chemistry proceedings

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Synthesis of Porphyrins with ABAB Symmetry from Dipyrromethanes as Potential Phototherapeutic Agents †

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† Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: https://ecsoc-24.sciforum.net/.

Received: date; Accepted: date; Published: date

Abstract: Asymmetrically *meso*-substituted porphyrins were synthesized with ABAB symmetry patterns. The approach required the formation of dipyrromethanes, which were obtained from the condensation of an aldehyde (pentafluorobenzaldehyde, 4-nitrobenzaldehyde or *N*,*N*-diphenylaminobenzaldehyde) with a large excess of pyrrole (1:47 aldehyde/pyrrole mol ratio), catalyzed by trifluoroacetic acid in 70–94% yields. Then, acid catalyzed condensation of these dipyrromethanes with an aldehyde (*N*,*N*-dimethylaminobenzaldehyde, 4-carboxymethyl benzaldehyde or *N*-ethyl-3-carbazolecarbaldehyde) (1:1 mol ratio) in dichloromethane, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone affords the diseased porphyrins in 10–42% yields. These ABAB-porphyrins are interesting starting materials to obtain photoactive molecular structures as potential phototherapeutic agents.

Keywords: porphyrin; tetrapyrrolic macrocycle; pyrrole; pentafluorophenyl; dipyrromethane; photosensitizer

1. Introduction

Porphyrin derivatives have been proposed as photosensitizers in the photodynamic inactivation of microorganisms [1,2]. However, depending on the substituents on the periphery of the tetrapyrrolic macrocycle, these molecules tend to aggregate, producing a loss of photodynamic activity. Thus, to achieve effective photoinactivation, these compounds can bind to different supports forming photoactive materials [3,4]. In this sense, it is interesting to develop porphyrins asymmetrically substituted in the *meso* positions by two different structures (A and B). In these compounds, structure A has a functional group that allows covalent attachment to other molecules, while B is substituted by groups that allows changing the properties of the tetrapyrrolic macrocycle [5,6].

A major limitation of available methods to synthesize tetrapyrrole macrocycles concerns the ability to place different substituents at the four *meso*-positions of the porphyrin. Thus, porphyrins bearing two different types of *meso*-substituents can be prepared by a binary mixed aldehyde condensation. However, this approach is statistical in nature and usually multiple porphyrin products are obtained [7]. Often, six porphyrins are formed, the work up is no simple because the tar present. The isolate requires slowly chromatographic separation and no pure porphyrin is always possible, resulting in low yields of the desired product. More direct approaches to obtain *trans*-substituted porphyrins (ABAB-porphyrins) are provided by condensation of dipyrromethanes with aldehydes. These porphyrins require access to *meso*-substituted dipyrromethane, which can be synthesized from the reaction of aldehyde with excess of pyrrole catalyzed by acid [8].

In the present work, ABAB-porphyrins were synthesized from the condensation of *meso*-(substituted)dipyrromethanes with benzaldehyde derivatives catalyzed by acid. These porphyrins are interesting starting materials to obtain photoactive molecular structures as potential phototherapeutic agents.

2. Materials and Methods

2.1. Equipment and Chemical Substances

Proton nuclear magnetic resonance spectra were achieved on a FT-NMR Bruker Avance DPX400 spectrometer (Bruker BioSpin, Rheinstetten, Deutschland). Mass spectra were attained on a Bruker micrO-TOF-QII (Bruker Daltonics, MA, USA) equipped with an ESI source (ESI-MS). Absorption spectra were recorded on a Shimadzu UV-2401PC spectrometer (Shimadzu Corporation, Tokyo, Japan), while fluorescence spectra were carried out on a Spex FluoroMax spectrofluorometer (Horiba Jobin Yvon Inc, Edison, NJ, USA). Compounds from Sigma-Aldrich (Milwaukee, WI, USA) were used as received. Silica gel thin-layer chromatography (TLC) plates 250 microns were purchased from Analtech (Newark, DE, USA) and silica gel 60 (0.040–0.063 mm, 230–400 mesh) from Merck (Darmstadt, Germany).

