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Cyclotetramerisations of sulfanyl substituted pyrazine-2,3-dicarbonitriles and phthalonitriles

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Abstract

Pyrazine-2,3-dicarbonitriles, substituted with strong to moderate electron withdrawing sulfanyl groups, have been synthesised. One of these pyrazines, substituted with two 5-methyl-1,3,4-thiadiazole-2-sulfanyl groups, has shown significant anticancer reactivity. Two phthalonitriles, substituted with thiadiazole-sulfanyl groups have been synthesised.

The reagents $Zn(OAc)_2$ and $Zn(quinoline)_2Cl_2$, dissolved in quinoline, were reacted with the above monomers to obtain zinc azaphthalocyanines and phthalocyanines. Only zinc azaphthalocyanines with moderate electron withdrawing sulfanyl groups were obtained, whereas one phthalonitrile, substituted with two 5-methyl-1,3,4-thiadiazole-2-sulfanyl groups, gave the corresponding zinc phthalocyanine. Some pyrazine-2,3-dicarbonitriles, substituted with one 2-thienyl and one sulfanyl group, gave mixtures of the corresponding zinc azaphthalocyanine constitutional isomers. New compounds were characterised by elemental analysis, UV–vis, IR, ^1H and ^{13}C NMR spectroscopies.

Keywords: Azaphthalocyanines; Zinc; Sulfanyl; Thienyl; Thiadiazole; Pyrazine

1. Introduction

Pyrazine-2,3-dicarbonitriles can be used as monomers for preparations of tetra(pyrazino)porphyrazines, also named azaphthalocyanines (AzaPcs). Several years ago we attempted [1] syntheses of four sulfanyl substituted MgAzaPcs, using the reagent magnesium propoxide in propanol. Some degree of solvent exchange was observed for the 4-methylbenzenesulfanyl and (5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl substituents whereas the aliphatic ethylsulfanyl and benzylsulfanyl substituents were stable under the same reaction conditions. One of the monomers which we prepared, i.e. 5,6-bis[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrazine-2,3-dicarbonitrile (**3a**, Scheme 1) has since been tested in a cancer screening program and shows significant anticancer activity [2a]. Therefore, further investigation of the chemical properties of **3a** is of interest, including new attempts of cyclotetramerisation. The primary goal for this work is syntheses of sulfanyl substituted ZnAzaPcs, where sulfanyl is bound to strong to moderate electron withdrawing groups.

2. Experimental

EI mass spectra were obtained on a Finnigan MAT 95XL spectrometer at 70 eV and 1.0 mA. IR spectra were obtained on a Nicolet 20-SXC FT IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 400 NMR spectrometer at 399.65 and 100.4 MHz, respectively. The pulse techniques COSY45 and HSQC (analogous to HETCOR) were used for compounds of low solubility, i.e. **4**, **5**, **6** and **9** where only the protonated carbons could be detected. HMBC was used for compound **3d**. UV–vis spectra were obtained on a Cary 50 UV–vis spectrometer. Melting points were obtained on a Büchi 530 melting point apparatus and are uncorrected. Microanalyses were performed by Analytische Laboratorien GmbH, Lindlar, Germany. The analytical

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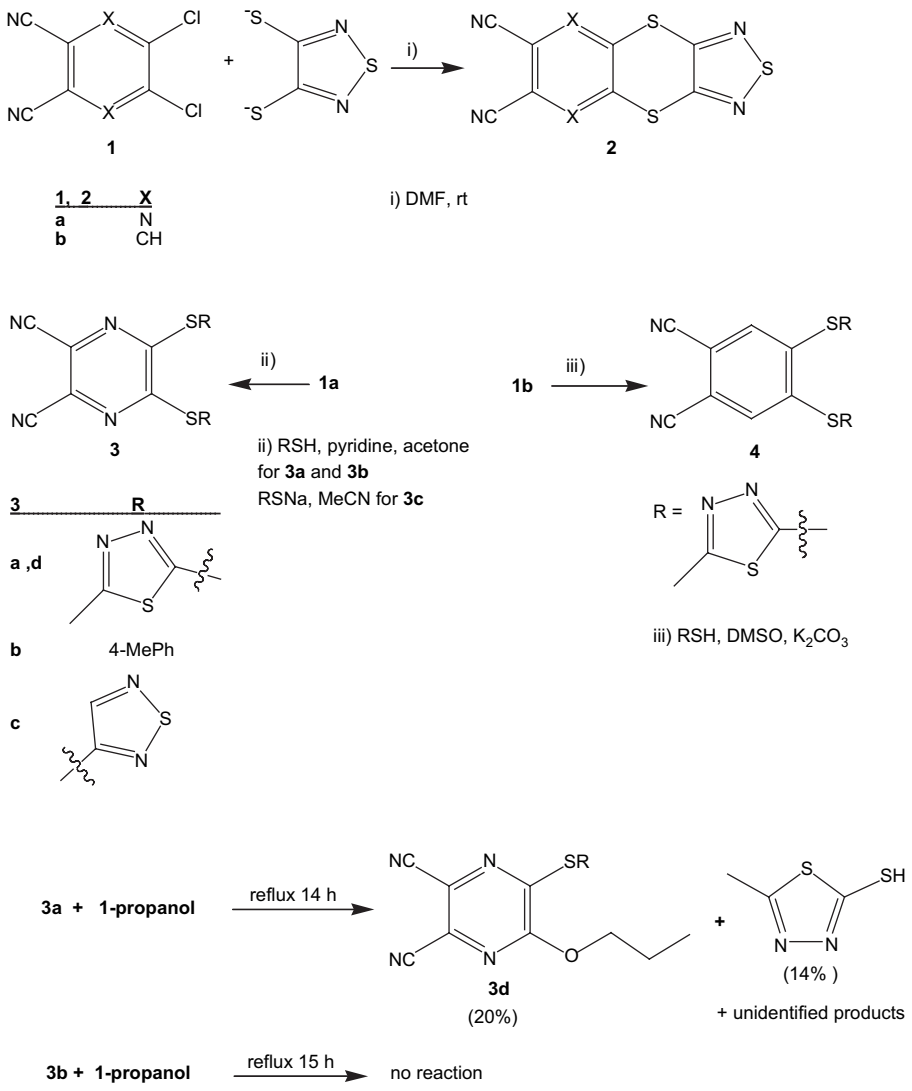


