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Short communication

S_NAr nucleophilic substitution of 1,9-dihalodipyrrins by S- and N-nucleophiles. Synthesis of new dipyrrins bearing pendant substituents☆

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ABSTRACT

5-Aryl-1,9-dichlorodipyrrins react with a series of S- and N- nucleophiles (both alkyl- and aryl- ones). Reagents with mercapto group yield product of double nucleophilic substitution of 5-pheny-1,9-dichlorodipyrrin, i.e. the respective 1,9-bis(alkyl-of arylthio)dipyrrin. On the contrary, 5-(4-nitrophenyl)-1,9-dichlorodipyrrin causes disulfides formation from the S-aliphatic substrates, whereas nucleophilic substitution remains the main path of the reaction for S-aryl ones. The reaction of N-Alkyl nucleophiles proceeds as mono-substitution. UV–Vis spectra feature a batochromic shift for bis-S-substituted products and a hypsochromic shift for mono-N-substituted ones, with respect to the starting dichlrorides.

1. Introduction

Dipyrrins (DPs) and their metal complexes [1,2] are attracting much of researchers attention, in spite of being somewhat in the shade of their boron derivatives (BODIPY) [3–6]. DP-metal complexes have been studied to be applied in dye-sensitized solar cells [7–9], catalysis [10] and as new fluorescent dyes [11]. They have been investigated as prospective substances of anti-tumor activities [12–14] Besides, DP-metal complexes can govern the geometry and composition of supramolecular aggregates [15,16] depending on both the mode of metal coordination and the geometry and steric demand of a DP ligand [17–19]. These factors also control the formation of metal-organic frameworks [20,21]. Extensive studies focused on the substituents' influence on the energies of the ground and excited states manifested in their redox properties and optical spectra.[22]. Additional substituents at the periphery of DP, bearing extra complexing groups, had also been shown to change complexes properties dramatically [23,24].

Known synthetic pathways to substituted DPs include condensation of substituted pyrroles [25–32]. Also, a series of methods such as electrophilic substitution, oxidative couplings, a direct H-substitution and halogenation-Pd-catalyzed cross coupling sequences have been shown to work for BODIPY derivatization [33,34] as well as conversion of a methyl group adjacent to the electronegative heterocycle to a double bond and nucleophilic substitution at the BODIPY core [5]. Some examples of these methods applied to non-borylated dipyrrins can also be found in literature [35]. Research groups led by Thompson, Ravikanth and Hao have developed synthetic methods leading to H-dipyrrins based on F-BODIPY deborylation by boron trihalides [36] or other Lewis acids [37], as well as by potassium tert-butoxide [38,39]. However the scope of these methods is rather limited, *e.g.* dipyrrins possessing groups with substantial Lewis basicity are not reported to stand these BF_2-removal conditions.

On the other hand the account on an aromatic nucleophilic substitution in free dipyrrins is not found in the literature, although there are papers devoted to the reactions of C-, S-, N- and O-nucleophiles with more electrophilic 1,9-dichloroBODIPY [40]. We were interested in access to 1,9-disubstituted dipyrrins that possess additional pendant complexing substituents. 1,9-Modification of the dipyrrin framework was employed for the sterical encumbering to be used in catalysis [27,41], the extension of a π-conjugation

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(regulated both by metal complexation [42] and hydrogen bonding [38]), applied in photophysical applications.

This communication reveals the first results of the study. It is aimed at filling this gap, being focused on the either bulky substrates or those possessing additional coordinating substituents. As there is an NH acidic proton in dipyrrin, the reaction of 5-aryl-1,9-dichlorodipyrrins **1** with C-nucleophiles is more difficult to study, so at first we limited the scope to N-, O- and S-nucleophiles.

2. Materials and methods

All solvents were distilled before their use. Reagents were purchased from Aldrich and Acros companies, solvents were bought from Reakhim. CH_3CN and triethylamine have been distilled from CaH_2. 1,9-dichloro-5-(4-nitrophenyl)-dipyrromethene, 1,9-dichloro-5-phenyl-dipyrromethene [43], methyl 2-mercaptobenzoate [44], methyl mercaptoacetate [45], and methyl 3-mercaptopropanoate [46] were prepared according to the literature procedures.

NMR spectra, unless otherwise stated, were recorded on Bruker Avance 400 spectrometer, at 400.13 MHz for ^1H (standard – HMDS, 0.05 ppm) and 100.13 for ^{13}C (standard – ^{13}C signal of the solvent, 77.0 ppm for $CDCl_3$). For APT experiments, signals of secondary and quarternary atoms are marked with an asterisk.

