Heterocyclic aromatic amide protecting groups for aryl and phthalocyaninesulfonic acids

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Abstract: Pyrroles, indole, imidazole, and a pyrazole were treated with 3,4-dibromobenzenesulfonyl chloride to form 3,4-dibromobenzenesulfonamides. The 1-(3,4-dibromophenylsulfonyl)pyrrole and 1-(3,4-dibromophenylsulfonyl)indole were stable to CuCN in DMF to produce 1-(3,4-dicyanophenylsulfonyl)pyrrole and 1-(3,4-dicyanophenylsulfonyl)indole, which upon treatment with ammonia in 2-*N*,*N*-dimethylaminoethanol gave the protected phthalocyanine-2,9,16,23-tetrasulfonamides. Base cleavage of these sulfonamides yielded the free acids. A mixed condensation of 4,5-diheptylphthalonitrile and 1-(3,4-dicyanophenylsulfonyl)pyrrole gave 9,10,16,17,23,24-hexakis(1-heptyl)-2-(1-pyrrolylsulfonyl)phthalocyanine. Cleavage of the latter yielded the lithium salt of the monosulfonic acid.

Key words: sulfonic acid blocking groups, phthalocyanine sulfonic acids, 1-(3,4-dicyanophenylsulfonyl)pyrrole, 1-(3,4-dicyanophenylsulfonyl)indole.

Résumé : La réaction du chlorure de 3,4-dibromobenzènesulfonyle avec des pyrroles, l'indole, l'imidazole et un pyrazole conduit à la formation de 3,4-dibromobenzènesulfonamides. Le 1-(3,4-dibromophénylsulfonyl)pyrrole et du 1-(3,4-dibromophénylsulfonyl)indole ont été soumis à l'action du CuCN dans le DMF pour produire du 1-(3,4-dicyanophénylsulfonyl)pyrrole et du 1-(3,4-dicyanophénylsulfonyl)indole qui, par traitement avec de l'ammoniac dans le 2-*N*,*N*-diméthylaminoéthanol conduit aux phtalocyanine-2,9,16,23-tétrasulfonamides protégés. Le clivage basique de ces sulfonamides conduit aux acides libres. Une condensation mixte du 4,5-diheptylphtalonitrile et du 1-(3,4-dicyanophénylsulfonyl)pyrrole conduit à la 9,10,16,17,23,24-hexakis(1-heptyl)-2-(1-pyrrolylsulfonyl)phtalocyanine. Le clivage de cette dernière fournit le sel de lithium de l'acide monosulfonique.

Mots clés : acide sulfonique comme agents bloqueurs, acides phtalocyanine sulfoniques, 1-(3,4-dicyanophénylsulfonyl)pyrrole, 1-(3,4-dicyanophénylsulfonyl)indole.

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Introduction

Phthalocyanine (Pc) sulfonic acids have potential as photodynamic therapy (PDT) agents of cancer tumours (1, 2). Although phthalocyanine -2,9,16,23-tetrasulfonic acid is commercially available as a mixture of isomers, it has been shown that phthalocyanine-2-sulfonic acid and phthalocyanine-2,9-disulfonic acid are more effective for direct cell kill (3–9). Unfortunately, only small samples obtained by high-performance liquid chromatography (HPLC) of these unsymmetrical phthalocyanine sulfonic acids (6–8) were available for PDT studies (9, 10). Some recent attempts at preparing mono sulfonated Pcs by the oxidation of sulfides (11) or trisulfonated Pcs (12, 13) via subphthalocyanines (14, 15) gave Pcs in low yield.

One roadblock in the development of a rich variety of readily available sulfonated Pcs is the paucity of suitable blocking groups or precursors of sulfonic acids. Sulfonamides are common compounds made from sulfonyl chlorides and amines, and sulfonamides are widely used as blocking groups of amines. Cleavage (16) of sulfonamides to recover the free amines is not a trivial operation, but a large number of sophisticated procedures (17) have been used to accomplish this task, often requiring harsh conditions such as the use of concentrated acid and high temperatures (18), or reducing agents (19). In most of these procedures little attention is paid to the sulfonic acid residue remaining after the cleavage, and indeed, the sulfonic acid group is often transformed in the process (17–19). The recent description of a neopentyl ester group as a blocking group (20) of sulfonic acid seemed interesting to us but early experiments indicated it to be unsuitable for phthalocyanine synthesis.

Aryl sulfonyl chlorides have been used as blocking groups of five-membered ring aromatic amines such as imidazole, (21, 22), pyrrole (23), and indole (24), and these were cleaved under a variety of conditions, liberating both the amine and recovered sulfonic acids, and hence we directed our attention to the use of these five-membered heterocyclic amines as blocking groups of aryl sulfonic acids. It proved to be essential to develop an aryl sulfonic acid blocking group that was stable to both phthalonitrile and phthalo-

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cyanine formation and yet could be cleaved under conditions in which the sulfonic acid groups remained intact.