2.2. Synthesis

meso-(Pentafluorophenyl)dipyrromethane (**1**). Pentafluorobenzaldehyde (0.55 mL, 4.45 mmol) and pyrrole (14.5 mL, 209 mmol) was purged with argon for 15 min. Then, trifluoroacetic acid (TFA) (70 L, 0.90 mmol) was added. The mixture was stirred for 45 min at room temperature. After that, the sample was diluted with 25 mL of dichloromethane (DCM) and three washes of 15 mL each were carried out with NaOH (0.1 M). The solvent and excess pyrrole were removed under reduced pressure using a rotary evaporator. The product was purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate/triethylamine (TEA) 80:20:1), obtaining 1.31 g (94%) of **2**. TLC (silica gel, cyclohexane/ethyl acetate/TEA 80:20:1) R_f = 0.46. ^{1}HNMR ($CDCl_3$, TMS) δ [ppm] 5.88 (s, 1H, *meso*-H), 6.00 (m, 2H, pyrrole-H), 6.15 (q, 2H, pyrrole-H), 6.74 (m, 2H, pyrrole-H) 8.10 (brs, 2H, pyrrole NH). ESI-MS [m/z] 310.0534 [M^+] (310.0529 calculated for $C_{15}H_7F_5N_2$).

meso-(4-Nitrophenyl)dipyrromethane (**2**). A solution of 4-nitrobenzaldehyde (2.50 g, 16.6 mmol) and pyrrole (55 mL, 780 mmol) was degassed by bubbling with argon for 15 min, and then TFA (321 L, 4.17 mmol) was slowly added. The solution was stirred for 20 min at room temperature. The mixture was diluted with DCM, washed with NaOH (0.1 M) and then washed with water. The solvent was removed under reduced pressure. The unreacted pyrrole was removed by vacuum distillation at room temperature. The product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate/triethylamine; 80:20:1) yielded 3.19 g (72%) of **3**. ^{1}HNMR (300.08 MHz, $CDCl_3$, TMS) δ [ppm] 5.58 (s, 1H, *meso*-H); 5.86 (m, 2H, pyrrole-H); 6.17 (q, 2H, pyrrole-H); 6.74 (m, 2H, pyrrole-H); 7.37 (d, 2H, J = 9.0 Hz); 8.01 (s, brs, 2H, pyrrole NH); 8.16 (d, 2H, J = 9.0 Hz). ESI-MS [m/z] 267.1014 [M^+] (267.1008 calculated for $C_{15}H_{13}N_3O_2$).

meso-[4-(*N*,*N*-Diphenylaminophenyl)]dipyrromethane (**3**). 4-(*N*,*N*-diphenylamino) benzaldehyde (1.98 g, 7.24 mmol) and pyrrole (24 mL, 340 mmol) was purged in an argon atmosphere for 15 min at room temperature. Then, 140 L (1.82 mmol) of TFA was added and the mixture stirred for 30 min. After that, 780 L (5.60 mmol) of triethylamine (TEA) was added and the solution was diluted with 50 mL of DCM. The solvent was removed under reduced pressure, and the unreacted pyrrole was removed by vacuum distillation at 60 °C. The product was purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate/TEA 80:20:1), yielding 1.97 g (70%) of **1**. TLC (silica gel, cyclohexane/ethyl acetate/TEA 80:20:1) R_f = 0.26. ^{1}H NMR ($CDCl_3$, TMS) [ppm] 5.43 (s, 1H, *meso*-H); 5.94 (m, 2H, pyrrole-H); 6.17(q, 2H, pyrrole-H); 6.72 (m, 2H, pyrrole-H); 6.94–7.12 (m, 10 H, ArH); 7.22 (m, 4 H, ArH); 7.98 (s, brs, 2H, pyrrole NH). ESI-MS [m/z] 389.1887 [M^+] (389.1892 calculated for $C_{27}H_{23}N_3$).

