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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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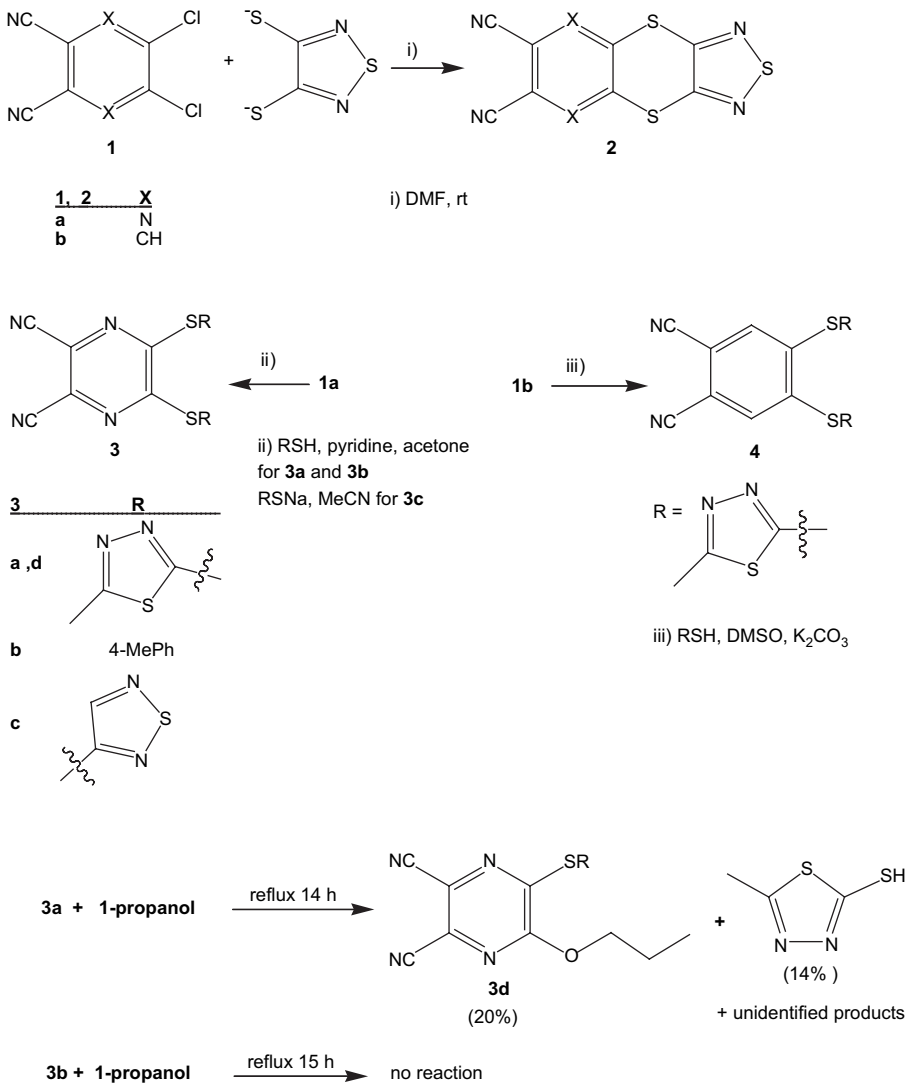

Scheme 1. Syntheses of pyrazine-dicarbonitrile and phthalonitrile precursors for cyclotetramerisations.

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