Scheme 1. Syntheses of pyrazine-dicarbonitrile and phthalonitrile precursors for cyclotetramerisations.

samples were dried at 50° C/HV prior to analyses. Merck Kieselgel 60F 254 was used for TLC and SDS silica 70–200 μm was used for column chromatography. Cellulose, Merck 2331, "Avicel" was used for chromatography of compounds **5** and **9b**. 5,6-Dichloropyrazine-2,3-dicarbonitrile (**1a**) was prepared as in [1,3], 4,5-dichloro-phthalonitrile (**1b**) as in [4] and 6-chloro-5-(2-thienyl)-2,3-pyrazine-dicarbonitrile (**7**) as in [5]. Disodium (1,2,5-thiadiazole)-3,4-dithiolate was prepared as in [6].

2.1. Synthesis of compounds *2a* and *2b*

2.1.1. General procedure

A mixture of **1** (0.4 g, 2 mmol) and disodium (1,2,5-thiadiazole)-3,4-dithiolate (0.58 g, 3 mmol) in DMF (6 ml) was stirred at ambient temperature, 2 h for **1a**, 8 h for **1b**, poured onto ice (100 g) and then extracted with DCM (3 × 50 ml). The DCM extract, which contained some DMF, was put on a silica column and eluted with DCM.

2.1.2. [1,2,5]Thiadiazolo[3′,4′:5,6][1,4]dithiino[2,3-b]-pyrazine-6,7-dicarbonitrile (*2a*)

Yield: 0.44 g (79%) of fluorescent yellow powder. Mp: 238–240 °C dec. EIMS, *m/z*, rel. int. 76 (100), 276 (M, 79.5), 277 (9.3), 278 (8.9), 279 (37.7), 280 (4.6), 281 (14.0). Calcd. for $C_8N_6S_3$: 275.93466. Found: 275.93467. IR (KBr) cm^{-1} 2239 (CN), 1572 (w), 1482 (s), 1336 (s), 1314, 1275, 1162 (s), 1078, 1042, 975, 813 (s), 768. ^{13}C NMR (DMSO-d_6) δ (ppm) 113.15 (CN), 128.89, 146.96, 154.74. UV–vis (DCM) λ_{max}, nm (ε): 405 (7400), 315 (9600), 275 (14 000), 249 (21 500).

2.1.3. [1,2,5]Thiadiazolo[3′,4′:5,6][1,4]dithiino[2,3-b]-benzene-6,7-dicarbonitrile (*2b*)

Yield: 0.42 g (77%) of fluorescent pale yellow powder. Mp: 254–257 °C dec. EIMS, *m/z*, rel. int. 274 (M, 100), 275 (14.8), 276 (14.2), 277 (4.6). Calcd. for $C_{10}H_2N_4S_3$: 273.9442. Found: 273.9441. IR (KBr) cm^{-1} 3006, 2234 (CN), 1569, 1519, 1472, 1425, 1330, 1316 (s), 1289, 1264

(s), 1221, 1122, 1037, 901 (s), 815 (s), 738, 658. ^{1}H NMR (DMF-d_7) δ (ppm) 8.68, 2H (s). ^{13}C NMR (DMF-d_7) δ (ppm) 114.60 (CN), 114.62, 133.76, 137.61, 150.65. UV–vis (DCM) λ_{max}, nm (ε): 320 (9100), 280 (29 000).

2.2. Compounds **3**

Compounds **3a**, 5,6-bis[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrazine-2,3-dicarbonitrile and **3b**, 5,6-bis(4-methylbenzenesulfanyl)pyrazine-2,3-dicarbonitrile have been reported previously [1], and 3-chloro-1,2,5-thiadiazole was prepared as in [7].

2.2.1. Synthesis of 5,6-bis[(1,2,5-thiadiazol-3-yl)-sulfanyl]pyrazine-2,3-dicarbonitrile (**3c**) [2b]

Sodium (1,2,5-thiadiazole-3-yl)thiolate was prepared as follows: sodium sulfide·nonahydrate (2.4 g, 10 mmol) was dissolved in water (5 ml) and added to a solution of 3-chloro-1,2,5-thiadiazole (0.85 g, 7 mmol) in ethanol (10 ml). The yellow/orange solution was stirred at ambient temperature for 21 h, and the solvent was removed under reduced pressure at 40 °C. The solid residue was extracted with ethanol (2 × 10 ml) and the combined ethanol extracts were taken down to dryness. The yellow solid was washed with diethyl ether and filtered. Yield: 0.84 g (86%). Mp: 260–262 °C dec. IR (KBr) cm^{-1} 3320 (s, broad), 2147 (w), 2073, 1649, 1436, 1292, 1262, 1141, 995, 970, 944, 865, 813, 792.

To a solution of **1a** (0.4 g, 2 mmol) in acetonitrile (40 ml) was added sodium(1,2,5-thiadiazol-3-yl)thiolate (0.56 g, 4 mmol), and the suspension was stirred at ambient temperature for 46 h. The solvent was removed under reduced pressure, and the residue was extracted with DCM. The DCM extract was chromatographed on silica to give compound **3c**, 0.27 g (37%). Mp: 160–165 °C. EIMS, *m/z*, rel. int. 364 (2.5), 363 (2.4), 362 (M, 13.2), 245 (100). Calcd. for $C_{10}H_2N_8S_4$: 361.9285. Found: 361.9283. IR (KBr) cm^{-1} 2239 (CN, w), 1495 (s), 1323, 1312, 1148 (s), 976, 940, 825, 786. ^{1}H NMR ($CDCl_3$) δ (ppm) 8.83 (2H, s). ^{13}C NMR ($CDCl_3$) δ (ppm) 112.27 (CN), 128.56, 144.67, 153.59, 156.57.

