrated hydrochloric acid, and extracted with toluene. The organic layer was separated, concentrated *in vacuo* to give an orange-red oil, yield 81%. Upon stirring in a minimal amount of SD3A for 16 hours a white solid precipitated, mp 54-55° (lit [2] mp = 42-44°); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 5.3 (bs, 1H), 7.10-7.81 (m, 9H).

Anal. Calcd. for $C_{13}H_{10}OS$: C, 72.87; H, 4.70; S, 14.96. Found: C, 72.93; H, 4.65; S, 15.03.

2-Mercaptobenzhydrylidenamine (**2**).

Following the identical procedure for compound **3** but adding an aqueous solution of ammonium chloride (58 g in 300 ml) to the water layer (instead of sodium hydroxide) a red solid precipitated, yield 51%, mp 112-114°; ^{1}H-nmr (dimethyl sulfoxide-d_6): 6.45-6.81 (bs, 2H), 6.90-8.30 (m, 9H).

3-Phenyl-1,2-benzisothiazole (**5**).

Compound **2** (48.0 g, 0.07 mole) was placed on an evaporating dish at room conditions. After a period of 13 days an ^{1}H-nmr showed an approximate 50% conversion to **5**. After 19 days, an ^{1}H-nmr showed only trace amounts of **2**. A sample was triturated with hexane to give a white solid, mp 70-71°; ms: m/z 212 (M+1).

Anal. Calcd. for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63; S, 15.18. Found: C, 73.95; H, 4.27; N, 6.68; S, 15.08.

2-(*alpha*-Aminobenzyl)benzenethiol (**6**).

Diborane (59.0 ml, 0.059 mole) was added dropwise to a stirred solution of **5** (5.0 g, 0.024 mole) in anhydrous tetrahydrofuran (250 ml). The reaction mixture was stirred at reflux for 22 hours. The reaction was then quenched with 6*N* hydrochloric acid (50 ml) and concentrated *in vacuo* to give solids which were washed with water and diethyl ether to give a yellow solid, yield 60%, mp 233°; ms: m/z 216 (M+1); ^{1}H-nmr (dimethyl sulfoxide-d_6): 3.38 (bs, 1H), 5.67 (s, 1H), 7.23-7.76 (m, 9H), 9.20-9.33 (bs, 3H).

Anal. Calcd. for $C_{13}H_{13}NS$ HCl•0.20H_2O: C, 61.14; H, 5.68; N, 5.48; S, 12.56. Found: C, 61.14; H, 5.65; N, 5.49; S, 12.50.

cis-6,12-Diphenyl-6*H*,12*H*-dibenzo[*b*,*f*][1,5]dithiocin-6,12-imine (**4**).

Compound **2** (5.5 g, 0.026 mole) was placed in a 200 ml

round bottom flask, stirred, and warmed to 120° for 2 hours. The original red color dissipated to give a light pink color. The solids were triturated with absolute ethanol to give a white solid, yield 80%, mp 212-213°; ir: ν (cm^{-1}) 3336 (NH); ms: m/z 410 (M+1); ^{1}H-nmr (dimethyl sulfoxide-d_6): 4.70 (s, 1H, disappeared in deuterium oxide), 6.92-7.58 (m, 18H).

Anal. Calcd. for $C_{26}H_{19}NS_2$: C, 76.25; H, 4.68; N, 3.42; S, 15.65. Found: C, 76.23; H, 4.73; N, 3.40; S, 15.63.

cis-6,12-Bis(4-methoxyphenyl)-6*H*,12*H*-dibenzo[*b*,*f*][1,5]-dithiocin-6,12-imine (**4a**).