Results and discussion

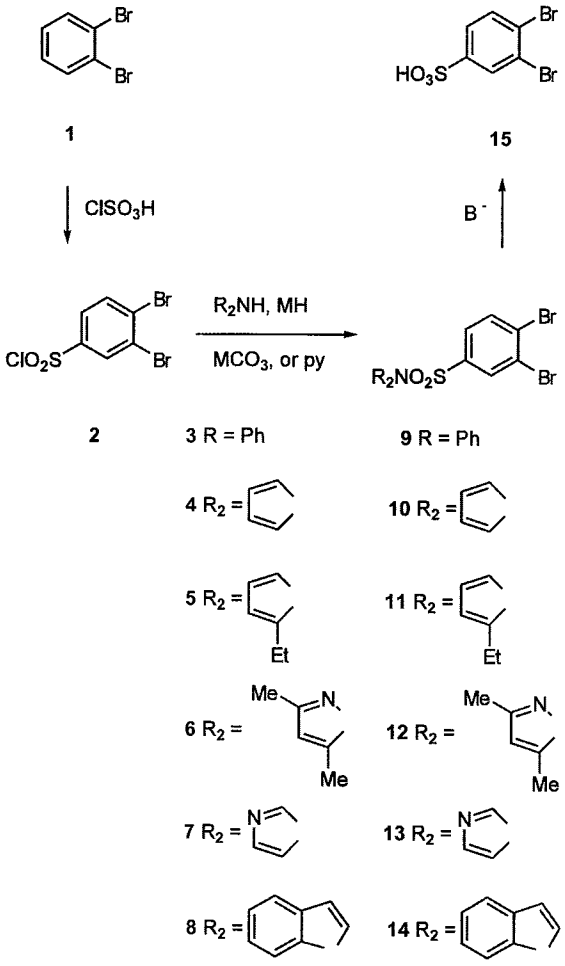
Chlorosulfonation of 1,2-dibromobenzene (**1**) readily gave 3,4-dibromobenzenesulfonyl chloride (**2**) (25). Solov'eva et al. (25) described the synthesis of a wide variety of *N,N*-dialkyl-3,4-dibromobenzenesulfonamides for use in phthalonitrile and phthalocyanine synthesis, but these sulfonamides are *not* readily cleaved to the free acids. We first decided to try to see if aryl groups such as diphenylamine (**3**) used in making *N,N*-diphenylbenzenesulfonamide would be useful in phthalocyanine synthesis and at the same time compare that analog with a series of heteroarylbenzenesulfonamides derived from pyrrole (**4**), 2-ethylpyrrole (**5**), 3,5-dimethylpyrazole (**6**), imidazole (**7**), and indole (**8**).

Treatment of sulfonyl chloride **2** with **3** in refluxing $CHCl_3$ and pyridine (py) afforded 3,4-dibromo-*N,N*-diphenylbenzenesulfonamide (**9**) in high yield. On the other hand, pyrroles **4** and **5** were first treated with NaH in tetrahydrofuran (THF) to form the sodium derivatives, which then reacted with **2** at room temperature to give 1-(3,4-dibromophenylsulfonyl)pyrrole (**10**), 1-(3,4-dibromophenylsulfonyl)-2-ethylpyrrole (**11**), and 1-(3,4-dibromophenylsulphonyl)-3,5-dimethylpyrazole (**12**) in 50, 3, and 84% yields, respectively. The reaction of imidazole (**7**) and indole (**8**) with base in $CHCl_3$ likewise gave 1-(3,4-dibromophenylsulfonyl)imidazole (**13**) and 1-(3,4- dibromophenylsulfonyl)indole (**14**) in 34 and 50% yields, respectively (Scheme 1). The low yield of **11** precluded further work on this compound, although we had envisioned that the ethyl group of **5** would afford enhanced solubility to the subsequent phthalonitrile and phthalocyanine.

At this point it was important to test the stability of sulfonamides **9**, **10**, and **12–14** to the conditions of (*i*) the Rosenmund – von Braun reaction (CuCN, 200°C, DMF) (26), (*ii*) phthalocyanine formation (MOR or NH_3), and (*iii*) sulfonamide cleavage. Sulfonamides **9**, **10**, **13**, and **14** were stable to the Rosemund – von Braun reaction, but **12** was not and was abandoned for further consideration. Sulfonamides **9**, **10**, and **14** were stable to $NaOCH_3$ at room temperature and NH_3 in 2-*N,N*-dimethylaminoethanol (DMAE), possible methods for use in phthalocyanine formation but **13** did not survive these conditions (Table 1) and was dropped as a potential candidate for Pc formation. Sulfonamides **10** and **14** were solvolyzed by $NaOCH_3$ in refluxing methanol to give 3,4-dibromophenylsulfonic acid (**15**) (27), but again **12** and **13** gave **15** simply upon stirring at room temperature as above (Table 1). All sulfonamides were stable to concentrated HCl at room temperature. Thus, only sulfonamides **9**, **10**, and **14** were suitable substrates for development for phthalocyanine synthesis.

The dibromosulfonamides **9**, **10**, and **14** were readily converted via CuCN in DMF to 3,4-dicyano-*N,N*-diphenylbenzenesulfonamide (**16**), 1-(3,4-dicyanophenylsulfonyl)pyrrole (**17**), and 1-(3,4-dicyanophenylsulfonyl)indole (**18**) in 29, 43, and 45% yields, respectively (Scheme 2). The *N,N*-diphenylsulfonamide **16** readily formed *N,N,N′,N′,N″,N″,N‴,N‴*-octaphenylphthalocyanine-2,9,16,23-tetrasulfonamide (**19**) in 50% yield when treated with lithium in DMAE at 70°C (28).

Scheme 1.



Since we had already shown that **10** and **14** are cleaved by metal alkoxides at refluxing methanol conditions, we treated **17** and **18** with NH_3 in DMAE to form *N,N′,N″,N‴*-tetrakis-(1-pyrrolyl)phthalocyanine-2,9,16,23-tetrasulfonamide (**20**) and *N,N′,N″,N‴*-tetrakis-(1-indolyl) phthalocyanine-2,9, 16,23-tetrasulfonamide (**21**) in 33 and 42% yields, respectively. Under similar conditions to the formation of **21** and **22**, but with the addition of $Zn(OAc)_2$, **17** and **18** were converted directly to *N,N′,N″,N‴*-tetrakis- (1-pyrrolyl)phthalocyanine-2,9,16, 23-tetrasulfonamide zinc(II) (**22**) and *N,N′,N″,N‴*-tetrakis-(1-indolyl)phthalocyanine-2, 9,16, 23-tetrasulfonamide zinc(II) (**23**) in 32 and 68% yields, respectively (Scheme 2).