2.2.2. Reaction of compound **3a** with 1-propanol

A solution of **3a** (0.234 g, 0.6 mmol) in 1-propanol (15 ml) and dioxane (5 ml) was heated under reflux for 14 h. The solvents were removed, and the red/brown residue was chromatographed on silica with DCM, and finally with acetone. The DCM fractions consisted of at least four compounds, three of them in small amounts. The last DCM fraction gave 0.04 g (20%) of 5-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-6-propoxy-pyrazine-2,3-dicarbonitrile, **3d**. Mp: 115–117 °C dec. EIMS, *m/z*, rel. int. 318 (M, 6.6), 319 (2.3). Calcd. for $C_{12}H_{10}N_6OS_2$: 318.03575. Found: 318.03575. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.12 (3H, t, $J = 7.4$ Hz, CH_3–CH_2–), 1.92 (2H, m, CH_3–CH_2–), 2.91 (3H, s, thiadiazole-CH_3), 4.55 (2H, t, $J = 6.6$ Hz, O–CH_2–). ^{13}C NMR ($CDCl_3$) δ (ppm) 10.25 (*C*-3, propoxy), 15.87 (*C*H$_3$-thiadiazole), 21.70 (*C*-2, propoxy), 72.27 (*C*-1, propoxy), 112.76 (*CN*), 112.77 (*CN*), 124.29, 127.32, 149.53, 154.04, 155.92 (*C*-6, pyrazine), 169.84 (*C*-5, thiadiazole). HMBC (long range H–C correlation) was shown between the hydrogen atoms on propoxy-C-1 and pyrazine-C-6 (4.5 and 155.92). HMBC correlation also was shown between the methyl hydrogen atoms on thiadiazole and thiadiazole-C-5 (2.9 and 169.84).

From the fraction eluted with acetone, a small amount of 5-methyl-1,3,4-thiadiazole-2-thiol was isolated, 0.023 g (14%). Mp: 173–176 °C dec., lit. [8] mp: 188–189 °C, and with TLC (DCM) identical to authentic 5-methyl-1,3,4-thiadiazole-2-thiol. The rest of this fraction was a semisolid which showed five different ^{1}H NMR singlets at 2–3 ppm, and only traces of signals for the propoxy group. This mixture, apparently consisting of 5-methyl-1,3,4-thiadiazole derivatives, was not investigated any further.

2.3. Synthesis of 4,5-bis[(5-methyl-1,3,4-thiadiazol-2-yl)-sulfanyl]phthalonitrile (**4**)

To a stirred solution of **1b** (2.36 g, 12 mmol) and 2-mercapto-5-methyl-1,3,4-thiadiazole (3.3 g, 25 mmol) in DMSO (50 ml) was added powdered potassium carbonate (6 × 20 mmol, 6 × 2.6 g) during 1 h at ambient temperature. The pale yellow slurry was stirred for another 20 h, then poured on ice (200 g). The white precipitate was collected by filtration, washed thoroughly with water, triturated with water and filtered. The white solid was stirred with DCM (100 ml), filtered, stirred with methanol (150 ml) at 40 °C, filtered and finally triturated with acetone (20 ml) and filtered. Yield: 3.5 g (75%). Mp: 246–249 °C dec. EIMS, *m/z*, rel. int. 257 (M–$C_3H_3N_2S_2$, 78.5), 258 (13.8), 317 (29.0), 318 (6.9), 388 (M, 1.3), 389 (1.3). Calcd. for $C_{11}H_5N_2S_2$: 256.99557. Found: 256.99546. IR (KBr) cm^{-1} 3087 (w), 2231 (s, CN), 1570 (s), 1460 (s), 1371, 1346 (s), 1195 (s), 1015 (s), 889, 660. ^{1}H NMR (DMF-d_7) δ (ppm) 2.82 (6H, s, thiadiazole-CH_3), 8.38 (2H, s, phenyl-*H*). ^{13}C NMR (DMF-d_7) δ (ppm) 15.6 (thiadiazole-CH_3), 137.2 (protonated phenyl carbons). The origins of these signals were verified by HSQC, ^{1}H/^{13}C correlation.

2.4. Cyclotetramerisations of compounds **2**, **3** and **4**

2.4.1. General procedure

Method A: Compound **2**, **3** or **4** (1 mmol) was stirred with dry $Zn(OAc)_2$ (1 mmol) and freshly distilled quinoline (0.6 ml) under a nitrogen blanket at rt for 15 min. The stirred reaction mixture was heated under nitrogen at 160–170 °C for 15–20 min, cooled to rt, then treated with methanol (20 ml) under sonification, and filtered. The dark solid was treated with acetone and finally with a mixture of acetone and DCM (10:1). *Method B*: Compound **2**, **3** or **4** (1 mmol) was ground in a mortar with dry Zn(quinoline)$_2$Cl$_2$ [9] (1 mmol), and transferred to a round bottom flask and was stirred under a nitrogen blanket at rt for 15 min. Freshly distilled quinoline (0.6 ml) was added, and the reaction mixture was heated and purified as described for method A.

Compound **2a** was reacted by *method A*. Yield 190 mg as a dark powder. UV–vis (pyridine) λ_{max}, nm (ε): 660 (21 000), 600 (9 000), 365 (30 000).

Compound **2b** was reacted by *method B*. Yield 98 mg as a dark powder. UV–vis (pyridine) λ_{max}, nm (ε): 700 (39 000), 655 (36 000).

Compound **3a** was reacted by methods A and B, but after gas evolution, black solids, insoluble in organic solvents, were obtained.