LDI-TOF spectra have been collected on Bruker Daltonics Autoflex II spectrometer, samples were irradiated by N_2 laser (λ = 337 nm), accelerating voltage 19 kV. High resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI) [47]. The measurements were done in a positive ion mode (interface capillary voltage – 4500 V); mass range from *m/z* 50 to *m/z* 3000 Da; external or internal calibration was done with Electrospray Calibrant Solution (Fluka). A syringe injection was used for solutions in methanol (flow rate 3 μL/min). Nitrogen was applied as a dry gas; interface temperature was set at 180 °C.

TLC has been performed on DC-Alufolien Kieselgel 60 F254 plates (Merck). Kieselgel 60 0.063–0.200 MM (Merck) was used for column chromatography.

UV–Vis spectra were measured on Agilent-8453, in all cases a drop of Et_3N had been added to the sample before measurement. Extinction coefficients were reported for $5\cdot10^{-5}$ M concentrations, unless otherwise stated.

2.1. General procedure for nucleophilic substitution

Dichlorodipyrrin (1 eq.) and dry acetonitrile were placed to three necked round bottom flask equipped with magnetic stirring bar, stoppered by rubber septa and flushed with argon *via* needles. Then a solution of the nucleophile (*ca.* 4 eq.) in CH_3CN and triethylamine (*ca.* 6 eq.) have been added by the syringe, reaction flask was immersed into an oil bath heated to 65 °C (unless otherwise specified). After a specified time period, the solvent was removed on rotary evaporator, the residue was dried on the vacuum line at $5*10^{-2}$ Torr at 80–90 °C to remove the base and one of the substrates and processed as cited below.

2.1.1. 1,9-bis(methoxycarbonylmethylthia)-5-phenyl dipyrrin (**7**). ***1a***

(8.9 mg, 30.1 μmol) in 4 ml of CH_3CN and **3a** (13.1 mg, 124 μmol) in 6 ml of CH_3CN and Et_3N (17 μl, 12.4 mg, 122 μmol), rxn time 48 h, purified by TCL Al_2O_3 neutral, hexane/$CHCl_3$ 2:1 + 1% CH_3OH. **7**: (6.4 mg, 14.93 μmol, 49%). ^1H NMR ($CDCl_3$): δ = 3.79 (6H, s), 3.88 (4H, s), 6.38 (2H, d, *J* = 4.1 Hz), 6.44 (2H, d, *J* = 4.1 Hz), 7.36–7.44 (5H, m) ppm. ^{13}C NMR ($CDCl_3$) δ = 35.56, 52.76, 120.42, 127.60, 128.58, 128.79, 130.77, 134.41, 136.77, 141.76, 147.65, 170.02 ppm. LDI-TOF: *m/z* = 429 $[M+H]^+$, 467$[M+K]^+$. HRMS (ES): $C_{21}H_{21}N_2O_4S_2$ Found 429.0921 Calculated 429.0337. λ_{max} = 453 nm ($\varepsilon = 2.4 \times 10^4$ $M^{-1}cm^{-1}$).

2.1.2. 1,9-bis(2-methoxycarbonylethylthia)-5-phenyl dipyrrin (***8***). ***1a***

(25.1 mg, 86.8 μmol) in 10 ml of CH_3CN and **3b** (41.7 mg, 347 μmol) in 4 ml of CH_3CN and Et_3N (48 μl, 35.2 mg, 348 μmol), rxn time 120 h, purified by TCL Al_2O_3 neutral, hexane/$CHCl_3$ 2:1. **8**: (33.0 mg, 72.3 μmol, 83%). ^1H NMR ($CDCl_3$): δ = 2.73 (4H, t, *J* = 7.2 Hz), 2.91 (4H, t, *J* = 7.2 Hz), 3.69 (6H, s), 6.38 (2H, d, *J* = 4.1 Hz), 6.44 (2H, d, *J* = 4.1 Hz), 7.36–7.44 (5H, m) ppm. ^{13}C NMR ($CDCl_3$) δ = 28.87*, 34.42*, 51.88, 120.77, 127.72, 128.44, 128.64, 130.75, 133.61*, 136.63*, 141.91*, 148.24*, 172.06* ppm. LDI-TOF: *m/z* = 458 $[M]^+$. HRMS (ES): $C_{23}H_{25}N_2O_4S_2$ Found 457.1242 Calculated 457.1250. λ_{max} = 456 nm ($\varepsilon = 1.9 \times 10^4$ $M^{-1}cm^{-1}$).

2.1.3. Nucleophilic substitution of ***1a*** with ***3b*** – conversion and products distribution

All the experiments have been carried out according to the general procedure. After the evaporation and high vacuum drying reaction mixtures have been analyzed by NMR.