As expected Pc **19** proved to be resistant to solvolysis, but Pc sulfonamides **20** and **21** were readily converted to phthalocyanine-2,9,16,23-tetrasulfonic acid (**24**) by treatment with lithium 2-*N,N*-dimethylaminoethoxide in DMAE (for **20**) or lithium methoxide in THF–MeOH for **21** (Scheme 2).

Early experiments towards the synthesis of a phthalocyanine monosulfonic acid via a mixed condensation of **17** and phthalonitrile gave insoluble residues difficult to separate by chromatography. To increase the solubility of the

Table 1. Synthesis of 3,4-dibromosulfonamides and their stability to bases and the Rosenmund – von Braun reaction.

Compound	Method (base/solvent)	Yield (%)	Stability at 20°C		
			NaOMe	NH_3	CuCN–DMF[a]
9	py/$CHCl_3$	65	Stable	Stable	Stable
10	NaH/THF	50	Stable[b]	Stable	Stable
12	NaH/THF	84	Unstable	Stable	—
13	Na_2CO_3/$CHCl_3$[c]	34	Unstable	Unstable	—
14	NaOH/CH_2Cl_2[d]	57	Stable[b]	Stable	Stable

[a]Refluxed.
[b]Unstable in refluxing MeOH.
[c]With MeOH.
[d]Bu_4NHSO_4 phase transfer reagent.

phthalocyanine product, **17** was condensed with 4,5-diheptylphthalonitrile (**25**) (29), as for the formation of **22**, to give 9,10,16,17,23,24-hexakis(1-heptyl)phthalocyanine-2-(*N*-pyrrolyl)sulfonamide (**26**) in 14.7% yield. Treatment of **26** with $Zn(OAc)_2$ in DMF readily afforded 9,10,16,17, 23, 24-hexakis(1-heptyl)phthalocyanine-2-(*N*-pyrrolyl)sulfonamide zinc(II) (**27**) in 86% yield. Hydrolysis of **27** with lithium methoxide in methanol afforded lithium 9,10,16,17,23,24-hexakis(1-heptyl)phthalocyanine-2-sulfonate zinc(II) (**28**) in 85% yield (Scheme 3).

Spectral data of all new compounds were consistent with their structures (see Experimental). Pcs **19–23** exhibited multiplets in their NMR spectra, consistent with the fact that they exist as mixtures of isomers. Mass spectra of all sulfonamides exhibited ions showing loss of SO_2 and peaks representing both fragments (30).

We have demonstrated that indole and pyrrole moieties can be successfully used to form sulfonamides as blocking groups in the synthesis of phthalocyanine sulfonic acids.

Experimental

All organic solvents were dried by appropriate methods and distilled before use. All reagents were freshly distilled, or were recrystallized and then dried under reduced pressure, before use. Unless otherwise noted, magnetic stirring methods under an inert atmosphere (Matheson High Purity argon) were utilized during distillation or reaction processes, and round-bottom glass vessels chosen such that the quantity of reagents and solvent did not exceed half of the available volume. Water-cooled condensers were used if reaction processes were held near, or at, reflux conditions. Melting points were determined using a Kofler hot-stage melting point apparatus and are reported uncorrected. Infrared spectroscopy was performed on either a Pye Unicam SP3-2000 or a Perkin Elmer 1310 infrared spectrophotometer and FTIR spectroscopy was performed on a Unicam Matheson 3000 FTIR spectrometer, using samples prepared as KBr discs unless otherwise noted. Mass spectral analyses were performed by Dr. B. Khouw (York University, Toronto, Ontario), Dr. R. Smith (McMaster University, Hamilton, Ontario), and Dr. R.N. Cerny (Midwest Center for Mass Spectrometry, University of Nebraska–Lincoln, Lincoln, Nebraska). HRMS were preformed by Dr. R. Smith (McMaster University, Hamilton, Ontario). Nuclear magnetic resonance (NMR) spectroscopy was performed at 295–300 K unless otherwise noted, using a Bruker ARX 400 high-field Fourier transform instrument. Chemical shifts are reported in parts per million relative to a tetramethylsilane (TMS) internal standard.

3,4-Dibromobenzenesulfonyl chloride (2)

To a flask containing 1,2-dibromobenzene (**1**) (20 g, 88.47 mmol) and dry $CHCl_3$ (120 mL), which was cooled to ca. –10°C by an ice–NaCl bath, was added chlorosulfonic acid (30 g) over 20 min. The light brown solution was stirred at room temperature for 20 h. The reaction mixture turned red during this period. The solution was refluxed for 1 h. After cooling to room temperature, the vigorously stirred reaction mixture was poured onto crushed ice (200 g). The aqueous and organic layers were separated. The former was washed with CH_2Cl_2 (100 × 2 mL). The combined organic layer was washed with aqueous $NaHCO_3$ (10%, 150 mL) followed by water until pH neutral. After drying over $MgSO_4$, and evaporating the solvent, vacuum distillation afforded a colourless solid product (120–125°C/5 mmHg (1 mmHg = 133.3 Pa), 22.7 g, 85%), mp 31–33°C (lit. (27) mp 34°C); ^1H NMR ($CDCl_3$) δ 8.28 (d, J = 1.8, 1H, H_4), 7.91 (d, J = 8.4, 1H, H_6), 7.85 (dd, J_1 = 1.8, J_2 = 8.4, 1H, H_5).