2.5. Octakis[(4-methylbenzenesulfanyl)-(octaza)-phthalocyaninato]zinc(II) (**5**)

Method B: The crude product was dissolved in DCM and filtered through cellulose. Yield: 0.1 g (27%) of dark shiny solid. Anal. Calcd. for $C_{80}H_{56}N_{16}S_8Zn + 2H_2O$ (1599): C, 60.08; H, 3.78; N, 14.01; S, 16.04; Zn, 4.09. Found: C, 60.58; H, 3.77; N, 14.39; S, 15.41; Zn, 3.33. IR (KBr) cm^{-1} 2917 (w), 1489 (s), 1397, 1241 (s), 1152 (s), 1085, 1016, 965 (s), 843, 801 (s), 776 (s), 689 (s). ^1H NMR ($CDCl_3$) δ (ppm) 2.50 (24H, br s, CH_3), 7.37 (16H, br d, J = ca. 5 Hz, *H*-phenyl), 7.84 (16H, br d, J = ca. 5 Hz, *H*-phenyl). ^{13}C NMR ($CDCl_3$) δ (ppm) 21.13 (*C*H$_3$), 130.3 (*C*H-phenyl), 134.1 (*C*H-phenyl). These signals were observed by HSQC, coupled signals are 2.50/21.13, 7.35/130.3, 7.84/134.1. UV–vis (pyridine) λ_{max}, nm (ε): 665 (171 000), 605 (36 000), 390 (103 000).

2.6. Octakis{[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-phthalocyaninato}zinc(II) (**6**)

Method A: A dark powder was obtained. Yield: 0.3 g (approx. 74%). Anal. Calcd. for $C_{56}H_{32}N_{24}S_{16}Zn + 2H_2O + Zn$ (1721): C, 39.09; H, 2.11; N, 19.53; S, 29.81; Zn, 7.60. Found: C, 39.18; H, 2.70; N, 18.44; S, 27.76; Zn, 7.38. IR (KBr) cm^{-1} 3073 (w), 1593, 1531, 1401, 1370 (s), 1337, 1280, 1184, 1109 (s), 1045 (s), 937, 744 (s), 772. ^1H NMR (pyridine-d_5) δ (ppm) 2.61 (CH_3, weak, br s), 2.71 (CH_3, strong, sharp s). ^{13}C NMR (pyridine-d_5) δ (ppm) 15.6 (*C*H$_3$), 15.8 (*C*H$_3$). HSQC analysis showed signal correlations: 2.61/15.6, 2.71/15.8. UV–vis (pyridine) λ_{max}, nm (ε): 705 (81 000), 665 (35 000), 370 (56 000).

Some of the product, 0.05 g, was chromatographed on silica with DMF. The green eluate was diluted with ice (200 g) and left at ambient temperature for four days. The finely divided green precipitate was filtered and washed with water, diethyl ether and acetone, and 0.038 g (56%) was obtained. Anal. Calcd. for $C_{56}H_{32}N_{24}S_{16}Zn + 2H_2O + Zn$ (1721): C, 39.09; H, 2.11; N, 19.53; S, 29.81; Zn, 7.60. Found: C, 39.39; H, 2.18; N, 19.11; S, 27.05; Zn, 6.36. UV–vis (pyridine) λ_{max}, nm (ε): 705 (90 000), 665 (37 000), 375 (60 000).

2.7. Synthesis of compounds **8**

5-Chloro-6-(thien-2-yl)pyrazine-2,3-dicarbonitrile, **7**, was prepared as reported [5] and purified by chromatography on silica with DCM. Yield: 61%. Mp: 124–125 °C, lit. [5] mp: 115–117 °C. ^1H NMR ($CDCl_3$) δ (ppm) 7.29 (1H, dd, J = 4 and 5 Hz, *H-4* thiophene), 7.86 (1H, dd, J = 5 and 1 Hz, *H-3* thiophene), 8.47 (1H, dd, J = 4 and 1 Hz, *H-5*, thiophene). ^{13}C NMR ($CDCl_3$) δ (ppm) 112.32 (CN), 112.39 (CN), 127.25, 129.69, 130.64 (*C-4* thiophene), 135.25 (*C-3* thiophene), 136.51 (*C-5* thiophene), 146.28, 149.93.

2.8. General procedure for preparation of compounds **8**

Compound **7** (0.49 g, 2 mmol) and either 5-methyl-1,3,4-thiadiazole-2-thiol, 4-methylbenzenethiol or 4-chlorobenzenemethanethiol (2 mmol) were dissolved in acetone (20 ml). Pyridine (0.16 g, 2 mmol) was added, and the reaction mixture was stirred at ambient temperature for 3 h. The solvent was removed under reduced pressure, water (20 ml) was added, and the water insoluble product was chromatographed on silica with DCM.

2.8.1. 5-(5-Methyl-1,3,4-thiadiazol-2-yl)sulfanyl-6-(thien-2-yl)-pyrazine-2,3-dicarbonitrile (**8a**)

Yield: 0.64 g (93%) of yellow fluorescent microcrystals. Mp: 183–185 °C. EIMS, *m/z*, rel. int. 342 (M, 100), 343 (15.5), 344 (11.7). Calcd. for $C_{13}H_6N_6S_3$: 341.98165. Found: 341.98165. IR (KBr) cm^{-1} 3070 (w), 2237 (CN, w), 1497 (s), 1415 (s), 1341, 1270, 1235, 1227, 1148, 1079, 1048, 911, 851, 733. ^1H NMR (DMSO-d_6) δ (ppm) 2.85 (3H, s, CH_3), 7.40 (1H, dd, J = 4 Hz and J = 5 Hz, *H4*-thiophene), 8.15 (1H, d, J = 5 Hz, *H5*-thiophene), 8.21 (1H, d, J = 4 Hz, *H3*-thiophene). ^{13}C NMR (DMSO-d_6) δ (ppm) 18.08, 116.04 (*CN*), 116.13 (*CN*), 130.19, 131.33, 132.19, 135.39, 138.04, 139.38, 149.95, 155.1, 157.34, 173.37. UV–vis (DCM) λ_{max}, nm (ε): 376 (18 000), 355 (20 000), 290 (13 000), 270 (13 000).