5,15-di(4-(*N*,*N*-dimethylaminophenyl)-10,20-di(pentafluorophenyl)porphyrin (**4**). A solution of 4-(*N*,*N*-dimethylamino)benzaldehyde (3.4 mmol) and dipyrromethane **1** (974 mg, 3.4 mmol) in 250

mL of DCM was bubbled with argon for 15 min. Then, boron trifluoride etherate ($BF_3{\cdot}OEt_2$, 1.1 mmol) was added. The solution was stirred for 80 min at room temperature. After that, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 2.25 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. The solvent was removed under reduced pressure and purification was performed by flash column chromatography (silica gel, DCM) giving **4** in 24% yield.^{1}HNMR ($CDCl_3$, TMS) δ [ppm] −2.86 (s, brs, 2H, N-H), 3.05 (s, 6H, $N(CH_3)_2$), 7.05 (d, 4H, J = 8.2 Hz, 3,5-ArH), 7.97 (d, 4H, J = 8.2 Hz, 2,6-ArH), 8.81–8.94 (m, 8H, -pyrrole-H). ESI-MS (m/z) 881.2447 $[M+H]^+$ (881.2451 calculated for $C_{48}H_{30}F_{10}N_6$ + H).

5,15-bis(4-Methoxycarbonylphenyl)-10,20-bis(pentafluorophenyl)porfirin (**5**). A solution of methyl 4-formylbenzoate (632 mg, 3.85 mmol) and dipyrromethane **1** (1.37 g, 4.38 mmol) in 450 mL of DCM was stirred for 15 min under argon atmosphere at room temperature. Then, TFA (0.50 mL, 6.54 mmol) was added and the solution was kept stirring for 45 min. The mixture was subsequently oxidized with DDQ (885 mg, 3.90 mmol) and stirred for 2 h in an atmosphere of air. Then, 20 mL of MeOH was added to remove excess DDQ and the mixture was kept stirred for 30 min. The solvent was removed under reduced pressure. The product was purified by silica gel filtration and flash column chromatography (silica gel, cyclohexane/DCM 40%), obtaining 90 mg (10%) of **5**. ^{1}HNMR ($CDCl_3$, TMS) δ [ppm] -2.86 (s, brs, 2H, N-H), 4.13 (s, 6H, $COOCH_3$), 8.31 (d, 4H, J = 8.0 Hz, 2,6-ArH), 8.47 (d, 4H, J = 8.0 Hz, 3,5-ArH), 8.83–8.93 (m, 8H, -pyrrole-H). ESI-MS (m/z) 911.1720 $[M+H]^+$ (911.1716 calculated for $C_{48}H_{24}F_{10}N_4O_4$ + H).

5,15-bis(4-Methoxycarbonylphenyl)-10,20-bis(4-nitrophenyl)porphyrin (**6**). A solution of 4-carboxymethylbenzaldehyde (2.46 g, 15 mmol) and meso-(4-nitrophenyl) dipyrromethane **2** (4.0 g, 15 mmol) in 1.5 L of DCM was purged with argon for 15 min. Then, TFA (1.85 mL, 24 mmol) was added slowly over 30 s. The solution was stirred for 30 min at room temperature. After that, DDQ (3.4 g, 15 mmol) was added and the mixture was stirred for 2 h at room temperature. The solvent was removed under vacuum and flash column chromatography (silica gel, DCM) yielded 1.29 g (21%) of **6**. ^{1}HNMR ($CDCl_3$, TMS) δ [ppm] -2.77 (s, brs, 2H, N-H), 4.14 (s, 6H, $COOCH_3$), 8.31 (d, 4H, J = 8.0 Hz, 2,6-ArH-COOEt), 8.40 (d, 4H, J = 8.3 Hz, 2,6-ArH-NO_2); 8.47 (d, 4H, J = 8.0 Hz, 3,5-ArH-COOEt), 8.65 (d, 4H, J = 8.3 Hz, 3,5-ArH-NO_2), 8.80–8.97 (m, 8H, -pyrrole-H). ESI-MS (m/z) 820.1720 $[M+H]^+$ (820.1716 calculated for $C_{48}H_{32}N_6O_8$ + H).