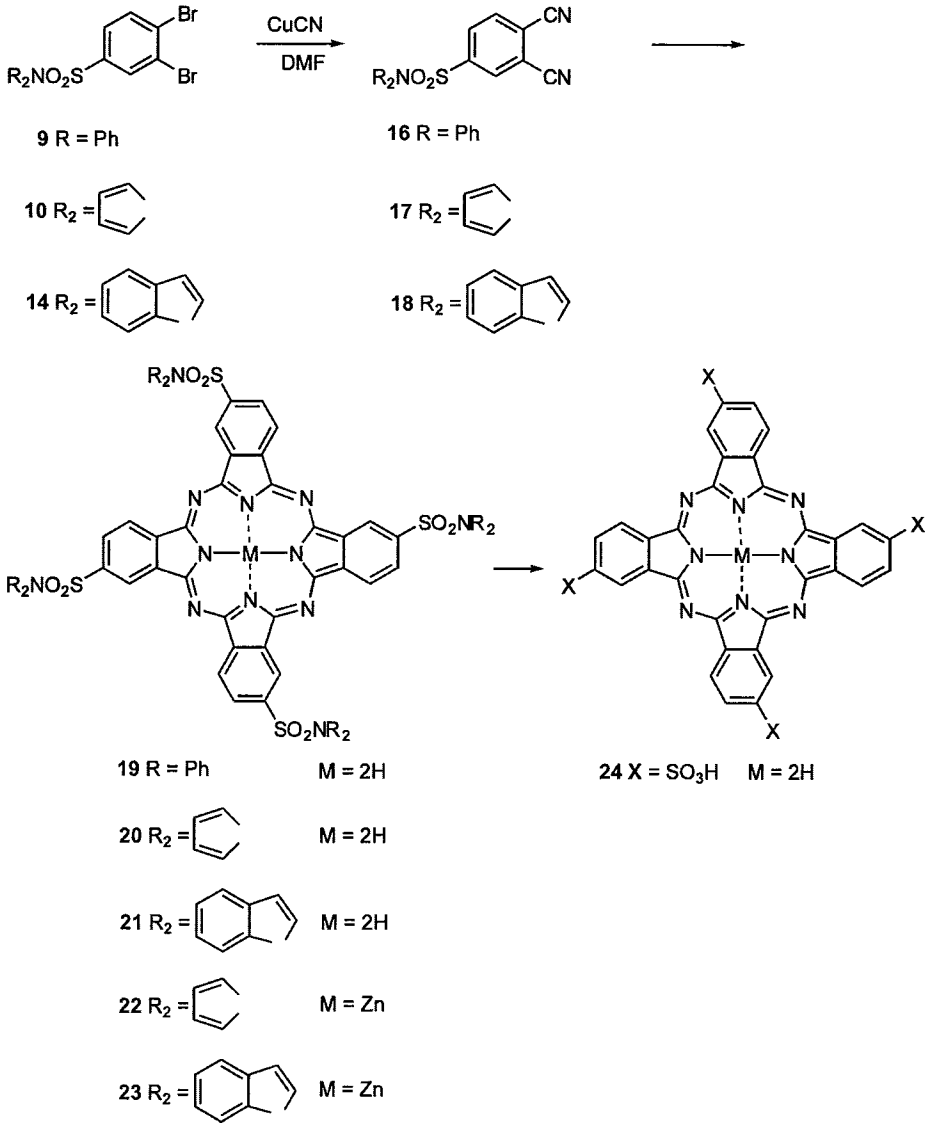
3,4-Dibromo-*N*,*N*-diphenylbenzenesulfonamide (9)

To a solution of 3,4-dibromobenzenesulfonyl chloride (**2**) (1.0 g, 3.2 mmol) in dry $CHCl_3$ (10 mL) were added diphenylamine (**3**) (0.7 g, 3.0 mmol) and pyridine (0.5 mL). The solution was refluxed for 14 h, and cooled at room temperature, washed with aqueous HCl (5%, 10 mL) and water until neutral. After drying over $MgSO_4$ and evaporating the solvent, the crude product was recrystallized from ethanol to give colourless crystalline needles (0.9 g, 65%), mp 160–161°C; IR (KBr cm^{-1}): 1957, 1886, 1589, 1449, 1446, 1351; ^1H NMR ($CDCl_3$) δ 7.93 (d, J = 2.0, 1H), 7.74 (d, J = 8.0, 1H), 7.45 (dd, J_1 = 8.0, J_2 = 2.0, 1H), 7.31 (m, 10H); MS (*m/z*, relative intensity): 469 (M^+, 15), 467 (M^+, 30), 465 (M^+, 14), 167 (100). Anal. calcd. for $C_{18}H_{13}NBr_2NO_2S$: C 46.25, H 2.78, N 3.00; found: C 46.41, H 2.66, N 2.96.

1-(3,4-Dibromophenylsulfonyl)pyrrole) (10)

To freshly distilled pyrrole (**4**) (220 mg, 30 mmol) in dry THF (5 mL), cooled to 0°C, was added NaH (300 mg, 60%

Scheme 2.