2.1.4. Methyl 3-({(2Z)-2-[(5-chloro-1H-pyrrol-2-yl) (phenyl) methylene]-2H-pyrrol-5-yl}thio)propanoate (***7'***) ***1a***

(30 mg, 104 μmol) in 8 ml of CH_3CN and **3b** (50.6 mg, 374 μmol) in 2 ml of CH_3CN and Et_3N (54 μl, 39.3 mg, 728 μmol), rxn time 17 h. Reaction mixture has been evaporated to dryness, then oily orange residue has been subjected to heating(95 °C, 40 min) at high vacuum ($1\cdot10^{-2}$ Torr) for the nucleophile excess to be dried off. The product was isolated by column chromatography (SiO_2 neutral, petroleum ether/ethyl acetate 4:1). **7'**: (13.5 mg, 34.8 μmol, 33%).): ^1H NMR ($CDCl_3$) δ = 2.83 (2H, t, J = 7.2 Hz), 3.31 (2H, t, J = 7.2 Hz), 3.72 (3H, s), 6.33 (1H, d, J = 4.2 Hz), 6.48 (1H, d, J = 4.2 Hz), 6.25 (1H, d, J = 4.2 Hz), 6.54(1H, d, J = 4.2 Hz), 7.40 (5H, m). ppm. ^{13}C NMR ($CDCl_3$) δ = 28.63, 29.28, 33.92, 51.5 8, 117.53, 118.64, 127.36, 128.68, 130.37, 135.62, 171.51 ppm. LDI-TOF: *m/z* = 373 $[M]^+$. HRMS (ES): $C_{20}H_{20}ClN_2O_2S$ Found 373.0778 Calculated 373.0772. λ_{max} = 454 nm ($\varepsilon = 0.9 \times 10^4$ $M^{-1}cm^{-1}$).

2.1.5. 1,9-bis(4-methylphenylthia)-5-phenyl dipyrrin (***9***). ***1a***

(14 mg, 48.4 μmol) in 8 ml of CH_3CN and **4** (24.1 mg, 194 μmol) in 2 ml of CH_3CN and Et_3N (27 μl, 19.7 mg, 194 μmol), rxn time 20 h (at 64 °C). Purified by column chromatography SiO_2, CCl_4. **9**: (21 mg, 45.2 μmol, 93%). ^1H NMR ($CDCl_3$): δ = 2.30 (6H, s) 6.27 (2H, d, *J* = 4.1 Hz), 6.44 (2H, d, *J* = 4.1 Hz), 7.13 (4H, d, *J* = 8.1 Hz), 7.33 (4H, d, *J* = 8.1 Hz), 7.37–7.41(5H, m), 12.2 (broad s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ = 21.23, 120.35, 127.64, 128.45, 128.57, 129.26*, 130.16, 130.75, 131.65, 134.46*, 136.66*, 136.66*, 138.14*, 141.91* ppm. LDI-TOF: *m/z* = 465 $[M+H]^+$. HRMS (ES): $[M+H]^+$ $C_{29}H_{24}N_2S_2$ Found 465.1464 Calculated 465.1454. λ_{max} = 462 nm ($\varepsilon = 2.1 \times 10^4$ $M^{-1}cm^{-1}$).

2.1.6. 1,9-bis(2-methoxycarbonylphenylthia)-5-phenyl dipyrrin (***10***). ***1a***

(14.6 mg, 50.5 μmol) in 8 ml of CH_3CN and **5** (43.8 mg, 260 μmol) and Et_3N (27 μl, 19.7 mg, 194 μmol), rxn time 72 h (at 76 °C). Purified by column chromatography SiO_2, hexane-EtOAc 4:1. Dried residue was chromatographed on Al_2O_3, hexane-EtOAc. **10**: (23 mg, 41.6 μmol, 82%). ^1H NMR ($CDCl_3$): δ = 3.91 (6H, s), 6.44 (2H, d, *J* = 4.4 Hz), 6.52 (2H, d, *J* = 4.4 Hz), 7.10–7.14 (2H, m), 7.21–7.27 (4H, m), 7.38–7.47 (5H, m), 7.85 (2H, dd, *J* = 7.8 Hz, 1.1 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ = 29.68, 52.25*, 122.60*, 126.50*, 127.73*, 128.65*, 128.79*, 129.55, 130.82*, 130.87*, 132.34*, 134.56, 136.54, 137.13, 147.03, 166.80 ppm. LDI-TOF: *m/z* = 465 $[M+H]^+$. HRMS (ES):