2.8.2. 5-(4-Methylbenzenesulfanyl)-6-(thien-2-yl)pyrazine-2,3-dicarbonitrile (**8b**)

Yield: 0.61 g (92%) of yellow fluorescent microcrystals. Mp: 226–227 °C. EIMS, *m/z*, rel. int. 333 (86.6), 334 (M, 100), 335 (28.3), 336 (10.7). Calcd. for $C_{17}H_{10}N_4S_2$: 334.03469. Found: 334.03512. IR (KBr) cm^{-1} 3100(w), 2231 (CN, w), 1488 (s), 1418 (s), 1326 (s), 1264, 1226, 1142, 1049, 907, 848, 809, 738. ^1H NMR ($CDCl_3$) δ (ppm) 2.48 (3H, s, CH_3), 7.31 (1H, m, *H4*-thiophene), 7.33 (2H, d, J = ca. 8 Hz, phenyl partly overlap with *H4*-thiophene), 7.42 (2H, d, J = 8 Hz, phenyl), 7.78 (1H, dd, J = 1 Hz and J = 5 Hz, *H5*-thiophene), 8.33 (1H, dd, J = 1 Hz and J = 4 Hz, *H3*-thiophene). ^{13}C NMR ($CDCl_3$) δ (ppm) 21.47, 113.16 (*CN*), 121.74, 126.94, 127.86, 128.95, 130.74, 132.66, 134.11, 135.48, 138.31, 141.364, 147.318, 158.85. UV–vis (DCM) λ_{max}, nm (ε): 385 (18 000), 345 (23 000), 275 (15 000).

2.8.3. 5-(4-Chlorobenzenemethanesulfanyl)-6-(thien-2-yl)-pyrazine-2,3-dicarbonitrile (**8c**)

Yield: 0.69 g (93%) of yellow fluorescent microcrystals. Mp: 153–157 °C dec. EIMS, *m/z*, rel. int. 125 (100), 126 (6.8), 127 (29.3), 368 (M, 15.2), 369 (3.3), 370 (6.4). Calcd. for $C_{17}H_9ClN_4S_2$: 367.99572. Found: 367.99613. IR (KBr)

cm^{-1} 3098 (w), 2232 (*CN*, w), 1487 (s), 1419, 1410, 1327, 1267, 1241, 1089, 1072, 910, 847, 738, 721. ^{1}H NMR ($CDCl_3$) δ (ppm) 4.48 (2H, s, C*H*$_2$), 7.22 (1H, dd, $J = 4$ Hz and $J = 5$ Hz, *H4*-thiophene), 7.32 (2H, d, $J = 8.7$ Hz, *H*-Ph), 7.39 (2H, d, $J = 8.9$ Hz, *H*-Ph), 7.72 (1H, dd, $J = 5$ Hz and $J = 1$ Hz, *H5*-thiophene), 8.47 (1H, dd, $J = 4$ Hz and $J = 1$ Hz, *H3*-thiophene). ^{13}C NMR ($CDCl_3$) δ (ppm) 35.65, 113.11 (*CN*), 113.20 (*CN*), 128.93, 129.01, 130.82, 132.72, 133.19, 134.09, 134.29, 138.13, 148.07, 157.17. UV–vis (DCM) λ_{max}, nm (ε): 385 (15 200), 345 (17 500), 285 (15 300).

2.9. Cyclotetramerisations of compounds **8**

Methods A and B were used as described for cyclisations of compounds **2**, **3** and **4**.

2.9.1. [Tetra(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl-tetra-(thien-2-yl)-(octazaphthalocyaninato)]zinc(II) (**9a**)

Method B. Yield of a dark powder, 0.1 g (30%). Anal. Calcd. for $C_{52}H_{24}N_{24}S_{12}Zn + 2H_2O$ (1471): C, 42.46; H, 1.92; N, 22.85; S, 26.15; Zn, 4.44. Found: C, 44.39; H, 2.23; N, 22.40; S, 24.63; Zn, 3.62. IR (KBr) cm^{-1} 3073 (w), 1515, 1416 (s), 1358, 1230 (s), 1195 (s), 1092, 920 (s), 854, 775, 709 (s), 694 (s). ^{1}H NMR (pyridine-d_5) δ (ppm) 2.94 (H, br s, C*H*$_3$-thiadiazole), 3.39 (H, br s, C*H*$_3$-thiadiazole), 7.64 (H, br s, *H4*-thiophene), 8.18 (H, br s, *H*-thiophene), 8.24 (H, br s, *H*-thiophene). Two methyl signals could arise from different constitutional isomers of **9a** or from aggregation of part of the sample. ^{13}C NMR (pyridine-d_5) δ (ppm) 15.8 (*C*H$_3$), 16.9 (*C*H$_3$), 124.1. HSQC correlation showed that the following ^{1}H and ^{13}C signals are coupled: 2.94/15.8, 3.39/16.9, 7.64/124.1. UV–vis (pyridine) λ_{max}, nm (ε): 675 (153 000), 610 (37 000), 395 (117 000).

Some of the product, 0.05 g, was chromatographed on silica with pyridine. A dark solid of 0.028 g (16%) was obtained. Anal. Calcd. for $C_{52}H_{24}N_{24}S_{12}Zn + 2H_2O$ (1471): C, 42.46; H, 1.92; N, 22.85; S, 26.15; Zn, 4.44. Found: C, 44.90; H, 2.10; N, 23.39; S, 22.39; Zn, 3.97. UV–vis (pyridine) λ_{max}, nm (ε): 675 (183 000), 610 (43 000), 395 (143 000).

2.9.2. [Tetra(4-methylbenzene)sulfanyl-tetra(thien-2-yl)-(octazaphthalocyaninato)]zinc(II) (**9b**)

Method A. The crude product was chromatographed on silica with pyridine. Yield of a dark powder, 0.18 g (53%). Anal. Calcd. for $C_{68}H_{40}N_{16}S_8Zn + 2H_2O$ (1439): C, 56.75; H, 3.08; N, 15.57; S, 17.82; Zn, 4.54. Found: C, 56.35; H, 3.13; N, 15.56; S, 16.86; Zn, 4.52. IR (KBr) cm^{-1} 3093 (w), 1490, 1282 (s), 1230, 1181, 1032, 920 (s), 803 (s), 775 (s), 695 (s). ^{1}H NMR (pyridine-d_5) δ (ppm): The tolyl signals were identified by COSY. *Isomer 1*: 2.67 (3H, s, C*H*$_3$), 7.67 (*H-3*, *H-5*), 8.18 (*H-2*, *H-6*). *Isomer 2*: 2.39 (3H, s, C*H*$_3$), 7.41 (*H-3*, *H-5*), 8.13 (*H-2*, *H-6*). ^{13}C NMR (pyridine-d_5) δ (ppm) – The tolyl system – ;*Isomer 1*: 22.0 (*C*H$_3$), 131.0 (*C-3*, *C-5*), 136.8 (*C-2*, *C-6*). *Isomer 2*: 21.5 (*C*H$_3$), 130.9 (*C-3*, *C-5*), 134.8 (*C-2*, *C-6*). HSQC analysis of the 2-thienyl system – ^{1}H/^{13}C δ (ppm): 8.87/131.9, 8.81/131.6, 8.63/131.9, 8.24/132.1, 7.88/132.0, 7.64/129.3. UV–vis (pyridine) λ_{max}, nm (ε): 675 (161 000), 610 (40 000), 395 (116 000).