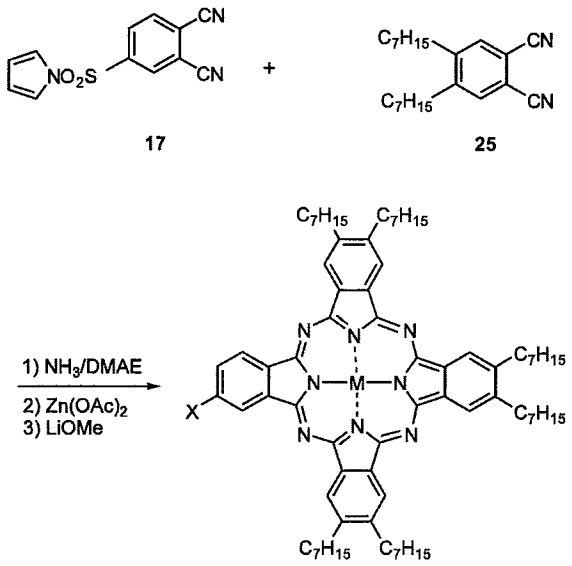


oil dispersion). 3,4-Dibromobenzenesulfonyl chloride (**2**) (1.0 g, 3.2 mmol) was added over 30 min. under Ar. After stirring at room temperature for 6 h, the brown reaction mixture was carefully poured into a saturated NH_4Cl solution (30 mL) placed in an ice bath. Ether (30 mL) was added and the aqueous layer was washed with ether (20 mL). The combined organic layer was washed with saturated NH_4Cl until neutral. After drying over $MgSO_4$ and evaporating the solvent, the crude product was recrystallized from ethanol to give colourless crystalline needles (545 mg, 50%), mp 141–142°C; IR (KBr cm^{-1}): 3075 (s, ArH), 1375 (s, SO_2N), 1186 (s, SO_2N); ^1H NMR ($CDCl_3$) δ 8.10 (d, J = 2.0, 1H), 7.77 (d, J = 8.4, 1H), 7.63 (dd, J_1 = 8.4, J_2 = 2.0, 1H), 7.16 (m, 2H), 6.36 (m, 2H); MS (*m/z*, relative intensity): 367 (M^+, 50), 365 (M^+, 95), 363 (M^+, 50), 299 (90), 235 (100). Anal. calcd. for $C_{10}H_7NBr_2$: C 32.88, H 1.92, N 3.84; found: C 33.72, H 1.87, N 3.91.

1-(3,4-Dibromophenylsulphonyl)-2-ethylpyrrole (11)

The crude product, obtained as described for **10** but using 2-ethylpyrrole (**5**), recrystallized from ethanol to give in 3% yield fine colourless crystals 78–79°C; IR (KBr cm^{-1}): 3074 (s, ArH), 1372 (s, SO_2N), 1180 (s, SO_2N); ^1H NMR ($CDCl_3$) δ 8.14 (d, J = 1.6, 1H), 8.03 (d, J = 7.8, 1H), 7.73 (dd, J_1 = 1.6, J_2 = 7.8, 1H), 7.41 (d, 1.7, 1H), 6.31 (t, 1H) (6.12 bs, 1H); 2.71 (q, J = 7.3, 2H), 1.24 (t, J = 7.3, 3H); MS (*m/z*,

Scheme 3.



relative intensity): 393 (M^+, 75), 379 (70), 315 (67), 299 (70), 80 (100). Anal. calcd. for $C_{12}H_{11}Br_2NO_2S$: C 36.64, H 2.80, N 3.56; found: C 37.27, H 2.74, N 3.52.

1-(3,4-Dibromophenylsulphonyl)-3,5-dimethylpyrazole (12)

The crude product, obtained as described for **10** but using 3,5-dimethylpyrazole (**6**), was recrystallized from ethanol twice to give 0.98 g of **12** in 84% yield, mp 145–147°C; IR (KBr cm^{-1}): 3082 (s, ArH), 1374 (s, SO_2N), 1188 (s, SO_2N); ^1H NMR ($CDCl_3$) δ 8.19 (d, J = 1.5, 1H), 7.75 (m, 2H), 5.94 (s, ^1H), 2.51 (s, 3H), 2.22 (s, 31H); MS (*m/z*, relative intensity): 394 (M^+, 10), 328 (100), 299 (30), 250 (40), 236 (50). Anal. calcd. for $C_{11}H_{10}Br_2N_2O_2S$: C 33.50, H 2.54, N 7.11; found: C 33.72, H 2.30, N 7.14.

1-(3,4-Dibromophenylsulfonyl)imidazole (13)

To a solution of (**3**) (1.0 g, 3.2 mmol) in a mixture of chloroform (5 mL) and methanol (1 mL) was added imidazole (**7**) in chloroform (2 mL) and Na_2CO_3 (1.0 g). The mixture was stirred at room temperature for 22 h, filtered, and the filtrate was washed with HCl (10%, 20 mL) and water until neutral. After drying over $MgSO_4$ and evaporating the solvent, the crude product was chromatographed with 40% ethyl acetate – hexane to give pure **13** as fine, colourless crystals (320 mg, 34%), mp 119–120°C; IR (KBr cm^{-1}): 1938 (m), 1768 (m), 1564 (s), 1464 (s), 1381 (s, SO_2N); ^1H NMR ($CDCl_3$) δ 8.19 (d, J = 2.0, 1H), 8.04 (s, 1H), 7.85 (d, J = 8.0, 1H), 7.73 (dd, J_1 = 8.0, J_2 = 2.0, 1H), 7.32 (brs, 1H); 7.16 (brs, 1H); MS (*m/z*, relative intensity): 366 (M^+, 95) 299 (100), 235 (100). Anal. calcd. for $C_9H_6Br_2N_2O_2S$: C 29.51, H 1.64, N 7.65; found: C 29.61, H 1.46, N 7.61.

1-(3,4-Dibromophenylsulfonyl)indole (14)

Ground NaOH (2.0 g) was mixed with tetrabutylammonium hydrogen sulfate (140 mg) in CH_2Cl_2 (30 mL). The reaction flask was cooled by a salt–ice bath to 0–4°C after which indole (**8**) (1.85 g, 15.8 mmol) was added. Sulfonyl chloride (**7**) (5.0 g, 15.0 mmol) was added over 30 min. and stirred for an additional 30 min. in the ice bath. The solution was stirred at room temperature for 20 h, washed with HCl (10%, 20 mL) and with water until neutral. After drying over $MgSO_4$ and evaporating the solvent, the crude product was chromographed with 20% ethyl acetate – hexane to give **14** as a fine, colourless crystals (3.1 g, 50% mp) 125–126°C; IR (KBr cm^{-1}): 3140, 3081 (s, ArH), 1376 (s, SO_2N); ^1H NMR ($CDCl_3$) δ 8.13 (d, J = 2.0, 1H), 7.99 (d, J = 8.0, 1H), 7.66 (m, 2H), 7.56 (m, 2H), 7.37 (m, 1H); 7.29 (m, 1H), 6.74 (d, J = 4.0, 1H); MS (*m/z*, relative intensity): 417 (M^+, 45), 415 (M^+, 88) 413 (M^+, 43) 116 (100). Anal. calcd. for $C_{14}H_9Br_2NO_2S$: C 40.68, H 2.18, N 3.39; found: C 40.79, H 1.95, N 3.37.