5,15-Bis[4 (-*N*,*N*-diphenylamino)phenyl]-10,20-bis[3-(*N*-ethylcarbazoyl)]porphyrin (**7**). A solution of *N*-ethyl-3-carbazolecarbaldehyde (0.56 g, 2.50 mmol) and dipyrromethane **3** (1.00 g, 2.50 mmol) in 310 mL of DCM was purged with argon for 15 min. After that, TFA (425 L, 5.50 mmol) was slowly added and the solution was stirred for 60 min at room temperature. Then, DDQ (1.50 g, 6.61 mmol) was added and the mixture was stirred for an additional 18 h, open to the atmosphere. The solvent was removed under reduced pressure. The obtained product was purified by flash column chromatography (silica gel, hexane/DCM/TEA 6:93.8:0.2) obtaining 622 mg (42%) of **7**. TLC (silica gel, hexane/DCM/TEA 6:93.8:0.2) Rf = 0.68. ^{1}HNMR ($CDCl_3$, TMS) δ [ppm] -2.60 (brs, 2H, pyrrole N-H), 1.68 (t, 6H, $-CH_3$, J = 7.1 Hz), 4.64 (q, 4H, $-CH_2-$, J = 7.1 Hz), 7.15 (d, 4H, J = 7.8 Hz), 7.34–7.50 (m, 22 H), 7.52–7.64 (m, 4 H), 7.75 (d, 2H, J = 8.3 Hz), 8.02 (d, 4H, J = 7.8 Hz), 8.20 (d, 4 H, J = 7.7 Hz), 8.34 (d, 2H, J = 8.3 Hz), 8.82–9.06 (m, 8H, -pyrrole-H). ESI-MS [m/z] 1183.5169 $[M+H]^+$ (1183.5176 calculated for $C_{84}H_{62}N_8$ + H).

2.3. Spectroscopic Studies

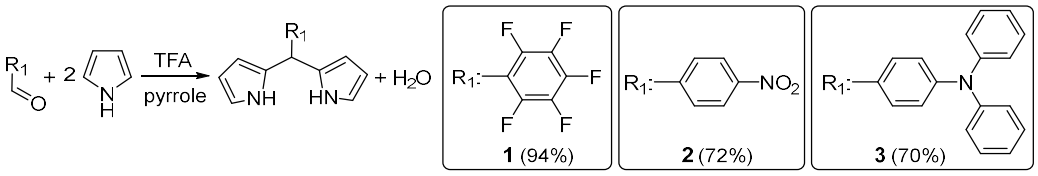
Absorption and fluorescence spectra were performed in a quartz cell of 1 cm path length using *N*,*N*-dimethylformamide (DMF) at 25.0 ± 0.5 °C. Absorbances (<0.05) were matched at the excitation wavelength (550 nm) and the areas of the emission spectra were integrated in the range 600–800 nm. The fluorescence quantum yield (Φ_F) of the porphyrins was calculated by comparison of the area below the corrected emission spectrum of 5,10,15,20-tetrakis(4-methoxyphenyl)porphyrin (TMP) as a reference [5].

3. Results and Discussion

3.1. Synthesis of Dipyrromethanes

Aldehydes and pyrrole undergo acid-catalyzed condensation at room temperature. Therefore, the condensation of substituted benzaldehydes with a large excess of pyrrole (1:47 aldehyde/pyrrole mol ratio) catalyzed by TFA affords *meso*-(substituted)dipyrromethane (**1–3**). The reaction mixture was stirred for 25 min at room temperature resulting in complete consumption of the aldehyde. Under this reaction condition, pyrrole serves as the reactant in excess and as the solvent for the reaction, giving direct formation of dipyrromethane (Scheme 1).

The dipyrromethanes were purified by flash chromatography on silica gel in a mildly basic medium, using n-hexane/ethyl acetate/TEA (80/20/1) as eluent. The use of neutral organic solvent leads to decomposition of the dipyrromethane on silica gel. Therefore, 1% TEA was added to prevent decomposition of the dipyrromethane on silica gel column, which is slightly acidic. Dipyrromethanes **1**, **2** and **3** were obtained in 94, 72 and 70%, respectively. These compounds are stable upon storage at 0 °C in nitrogen atmosphere and absence of light. Consequently, dipyrromethanes can be easily obtained with high purity, which is essential for its application in the synthesis of asymmetric *meso*-substituted porphyrins.



