

Synthesis of *meso*-tetrakis (2-chloroquinolin-3-yl) porphyrins

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Abstract

meso-Tetrakis (-2-chloroquinolin-3-yl) porphyrins were synthesized from 2-chloroquinoline-3-carboxaldehydes and pyrrole in 1:1 ratio in propionic acid at 140 °C for 4 hours. Different substituted 2-chloroquinoline-3-carboxaldehydes were synthesized from corresponding N-aryl acetamides by Vilsmeier–Haack cyclization. The aldehydes were obtained in better yields, when acetamides, dimethyl formamide and POCl₃ were taken in 1:3: 7 molar ratios at 70-75 °C

Keywords: N-aryl acetamides, Vilsmeier–Haack cyclization, 2-chloroquinoline-3-carboxaldehydes, *meso*-Tetrakis(-2-chloroquinoline-3-yl) porphyrins

Introduction

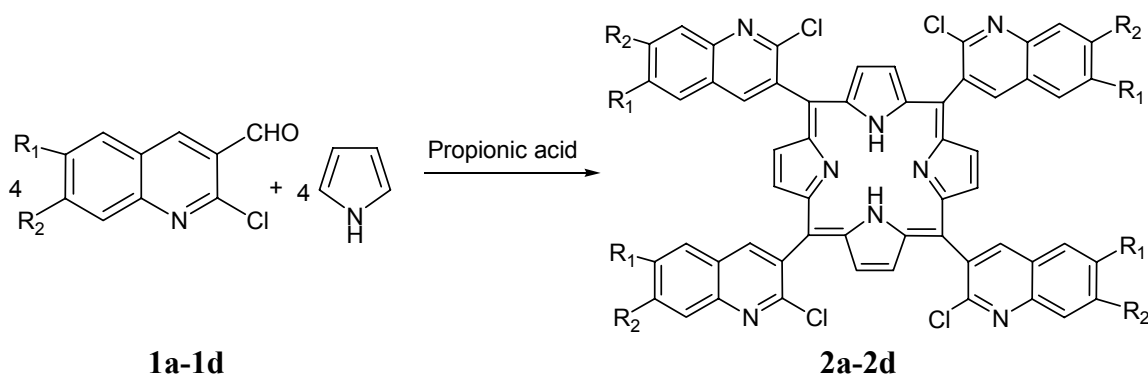
There is a particular interest for synthesis of porphyrins bearing heterocyclic moieties due to varied biological¹, photophysical² and electronic properties³. The heteroaryl porphyrin with diverse substituents is important for the studies of biomimetic and molecular recognition properties^{4,5}. A good number of porphyrins containing nitrogen heterocycles have been prepared and their properties were studied. Substituted nitrogen heterocyclic porphyrins are of particular interest⁶ as they provide sites for metal coordination, hydrogen bonding, alkylation and modulating electronic properties. Indeed, pyridine substituents have yielded a broad array of metal coordinated multi porphyrin architectures⁷ and imidazole groups have yielded stacked multi porphyrin assemblies⁸. Pyrimidine⁹, purine¹⁰ or pyrazole¹¹ units have enabled molecular recognition and self-assembly studies of porphyrins with complementary molecules. Several quinoline derivatives have been found to possess useful biological activities such as bactericidal¹², antitumor¹³, antimalarial¹⁴, antiinflammatory¹⁵. The benzo and hetero fused quinolines are known to bind to DNA topoisomerase and display cytotoxic and antitumor activities¹⁶. [5,15-Bis(8-quinolyl)porphyrinato]zincII has been used for molecular recognition of carbohydrates¹⁷. The above applications of the *meso*-substituted heterocyclic porphyrins inspired us to synthesize the new *meso*-tetrakis(2-chloroquinolin-3-yl)porphyrins (**2a-2d**). Porphyrins themselves are having high applications in organic chemistry, so by substituting quinoline

moiety in *meso* position of porphyrins, it may possess high potential towards the biological applications.

Results and Discussion

2-Chloroquinoline-3-carboxaldehydes (**1a-1d**) were synthesized starting from N-aryl acetamides by Vilsmeier–Haack cyclization¹⁸. Several experiments were conducted to produce these aldehydes in better yields by changing the ratios of N-aryl acetamide, POCl₃ and dimethyl formamide at different temperatures. 2-Chloroquinoline-3-carboxaldehydes (**1a-1d**) were obtained in higher yields at 70-75 °C using N- aryl acetamides, DMF and POCl₃ in 1:3: 7 molar ratios.

meso-Tetrakis(-2-chloroquinolin-3-yl) porphyrins (**2a-2d**) were synthesized in 10-12% yield by treating the 2-chloroquinoline-3-carboxaldehydes (**1a-1d**) with pyrrole in 1:1 ratio in propionic acid at 140 °C for 4 hours (**Scheme 1**). When the reaction was conducted according to the Lindsey procedure (TFA / DCM), the porphyrin obtained was in negligible quantity¹⁹, where as by using more propionic acid (25 ml /1 millimole of aldehyde), the yield of porphyrin got increased. The porphyrins (**2a-2d**) were purified by passing through a flash-column using a mixture of chloroform and methanol (98:2) as eluent.