3,4-Dibromobenzenesulfonic acid (15)

Compound **13** (50 mg, 0.14 mmol) was dissolved in methanol (5 mL) and NaOMe (40 mg, 0.74 mmol) was added.

The reaction solution was stirred at room temperature for 20 h. The solvent was evaporated. The residue was dissolved in water (50 mL) and washed with ether (10 mL) followed by neutralization with aqueous HCl (36%). The solvent was evaporated, the residue recrystallized from water, and the product was further purified by ion-exchange resin (Dowex 50X8-400). Recrystallization from EtOH (80%) afforded pale, yellow needles of **15** (26 mg, 60%), mp 64–66°C (lit. (27) mp 66.5–67.5°C); ^{1}H NMR (D_2O) δ 7.99 (s, 1H), 7.74 (d, 1H), 7.52 (dd, 1H). In a similar manner **12** gave **15** in 69% yield, while **10** and **14** were cleaved in methanol at reflux to give **15** in 72 and 57% yield, respectively.

3,4-Dicyano-*N,N*-diphenylbenzenesulfonamide (16)

To a solution of **9** (1.80 g, 3.87 mmol) in dry DMF (20 mL) was added CuCN (1.80 g, 20 mmol). The reaction solution was gently refluxed for 6 h, cooled to room temperature, and CH_2Cl_2 (200 mL) was added. A fine insoluble powder precipitated overnight. The crude product was purified by chromatography with 30% ethyl acetate – hexane as eluent to give colourless, scaly crystals (395 mg, 29%), mp 185–187°C; IR (KBr cm^{-1}): 3091 (s, ArH), 2235, (s, CN), 1360 (s, SO_2N), 1186 (s, SO_2N); ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.82 (d, J = 8.0, 1H), 7.76 (d, J = 8.0), 7.19 (m, 5H), 7.07 (m, 5H); MS (*m/z*, relative intensity): 359 (M^+, 60), 168 (100). Anal. calcd. for $C_{20}H_{13}N_3O_2S$: C 66.85, H 3.62, N 11.70; found: C 66.36 H 3.33, N 11.56.

1-(3,4-Dicyanophenylsulfonyl)pyrrole (17)

In a manner identical to that of **16**, **10** gave a crude product **17**, which on flash chromatography with 30% ethyl acetate – hexanes as eluents yielded fine, colourless crystals (43%), mp 155–157°C; IR (KBr cm^{-1}): 2235 (s, CN), 1388, 1287 (s, SO_2N); ^{1}H NMR ($CDCl_3$) δ 8.22 (d, J = 1.2, 1H), 8.17 (dd, J_1 = 1.2, J_2 = 8.2, 1H), 7.97 (d, J = 8.2, 1H), 7.16 (d, J = 1.8, 2H), 6.41 (d, J = 1.8, 2H); MS (*m/z*, relative intensity): 257 (M^+, 100), 193 (70). Anal. calcd. for $C_{12}H_7N_3O_2S$: C 56.03, H 2.72, N 16.34; found: C 56.17 H 2.62, N 16.34.

1-(3,4-Dicyanophenylsulfonyl)indole (18)

As for **16** above, **14** gave a crude product, which on purification by flash chromatography with 30% ethyl acetate – hexane as eluents, yielded pale yellow, fine crystals (45%), mp 171–173°C; IR (KBr cm^{-1}): 3110 (s, ArH), 2242 (s, CN), 1391 (s, SO_2N); ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H, H_1), 8.17 (dd, J_1 = 1.6, J_2 = 8.5, 1H, H_3), 7.96 (d, J = 8.5, 1H, H_2), 7.88 (d, J = 8.0, 1H, H_4), 7.58 (d, J = 7.7, 1H, H_7), 7.51 (d, J = 3.5, 1H, H_9), 7.40 (t, J_1 = 8.0, J_2 = 7.3, 1H, H_5), 7.32 (t, J_1 = 7.3, J_2 = 8.0, 1H, H_6), 6.79 (d, J = 3.5, 1H, H_8); MS (*m/z*, relative intensity): 3.07 (M^+, 53), 116 (52), 105 (100). Anal. calcd. for $C_{16}H_9N_3O_2S$: C 62.54, H 2.93, N 1368; found: C 62.95, H 2.81, N 13.62.

***N,N,N,N,N″,N″,N‴,N‴*-Octaphenylphthalocyanine-2,9,16,23-tetrasulfonamide (19)**

Small pieces of metal lithium (30 mg, 4.3 mmol) were dissolved in DMAE (2 mL) to which **16** (100 mg, 0.28 mmol) was added. The reaction solution was stirred at 60–70°C (oil bath) for 20 h, cooled to room temperature, and the sticky blue solution was poured into a mixture of ice (5 g) and aqueous HCl (10 mL, 4 M). The precipitate was collected by filtration, and the crude product was purified using flash chromatography with 5% THF–CH_2Cl_2 as eluent to give a dark blue, fine powder of **19** (11 mg, 11%), mp >310°C. IR (KBr cm^{-1}): 1394, 1164 (s, SO_2N); UV-vis (THF) (λ_{max}): 698, 664, 636, 604, 344, 238; ^{1}H NMR (pyridine-d_5): 8.91 (s) 8.46 (s), 7.85 (m), 7.37 (m), 6.96 (s); MS (FAB$^+$, *m/z* relative intensity): 1438 (M^+). Anal. calcd. for $C_{80}H_{54}N_{12}O_8S_4$: C 66.76, H 3.75, N 11.68; found: C 66.95, H 3.66, N 10.82.