Scheme 1. Synthesis of dipyrromethanes **1** and **3**.

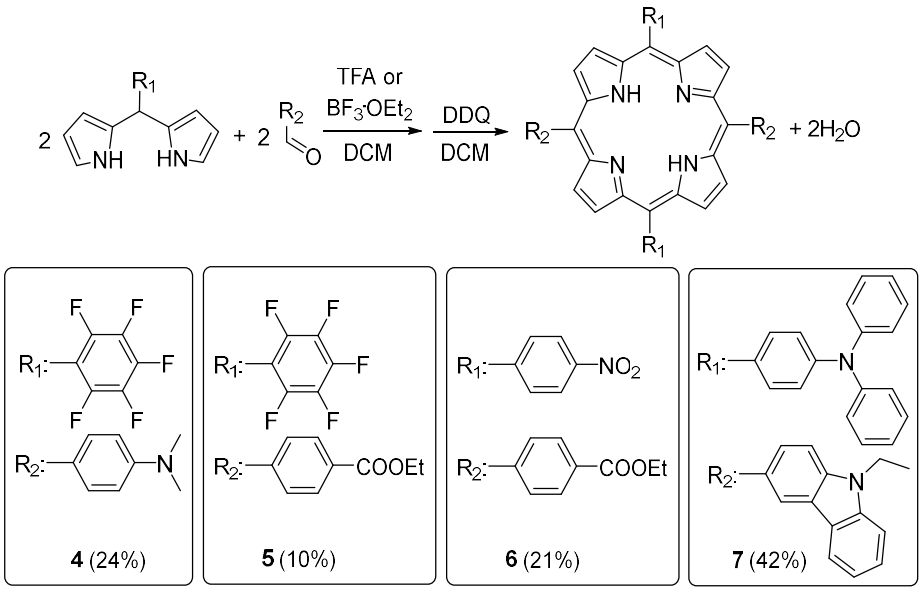
3.2. Synthesis of ABAB-Porphyrins

ABAB-porphyrins **4–7** were synthesized by the acid-catalyzed condensation of dipyrromethane **1–3** and the correspondent substituted benzaldehyde (Scheme 2). Mixed-benzaldehyde dipyrromethane condensations were performed using about [1:1] molar relation of dipyrromethane and substituted benzaldehyde. The reaction was performed using catalytic among of TFA or $BF_3{\cdot}OEt_2$ and DCM as solvent at room temperature. The reaction mixture was subject to oxidation with DDQ. Thus, this mixed condensation affords the corresponding ABAB-porphyrin.

These porphyrins were easily separated by flash chromatography with high purity using DCM/methanol gradient. In all these cases, the first purple band corresponds to the ABAB-porphyrin. Under these conditions, ABAB-porphyrins **4**, **5**, **6** and **7** were obtained in 24, 10, 21 and 42% yields, respectively.

This procedure was previously used to obtain ABAB-porphyrins from the condensation of a dipyrromethane bearing a sterically hindered substituent with an aldehyde [9].

The pentafluorophenyl group attached at the *meso* position of the porphyrins **4** and **5** can easily undergo a regiospecific nucleophilic aromatic substitution of the *para*-fluorine atom by a diverse set of nucleophiles [3,10]. Thus, this substituent was used to covalently link the porphyrin ring to several functionalized structures [4]. In porphyrin **4**, *N*,*N*-dimethylaminophenyl substituent can be used to obtain cationic intrinsic charge by methylation [5]. In addition, aminophenyl substituents can be obtained in porphyrin **6** by reduction of nitrophenyl group [11]. Moreover, porphyrin **5** and **6** can be hydrolyzed to form carboxylic acid groups, which can be linked to several structures [11]. Finally, both electroactive substituents of porphyrin **7** can form different polymers [12].