Compound	R ₁	R ₂
1a	H	H
1b	OCH ₃	H
1c	CH ₃	H
1d	H	OCH ₃

Scheme 1

meso-Tetrakis(-2-chloroquinolin-3-yl) porphyrins (**2a-2d**) exhibit the phenomenon of atropisomerism, a typical feature of *meso*- (2-substituted-aryl)porphyrins²⁰. This is due to a high rotational energy barrier caused by steric hindrance between the quinoline 2-chloro group and

the porphyrin β -protons. Four distinct bands were observed by TLC for porphyrins **2a-2d**. Attempts were made to separate these atropisomers by column chromatography (flash silica gel 230-400 mesh). TLC studies indicate that each one of the individual isomeric fractions of **2a-2d**, becomes a mixture of atropisomers, on standing at ambient temperature. The ^1H NMR spectra show a complex resonances for the central porphyrin N-H and β -protons for porphyrins **2a-2d**. Where as, the C_4 proton of the quinoline appears as a singlet around δ 8.60 ppm in all the porphyrins. UV-Vis spectra of quinoline porphyrins were recorded at 1×10^{-5} mol concentrations in CHCl_3 . Highly characteristic spectra were obtained for quinoline porphyrins **2a-d**, in which the B band is prominent at 430 nm and Q bands are observed at 520, 600 and 661nm. The IR spectra contain a characteristic macrocyclic bending frequency of 970cm^{-1} for **2a-2d**.

Experimental Section

General Procedures. UV-vis spectra were recorded on a SHIMADZU UV 160 A UV-vis-NIR spectrophotometer, using chloroform as solvent. IR spectra were recorded as KBr pellets using a SHIMADZU 8010 FTIR spectrophotometer. ^1H NMR spectra were recorded on a VARIAN FT 500 MHz instrument using CDCl_3 and $\text{DMSO-}d_6$ as solvent and TMS as internal reference. FAB- Mass spectra were recorded on a VG Micromass 7070H (F, or CI) auto spectrometer. The C, H, N analysis of the compounds was performed on a Carlo Erba Model EA 1108 CHNS-O elemental analyzer. Porphyrins were purified by flash column chromatography using 230-400 mesh silica gel (Aldrich).

Synthesis of meso- tetrakis(2-chloroquinolin-3-yl)porphyrin (2a). 2-Chloroquinoline-3-carboxaldehyde (**1a**, 383 mg, 2 mmol) was dissolved in 50 ml of freshly distilled propionic acid and pyrrole (134 mg, 2 mmol) was added. The reaction mixture was stirred at 140°C in open air for 4 h. Then the propionic acid was distilled off under reduced pressure and the residue was cooled to room temperature. 30 ml of cold water was added to the residue and neutralized carefully with saturated sodium bicarbonate solution. The dark colored residue was filtered and dried. The crude product was purified by flash column chromatography using chloroform: methanol (95: 5) mixture as eluent. Four separate atropisomeric fractions were collected, which after concentration gave a dark purple solid **2a** (58 mg, 12.1%). Identification and characterization of all the four fractions indicated that they contain the same compound. The first fraction was isolated as a single isomer. Mp: $>300^\circ\text{C}$. Anal. calcd. for $\text{C}_{56}\text{H}_{30}\text{N}_8\text{Cl}_4$: C, 70.38; H, 3.16; N, 11.71. Found: C, 70.25; H, 3.22; N, 11.73%. FAB-MS m/z 957 ($\text{M}+1$)⁺ requires 956. UV: λ_{max} nm (CHCl_3) (log ξ): 430 (5.504), 520(4.53), 601 (4.30), 660 (4.00). ^1H NMR (CDCl_3 + $\text{DMSO-}d_6$) δ ppm: 9.05 (m, 8H, pyrrole β -protons), 8.67 (s, 4H, quinoline C_4 -H), 8.07 (m, 8H, quinoline C_5 & C_8 -H), 7.82(m, 4H, quinoline C_6 -H), 7.60 (m, 4H, quinoline C_7 -H), -2.63 (s, 2H, porphyrin N-H). IR (KBr) cm^{-1} : 3436 (w, porphyrin N-H stretch), 1570, 1458, 1420, 1362

(m, aromatic C=C, C=N ring stretch), 973, 956 (m, porphyrin macrocyclic bend), 801, 785, 758 (s, aromatic C=C-H out-of plane bend).