2.9.3. [Tetra(4-chlorobenzyl-1-yl)sulfanyl-tetra(thien-2-yl)-(octazaphthalocyaninato)]zinc(II) (**9c**)

Method A. Yield of a dark powder, 0.18 g (48%). Anal. Calcd. for $C_{68}H_{36}Cl_4N_{16}S_8Zn + 2H_2O$ (1577): C, 51.79; H, 2.56; Cl, 8.99; N, 14.21; S, 16.27; Zn, 4.15. Found: C, 51.95; H, 3.23; Cl, 7.77; N, 14.29; S, 15.05; Zn, 4.70. IR (KBr) cm^{-1} 1488, 1421, 1281, 1254, 1197, 1126, 1090, 1013, 923, 855, 774, 695. ^{1}H NMR (pyridine-d_5) δ (ppm): 4.88 (8H, s, *CH*$_2$), 7.37 (4H, m, *H4*-thiophene), 7.59 (8H, m, overlap phenyl and pyridine), 7.69 (8H, m, phenyl), 7.78 (4H, m, *H5*-thiophene), 8.58 (4H, m, *H3*-thiophene). ^{13}C NMR (pyridine-d_5) δ (ppm) 128.7, 131.2, 132.7, 133.4. HSQC correlation for coupling of ^{1}H/^{13}C signals: 7.37/128.7, 7.59/128.7, 7.69/128.7, 7.78/131.2, 8.58/133.4. UV–vis (pyridine) λ_{max}, nm (ε): 670 (223 000), 605 (47 000), 395 (145 000).

3. Results and discussion

In the present study we explore cyclotetramerisations of pyrazine-2,3-dicarbonitriles substituted with sulfanyl bound to strong to moderate electron withdrawing groups. In order to compare cyclisations of thiadiazole-substituted pyrazine-dicarbonitriles and phthalonitriles, two substituted phthalonitriles also were prepared. The phthalonitriles are expected to be more stable, and undergo cyclisations more easily, than the pyrazines. The syntheses of pyrazine and phthalonitrile monomers are outlined in Scheme 1.

3.1. Syntheses of symmetrical monomers

The strongest electron withdrawing group available to us, 1,2,5-thiadiazole, was used to prepare sulfanyl substituted monomers **2**. 5,6-Dichloropyrazine-2,3-dicarbonitrile, **1a**, was reacted with disodium 1,2,5-thiadiazole-3,4-dithiolate dissolved in DMF, and the tricyclic compound **2a**, a high melting yellow fluorescent powder, was obtained in 79% yield. The condensed phthalonitrile **2b**, a high melting fluorescent powder, was obtained in similar yield.

The symmetrically substituted pyrazines **3** were obtained from **1a** and pyridinium thiolates. Compounds **3a** and **3b** have been reported by us [1], but **3c**, which shows somewhat less anticancer activity than **3a** [2a], was prepared by us [2b], but has not been reported earlier. The synthesis of **3c**, as presented here, has not been optimized since we see no potential use for **3c**. Phthalonitrile **4**, which is practically insoluble in most organic solvents, was obtained from **1b** and potassium (5-methyl-1,3,4-thiadiazole)-2-thiolate.

3.2. Cyclotetramerisations of symmetrical monomers

The most common reaction condition for cyclotetramerisations, i.e. suspension of a metal alkoxide in alcohol, was found unsuitable for reactions of arylsulfanyl or heteroarylsulfanyl substituted pyrazine-2,3-dicarbonitriles due to substituent