A solution of TMEDA (115.0 g, 0.99 mole) in cyclohexane (500 ml) was cooled to 0° and 2.5*M* *n*-butyllithium (400 ml, 0.99 mole) was added. To this solution, thiophenol 50 g, 0.45 mole) in cyclohexane (100 ml) was slowly added and then the reaction mixture was stirred at room temperature for 17 hours. To this resulting slurry, 4-methoxybenzonitrile (59.9 g, 0.45 mole) was added quickly and then stirred for 17 hours at room temperature. Water (500 ml) was added and the resulting layers were stirred for an additional 30 minutes at room temperature. The aqueous layer was separated and 500 ml of 6*N* hydrochloric acid was added; the mixture was then stirred at 60° for 1 hour and then extracted with dichloromethane to give 81.7 g of a viscous red-orange oil. This oil was partitioned between 1 l of 1*N* sodium hydroxide and 500 ml of diethyl ether. The aqueous basic layer was separated and acidified with 6*N* hydrochloric acid to yield 34.5 g of a yellow solid. An ^{1}H-nmr of this solid showed it to be the hydrochloride salt of the thioimine **2a**. A 5 g sample of **2a** was basified with potassium carbonate in water to give 4.4 g of a bright red solid, free base of **2a**. This isolated solid was warmed to 190° for 2 hours, and then washed with acetone to afford **4a** as a pale pink solid, yield 63% from **2a**, mp 197-199°; ms: m/z 470 (M+1); ^{1}H-nmr (dimethyl sulfoxide-d_6): 3.73 (s, 6H), 4.37 (s, 1H), 6.90-7.48 (m, 16H).

Anal. Calcd. for $C_{28}H_{23}NO_2S_2 \cdot 0.5H_2O$: C, 70.26; H, 5.05; N, 2.93; S, 13.40. Found: C, 70.57; H, 4.83; N, 3.01; S, 13.67.

cis-6,12-Bis(4-(trifluoromethyl)phenyl)-6*H*,12*H*-dibenzo[*b*,*f*]-[1,5]dithiocin-6,12-imine (**4b**).

A solution of TMEDA (66.8 g, 0.57 mole) in cyclohexane (300 ml) was cooled to 0° and 2.5*M* *n*-butyllithium (230 ml, 0.57 mole) was added. To this solution, thiophenol (31.6 g, 0.29 mole) in cyclohexane (50 ml) was slowly added and then the reaction mixture was stirred, warming to room temperature for 17 hours. To this resulting slurry, α,α,α–trifluoro-*p*-tolunitrile (49.1 g, 0.29 mole) was added quickly and then stirred at room temperature for 17 hours. Water (900 ml) was added to this purple slurry and the resulting layers were stirred for an additional 30 minutes at room temperature. The aqueous layer was separated, acidified with concentrated hydrochloric acid and extracted with dichloromethane. The organic layer was separated, dried and concentrated *in vacuo* to give solids which were triturated with petroleum ether to give 30.9 g of a brown solid. This solid was triturated with 1*N* sodium hydroxide for 1 hour, filtered and then triturated with warm methanol to give a tan solid, yield 33%, mp 187-189°; ms: m/z 546 (M+1); ^{1}H-nmr (dimethyl sulfoxide-d_6): 5.25 (s, 1H), 7.00-7.20 (m, 8H), 7.77 (s, 8H).

Anal. Calcd. for $C_{28}H_{17}F_6NS_2$: C, 61.64; H, 3.14; N, 2.57; S, 11.75. Found: C, 61.81; H, 3.06; N, 2.90; S, 11.53.

cis-6,12-diphenyl-6,12-epoxy-6*H*,12*H*-dibenzo[*b*,*f*][1,5]-dithiocin (**7**).

To **3** (26.6 g, 0.124 mole) in 200 ml of acetonitrile was added boron trifluoride etherate in 50 ml of acteonitrile. The reaction mixture was refluxed for 4 hours and concentrated *in vacuo* to give an oily residue. Chromatography on silica gel using hexanes:ethyl acetate (4:1) as eluant afforded 6.6 g of a solid which was recrystallized from dichloromethane/hexanes mixture to give a white solid, yield 17%, mp 204-205°; ms: m/z 411 (M+1); ^{1}H-nmr (dimethyl sulfoxide-d_6): 6.98-7.18 (m, 6H), 7.25-7.51 (m, 8H), 7.53-7.58 (m, 4H).

Anal. Calcd. for $C_{26}H_{18}OS_2$: C, 76.06; H, 4.42; S, 15.62. Found: C, 75.82; H, 4.37; S, 15.52.

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