2,9,16,23-Tetrakis(1-pyrrolysulfonyl)phthalocyanine (20)

Compound **17** (200 mg, 0.78 mmol) was dissolved in *N,N*-dimethylaminoethanol (DMAE) (2 mL). As ammonia gas was bubbled through, the reaction mixture was heated to 100–110°C (sand bath) for 1 h and then refluxed for 4 h. The reaction mixture was cooled to room temperature, the solvent evaporated, and water (10 mL) was added to the resulting sticky solution. The blue precipitate was collected by filtration or centrifugation and purified by flash chromatography using 5% THF–CH_2Cl_2 as eluent to give in the first fraction phthalocyanine **20** as dark blue crystals (66 mg, 33%), mp >310°C; IR (KBr cm^{-1}): 3141 (m, ArH), 1374 (s, SO_2N), 1191 (s, SO_2N); UV-vis (THF), (λ_{max}): 696, 662, 634, 608, 394, 348; ^{1}H NMR (THF-d_8) δ 9.40, 9.38, 8.45 (m, 4H, H_3), 7.79 (m, 4H, H_4), 6.95, 5.87 (m, 8H, H_1), 6.93 (m, 8H, H_2), 664 (m, 4H, H_5); MS (FAB$^+$, *m/z*, relative intensity): 1030 (M^+). Anal. calcd. for $C_{48}H_{130}N_{12}O_8S_4$: C 55.92, H 2.91, N 16.31; found: C 55.80, H 2.90, N 15.78.

2,9,16,23-Tetrakis(1-indolylsulfonyl)phthalocyanine (21)

As for **20**, but from **18**, phthalocyanine **21** was obtained as dark, blue crystals in 42% yield, mp >310°C; IR (KBr cm^{-1}): 1387 (s, SO_2N) 1173 (s, SO_2N); UV-vis (THF) (λ_{max}): 698, 666, 634, 612, 346, 248; ^{1}H NMR ($CDCl_3$) δ: 9.56 (m, br), 8.88 (m, br), 8.70 (m, br), 8.54 (m), 8.14 (m), 8.03 (m), 7.67(m), 7.55 (m), 7.01 (m), 6.92 (m); MS (FAB$^+$, *m/z*, relative intensity): 1230 (M^+, 40), 671 (70), 539 (100). Anal. calcd. for $C_{64}H_{38}N_{12}O_8S_4$: C 62.44, H, 3.09, N 13.66; found: C 62.85, H 3.32, N 13.27.

2,9,16,23-Tetrakis(1-pyrrolylsulfonyl)phthalocyanine zinc(II) (22)

Compound **17** (200 mg, 0.78 mmol) was dissolved in 2-*N,N*-dimethylaminoethanol (DMAE) (2 mL) containing anhydrous $Zn(OAc)_2$ (200 mg). The reaction mixture was heated to 100–110°C (sand bath) and kept at that temperature for 1 h while ammonia gas was bubbled through it. The solution was refluxed for 4 h and cooled to room temperature. The solvent was evaporated and water (10 mL) was added to the resulting sticky solution. The blue precipitate was collected by filtration or centrifugation and purified by flash column chromatography using 50% THF–CH_2Cl_2 as eluent to give in the first fraction **22** as dark crystals (68 mg, 32%), mp >310°C; IR (KBr cm^{-1}): 1371 (m, SO_2N) 1167 (s, SO_2N); UV-vis (THF) (λ_{max}): 672, 610, 350, 242; ^{1}H NMR (THF-d_8) δ 9.73 (br), 7.36–8.66 (m, br), 6.59–6.90 (m, br). MS (FAB$^+$, *m/z*, relative intensity): 1093 (M^+ + 1250), 964 (20), 625 (52) 558 (100). Anal. calcd. for $C_{48}H_{128}N_{12}O_8S_4Zn$: C 52.70, H 2.56, N 15.37; found: C 52.29, H 2.80, N 14.46.

2,9,16,23-Tetrakis(1-indolylsulfonyl)phthalocyanine zinc(II) (23)

As for **22**, **18** yielded a crude product which was purified by flash chromatography by using 40% THF–benzene as eluent to give **23** as dark blue crystals (68%), mp >310°C; IR (KBr cm^{-1}): 1376 (m, SO_2N), 1173 (s, SO_2N); UV-vis (THF) (λ_{max}): 676, 610, 360, 244; ^1H NMR ($CDCl_3$) δ 9.79 (m), 9.12 (m), 8.68 (m), 8.31 (m), 8.04 (m), 7.60 (m), 7.17 (m), 6.86 (m), 6.62 (m); MS (FAB+, *m/z*, relative intensity): 1293 (M^+, 60), 1113 (50), 919 (100). Anal. calcd. for $C_{64}H_{36}N_{12}O_8S_4Zn$: C 59.40, H 2.78, N 12.99; found: C 59.19; H 3.09, N 12.65.