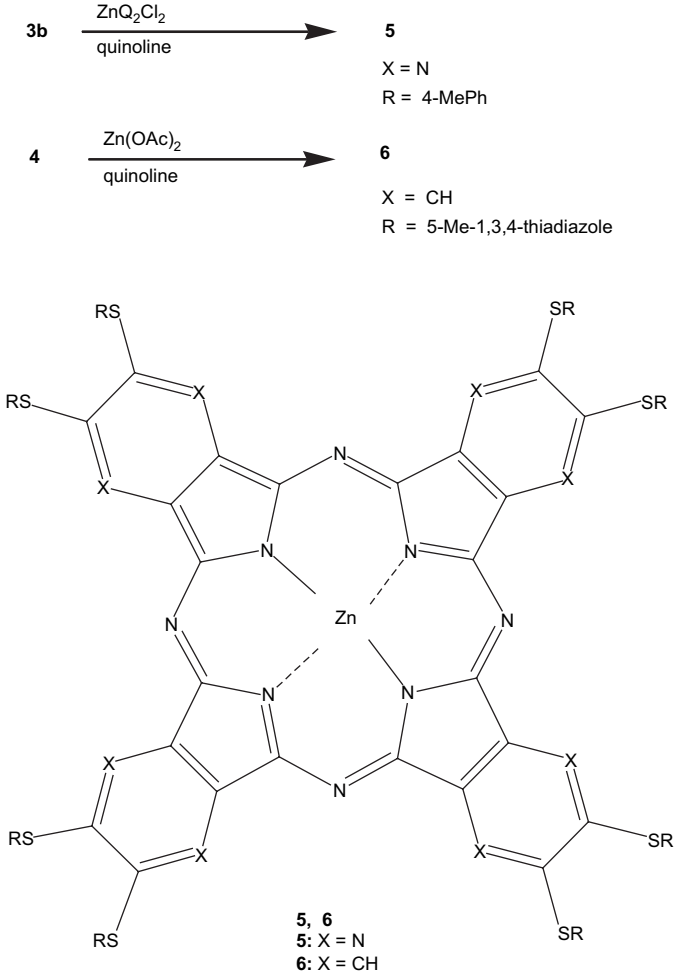
exchange with the solvent [1]. The obvious reason seems to be stability of the leaving groups. Recently we met similar problems with pyrazole- and imidazole-substituted pyrazine-2,3-dicarbonitriles, and we found the complex Zn(quinoline)$_2$ Cl$_2$, (ZnQ_2Cl_2), as a useful reagent for preparing nitrogen substituted zinc azaphthalocyanines [9]. Temperatures between 170 and 190 °C were used for those reactions. However, when we tried using the same temperatures for reactions of ZnQ_2Cl_2 with compounds **2**, **3** and **4**, mp 200–250 °C, dry reaction mixtures were obtained with only a trace of green colour. Reaction temperatures above 200 °C led to extensive decomposition for most of these compounds. The best results were obtained when the monomer was reacted with ZnQ_2Cl_2 in the presence of a small amount of quinoline at approximately 170 °C. The known combination of Zn(OAc)$_2$ and quinoline (method A) was compared with ZnQ_2Cl_2 and quinoline (method B) for cyclotetramerisations of compounds **2**. However, both attempts led to much decomposition in addition to impure zinc complexes. The UV–vis absorption of the product from **2a** has λ_{max} 660 nm (21 000) and the product from **2b** has λ_{max} 700 nm (39 000). The low solubility of these products made purification difficult, and since our main purpose was to get an indication of how suitable compounds **2** are for cyclotetramerisations, we did not pursue these reactions any further.

We had observed substantial exchange of the methylthiadiazolesulfanyl substituents of **3a** upon reaction with magnesium propoxide in propanol [1]. Therefore, in order to test the stability of **3a** towards a weaker nucleophile, a solution of **3a** in 1-propanol was heated under reflux for 14 h. The solution turned orange in less than 1 h, but there was no further change in colour. The reaction mixture was chromatographed on silica with DCM and finally with acetone. The only product that could be identified from the DCM fractions was 5-(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl-6-propoxypyrazine-2,3-dicarbonitrile, **3d** (20%). A small amount (14%) of 5-methyl-1,3,4-thiadiazole-2-thiol was isolated from the acetone fraction. This fraction contained several additional compounds, but TLC showed no residual **3a**. ^{1}H NMR analysis showed five proton singlets at 2–3 ppm in the area for thiadiazole methyl protons. However, further investigation of this product mixture was of little use since decomposition was obvious after about one day. A solution of compound **3b** in 1-propanol was similarly heated under reflux for 15 h, but no reaction was observed.

Attempted cyclisations of compound **3a** by methods A and B gave black tarry products in addition to gas evolution from the reaction mixtures.

The cyclotetramerisations of compounds **3b** and **4** are outlined in Scheme 2.

The 4-methylphenyl sulfanyl group of compound **3b** is less electron withdrawing than the thiadiazole-sulfanyl groups of **2a** and **3a**, and apparently sufficiently stable so that ZnAzaPc **5** (27%), UV–vis λ_{max} 665 nm ($\varepsilon = 171\,000$), was obtained by method B. Phthalonitrile **4** gave ZnPc **6** by method A. The UV–vis spectrum had the expected λ_{max} at 705 nm ($\varepsilon = 81\,000$), i.e. red shifted by 40 nm compared to compound **5**. The relatively low-value and almost twice the expected



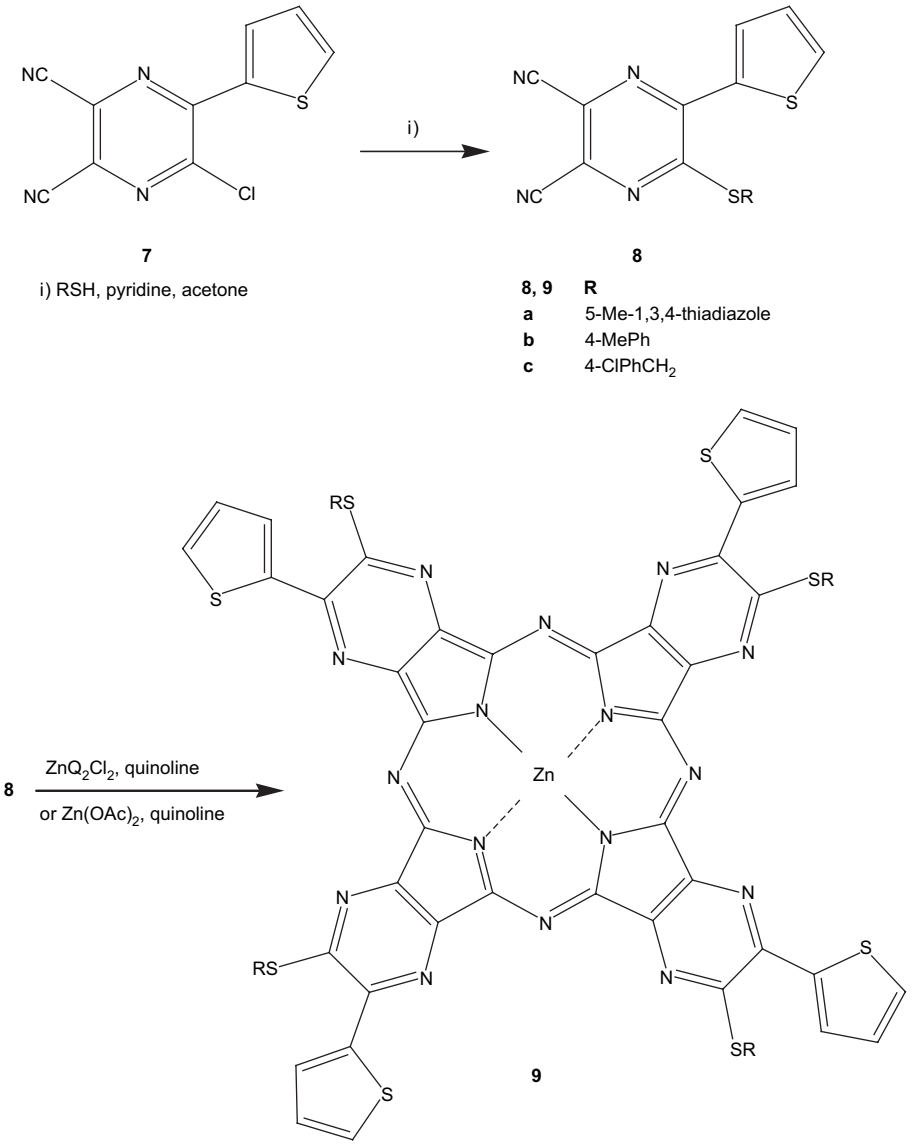
Scheme 2. Synthesis of zinc azaphthalocyanines **5** and zinc phthalocyanine **6**.