Scheme 2. Synthesis of ABAB-porphyrins **4–7**.

3.3. UV-Visible Absorption Spectroscopic Properties

Porphyrin **4–7** showed the typical Soret band at ~420–430 nm and the four Q-bands between 512–653 nm, which are characteristics of *meso*-tetraphenylporphyrin derivatives [5,6]. The spectroscopic properties of the porphyrins are summarized in Table 1. The Q band of the free base porphyrin moiety consists of four components: $Q_x(0,0)$, $Q_x(1,0)$, $Q_y(0,0)$ and $Q_y(1,0)$, which are associated with D_{2h} symmetry [13]. The maximum of the Soret band of carbazoyl porphyrin derivative **7** showed a 10 nm bathochromic shift respect to 5,10,15,20-tetrakis(phenyl)porphyrin in DMF due to the auxochromic effect of the carbazoyl groups [14].

The steady-state fluorescence emission spectra of these porphyrins were obtained in DMF (Table 1). The two bands are characteristic for similar *meso*-substituted porphyrin [5,6]. These bands have been assigned to $Q_x(0\text{-}0)$ and $Q_x(0\text{-}1)$ transitions [5]. This is a typical behavior for porphyrins with D_{2h} symmetry, like the free bases, and indicates that the porphyrin vibronic structure remains practically unchanged upon excitation. From the intersection of the absorption and fluorescence spectra of the $Q_x(0\text{-}0)$ band, Stokes shifts of ~10 nm were calculated for the tetrapyrrolic macrocycles. Small Stokes shifts indicated that in these molecules the spectroscopic energies are similar to the relaxed energies of the lowest singlet excited state S_1, according to the rigid planar structure of porphyrins. That suggests that only a minor geometric relaxation occurs in the first excited state. Fluorescence quantum yields (Φ_F) of these photosensitizers were calculated by comparison with TMP as a reference. The values of Φ_F for these porphyrins agree with values previously reported by similar porphyrin derivatives [5,15].

Table 1. Spectroscopic properties of porphyrins **4–7** in DMF.

PS	Absorption$_{max}$ (nm)	$\varepsilon^{Soret\ a}$	Fluorescence$_{max}$ (nm)	Φ_F [b]
4	418 510 542 589 647	4.67×10^5	651 712	0.063 ± 0.003
5	420 512 543 590 648	4.72×10^5	652 712	0.054 ± 0.002
6	421 516 551 591 647	4.72×10^5	652 717	0.10 ± 0.01
7	428 520 563 596 653	3.15×10^5	668 729	0.12 ± 0.01

[a] molar absorption coefficient (L mol^{-1} cm^{-1}), [b] fluorescence quantum yield.

4. Conclusions

The following two basic steps were used sequentially in the synthesis of ABAB-porphyrin: (1) *meso*-(4-substituted) dipyrromethane was formed from correspondent benzaldehyde derivative and pyrrole catalyzed by acid, (2) condensation of dipyrromethane with appropriate benzaldehydes yields the ABAB-porphyrin, which was easily purified by flash chromatography. Thus, the desired ABAB-porphyrins **4–7**, bearing different substituents were obtained with appreciable yields of 10–42%. Thus, the dipyrromethanes react with an aldehyde under the conditions of the two-step one-flask porphyrin synthesis, affording direct access to ABAB-porphyrins. Moreover, it has a relatively simple reaction work up and high yields. These *trans*-substituted porphyrins contain precursor groups of positive charges, which can be used to obtain cationic photosensitizers. Moreover, these tetrapyrrolic macrocycles can be covalently attached to molecular structures and be used to form polymeric materials.Therefore, these ABAB-porphyrins are interesting starting materials to obtain photoactive molecular structures as potential phototherapeutic agents.

Acknowledgments: This work was supported by CONICET, PIP-2015 1122015 0100197 CO, UNRC-SECYT, PPI-2020 and ANPCYT, PICT 0667/16. M.E.M. and E.N.D. are Scientific Members of CONICET. M.E.P. thanks CONICET for the research fellowship.

Conflicts of Interest: The authors declare no conflict of interest.

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