Phthalocyanine-2,9,16,23-tetrasulfonic acid (24)

Method A

Small pieces of metal lithium (400 mg, 58 mmol) were dissolved in DMAE (20 mL) and **20** (100 mg, 0.097 mmol) was added. The solution was stirred at 60–70°C for 30 h. An aliquot was taken and added to a mixture of water and CH_2Cl_2. The organic solution appeared colourless. The reaction mixture was cooled to room temperature, water was added, and the solvent was reduced to half volume under vacuum. After acetone (15 mL) was added, the precipitates were separated by centrifugation and washed with aqueous HCl (36%, 5 × 3 mL). Drying under high vacuum gave a dark blue powder of **24** (25, 31) (70 mg, 86%), mp >310°C; IR (KBr cm^{-1}): 3400 (s, SO_3H), 1472 (s, SO_3H); UV-vis (MeOH) (λ_{max}): 692, 656; ^1H NMR (DMSO-d_6) δ 10.19 (br, 4H), 9.71 (br, 4H), 9.53 (m, 4H), 8.60 (m, 4H); MS (electrospray, *m/z*): 834.13 $(M + 1 - H)^-$, 753.50 $(M + 1 - H\text{-}SO_3H)^-$, 416.11 $(M - 2H)^{2-}$, 277.07 $(M - 3H)^{3-}$, 250.19 $(M + 1 - SO_3H\text{-}3H)^{3-}$, 207.49 $(M - 4H)^{4-}$.

Method B

Small pieces of metal lithium (40 mg, 5.8 mmol) were dissolved in a mixture of methanol (2 mL) and THF (2 mL) to which **21** (20 mg) was added. The solution was refluxed for 20 h. TLC with 5% THF–CH_2Cl_2 as eluent showed that the starting material had disappeared. The solvent was evaporated and the residue was washed with aqueous HCl (36%, 5 × 3 mL) to give a product identical with that from method A (23 mg, 84%).

9,10,16,17,23,24-Hexakis-(1-heptyl)-2-(1-pyrrolylsulfonyl)phthalocyanine (26)

Excess 4,5-diheptylphthalonitrile (**25**) (29), prepared by our previously described method (32), (200 mg, 0.69 mmol) and **17** (20 mg, 0.078 mmol) were dissolved in DMAE (3 mL). As ammonia gas was bubbled through, the reaction mixture was heated to 100–110°C (sand bath). After 1 h, the solution was raised to reflux temperatures and refluxed for 20 h. The reaction mixture was cooled to room temperature, ice (5 g) was added to the resulting sticky solution, and the precipitates were separated by centrifugation followed by sequential washing with water (10 × 2 mL) and methanol (10 × 2 mL). The blue precipitate was collected by filtration or centrifugation and purified by flash column chromatography using CH_2Cl_2 as eluent. After evaporation of the solvent, the residue was rechromatographed with 10% EtOAc–hexanes and then 5% THF–CH_2Cl_2 as eluents. The first fraction contained two spots, which was rechromatrographed later. The second fraction was a mixture of multisulfonate Pcs (8.7 mg). The first fraction was separated by column chromatography using 50% CH_2Cl_2–hexanes to give **26** (4.5 mg, 4.7%), mp >310°C; IR (KBr cm^{-1}): 1337 (m, SO_2N), 1167 (s, SO_2N); UV-vis (THF) (λ_{max}): 714, 692, 686, 656; ^1H NMR ($CDCl_3$) δ 9.54 (s, 1H), 9.03 (s, 1H), 8.71 (m 3H), 8.50 (m, 2H), 8.25 (d, J = 7.6, 1H), 7.69 (s, 1H), 7.57 (s, Py-H, 2H), 6.42 (s, Py-H, 2H), 3.15 (m, 12H), 1.49 (m, 78H); MS (FAB+ *m/z*): 1232 (M^+ + 1). Anal. calcd. for $C_{78}H_{105}N_9O_2S$: C 76.04, H 8.53, N 10.24; found: C 76.62, H 8.85, N 9.52.

9,10,16,17,23,24-Hexakis-(1-heptyl)-2-(1-pyrrolylsulfonyl)-phthalocyanine zinc(II) (27)

Metal-free Pc **26** (10 mg, 0.008 mmol) was dissolved in a mixture of toluene (3 mL) and DMF (3 mL) to which anhydrous $Zn(OAc)_2$ was added. The reaction solution was refluxed for 24 h, the solvent evaporated, and the residue washed with water (10 mL × 2) and methanol (10 mL × 2). After drying under vacuum, the crude product was purified by column chromatography using 5% THF–CH_2Cl_2 as eluent to give **27** as a dark blue powder (9 mg, 86%), mp >310°C; IR (KBr cm^{-1}): 1339, 1166 (s, SO_2N); UV-vis (THF) (λ_{max}): 692, 666, 634, 604, 354; ^1H NMR (C_6D_6) δ 9.96 (br, 1H), 9.10–8.12 (m, 8H), 7.45 (py-H, 2H), 6.13 (py-H, 2H), 3.15 (m, 12H), 1.70 (m, 60H), 1.01(m, 18H); MS (FAB+, *m/z*, relative intensity): 1295 (M^+ + 1, 100), 736 (60). Anal. calcd. for $C_{78}H_{103}N_9O_2SZn$: C 72.33, H 7.96, N 9.74; found: C 72.12, H 8.21, N 9.14.

Lithium 9,10,16,17,23,24-hexakis-(1-heptyl)phthalocyanine-2-sulfonate zinc(II) (28)

To a solution of lithium (40 mg) in MeOH (2 mL) was added **27** (17 mg). The solution was refluxed for 24 h, the solvent evaporated, and the crude product purified by column chromatography (Si-gel, 70–230 mesh) using 40% EtOAc–hexanes and methanol as eluents to give **28** as a dark blue fine powder (14 mg, 85%), mp >310°C; IR (KBr cm^{-1}): 1110 (s, SO_3Li). UV-vis (THF) (λ_{max}): 676, 616, 346, 240 (0.47); ^1H NMR (DMSO-d_6) δ 9.60 (br, 1H), 9.31 (d, J = 8.0, 1H), 9.15 (m, 6H), 8.42 (d, J = 8.0, 1H), 1.94 (m, 6H), 1.38 (m, 60H), 0.92 (m, br, 18H); MS (FAB+, *m/z*, relative intensity): 1251 (M^+, 100).

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