content of zinc indicate that compound **6** was not pure. Even so, the fact that **6** was formed from the phthalonitrile **4** confirms that the 5-methyl-1,3,4-thiadiazole-2-sulfanyl group is extremely labile when bound to pyrazine-dicarbonitrile, but more stable as a phthalonitrile substituent.

3.3. Syntheses and cyclotetramerisations of unsymmetrical monomers

The synthesis of unsymmetrically substituted pyrazine-dicarbonitriles **8a–c** is outlined in Scheme 3. Compounds **8a–c** were obtained from reactions of the known [5] compound **7**, 5-chloro-6-(thien-2-yl)pyrazine-2,3-dicarbonitrile, and pyridinium salts of thiols.

Compounds **8** are substituted with one 2-thienyl group in addition to 5-methyl-1,3,4-thiadiazole-sulfanyl, (**8a**), 4-methylphenyl-sulfanyl, (**8b**), or 4-chlorophenylmethyl-sulfanyl, (**8c**). Thus, compound **8c** has the least electron-attracting sulfanyl substituent of this series. There are several reasons for incorporating 2-thienyl in compounds **8**. The carbon–carbon bond between pyrazine and 2-thienyl certainly will be stable during cyclotetramerisations. The observed 15 nm red shift of some 2-thienyl substituted ZnAzaPcs [9] is expected for compounds



Scheme 3. Pyrazine-dicarbonitrile precursors and Zn-azaphthalocyanines **9** with 2-thienyl and sulfanyl substituents. One constitutional isomer of compounds **9** is shown.

9 as well, and would be of value for potential use in photodynamic therapy (PDT). Finally, the electron donating 2-thienyl group of **8** might stabilise the electron deficient pyrazine system during cyclotetramerisations. The ZnAzaPcs **9a–c** were obtained from reactions of **8** with either $Zn(OAc)_2$ and quinoline (method A) or with ZnQ_2Cl_2 and quinoline (method B). All the sulfanyl groups apparently were somewhat unstable during those reaction conditions, since compounds **9** contain slightly lower amounts of sulfur than calculated. However, the UV–vis spectra of compounds **9**, λ_{max} 670–675 nm ($\varepsilon = 150\,000$–$200\,000$), leave little doubt as to the identity of these compounds.

*3.4. NMR results for ZnAzaPcs **5** and **9** and ZnPc **6***

Due to low solubility of these macrocycles, the NMR studies were limited to observations of proton signals, and signals for the corresponding protonated carbons. The use of NMR pulse techniques COSY45 and HSQC allowed complete identifications of all ^{1}H signals and corresponding ^{13}C NMR signals for the prepared macrocycles.

The expected methyl and aromatic proton signals were found for **5** dissolved in deuterated chloroform, and the corresponding carbon signals were observed by HSQC analysis. The low solubility in organic solvents of compounds **6** and **9**, limited the choice of solvent to pyridine-d_5. ZnPc **6**, with an excess content of zinc, has one strong, and one weak set of the expected methyl proton and carbon signals. The expected benzene CH proton signals could not be found. One reason would be the strong pyridine signals and satellites, at 7–7.5 ppm, which practically cover other weaker signals in this region. Furthermore, the aromatic CH proton signals are expected to be weaker than normal, due to shorter relaxation times, caused by the closer proximity to zinc of

CH than the tolyl methyl group. Strong additional proton signals at 8.5–9.0 ppm, around the pyridine signal, might indicate some complexation of excess zinc present in this compound.

The unsymmetrically substituted ZnAzaPcs **9** are mixtures of four constitutional isomers, and might show multiple signals for each methyl group or protonated aromatic carbon. Unfortunately some aromatic proton signals for compounds **9** were hidden under the strong pyridine signals. Compound **9a** has two sets of about equally strong methyl signals, $^{1}H/^{13}C$ at 2.94/15.8 and 3.39/16.9 ppm. This can be attributed to either two constitutional isomers, or to aggregation of about half of the molecules, but certainly not to impurities in the sample. Only one set of thienyl signals was found at 7.64/124.1 ppm; 8.18 and 8.24 ppm, the latter two could not be correlated to any carbon signals. The most shielded proton signal at 7.64 ppm certainly belongs to H-4 of thienyl, whereas the H-3 and H-5 signals could be either at 8.18 or 8.24 ppm. Compound **9b** gives two sets of signals for the 4-methylphenyl system, and complete identification of the signals was made by use of COSY45 and HSQC. The 2-thienyl system also gives two sets of signals, where the H-4 signals were identified as the most shielded ones, and the signals at higher parts per million could be associated with either H-3 or H-5. The origin of two sets of signals for compound **9b** could either be different constitutional isomers or partial aggregation. As opposed to **9a** and **9b**, compound **9c** has only one set of signals for both the 4-chlorophenylmethyl system and for the 2-thienyl system. The benzylic methylene group will make this system less rigid, and aggregation will be less likely for compound **9c**. In view of this we suggest that the two sets of NMR signals for compounds **9a** and **9b** are caused by partial aggregation of the samples.

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