Synthesis of *meso*- tetrakis(2-chloro-6-methoxyquinolin-3-yl)porphyrin (2b). A mixture of 443 mg (2 mmol) of 2-chloro-6-methoxyquinoline-3-carboxaldehyde (**1b**) and 134 mg (2 mmol) of freshly distilled pyrrole was dissolved in 50 ml of propionic acid and heated at 140°C for 4hrs with stirring. After the usual workup procedure was conducted as described above, the black residue obtained was subjected to column chromatography on flash silica gel using chloroform : methanol (98 : 2) mixture as eluent. Four separate purple colored atropisomeric fractions were collected, which after concentration gave a dark purple solid **2b** (62 mg, 11.5%). It was observed that all the four fractions contain the same compound. The first fraction was isolated as a single isomer. Mp: >300 °C Anal. calcd. for C₆₀H₃₈N₈O₄Cl₄ : C, 66.92; H, 3.56; N, 10.41. Found: C, 66.86; H, 3.62; N, 10.50%; FAB-MS m/z 1077 (M+1)⁺, requires 1076. UV: λ_{max} nm (CHCl₃) (log ξ): 430 (5.53), 520(4.84), 600 (4.31), 661 (4.00). ¹H NMR (CDCl₃ + DMSO- d₆) δ ppm : 9.06 (m, 8H, pyrrole β-protons), 8.66 (s, 4H, quinoline C₄-H), 7.94 (d, 4H, quinoline C₈-H), 7.52 (d, 4H, quinoline C₇-H), 7.18 (s, 4H, quinoline C₅ -H), 3.96 (s, 12H, 4x O-CH₃), -2.60 (s, 2H, porphyrin N-H). IR (KBr) cm⁻¹: 3426 (w, porphyrin N-H stretch), 1622, 1588, 1494, 1462 (m, aromatic C=C, C=N ring stretch), 969, 959 (m, porphyrin macrocyclic bend), 831,797 (s, aromatic C=C-H out-of plane bend).

Synthesis of *meso*- tetrakis(2-chloro-6-methylquinolin-3-yl)porphyrin (2c). A mixture of 410 mg (2 mmol) of 2-chloro-6-methylquinoline-3-carboxaldehyde (**1c**) and 134 mg (2 mmol) of freshly distilled pyrrole was dissolved in 50 ml of propionic acid and heated at 140°C for 4hrs with stirring. After the usual work up procedure was conducted as described above, the black residue obtained was subjected to column chromatography on flash silica gel using chloroform : methanol (97 : 3) mixture as eluent. Four separate purple colored atropisomeric fractions were collected, which after concentration gave a dark purple solid **2c** (54 mg, 10.6%). Identification and characterization of all the four fractions indicated that they contain the same compound. The first fraction was isolated as a single isomer. Mp : > 300 °C. Anal. calcd. for C₆₀H₃₈N₈Cl₄ : C, 71.15; H, 3.78; N, 11.06. Found: C, 71.02; H, 3.86; N, 11.12%. FAB-MS m/z 1013 (M+1)⁺, requires 1012. UV: λ_{max} nm (CHCl₃) (log ξ): 430 (5.566), 520(4.64), 601 (4.11), 661 (4.00). ¹H NMR (CDCl₃ + DMSO- d₆) δ ppm : 9.07 (m, 8H, pyrrole β-protons), 8.56 (s, 4H, quinoline C₄-H), 7.95 (d, 4H, quinoline C₈-H), 7.65 (m, 8H, quinoline C₅ & C₇ -H), 2.56 (s, 12H, 4x -CH₃), -2.60 (s, 2H, porphyrin N-H). IR (KBr) cm⁻¹: 3432 (w, porphyrin N-H stretch), 1602, 1578, 1484, 1452 (m, aromatic C=C, C=N ring stretch), 970, 956 (m, porphyrin macrocyclic bend), 812, 786 (s, aromatic C=C-H out-of plane bend).

Synthesis of *meso*- tetrakis(2-chloro-7-methoxyquinolin-3-yl)porphyrin (2d). A mixture of 443 mg (2 mmol) of 2-chloro-7-methoxyquinoline-3-carboxaldehyde (**1d**) and 134 mg (2 mmol) of freshly distilled pyrrole was dissolved in 50 ml of propionic acid and heated at 140 °C for 4h while stirring. Following the usual workup procedure as described above, the black residue procured was subjected to column chromatography on flash silica gel using chloroform :

methanol (98 : 2) mixture as eluent. Four separate purple colored atropisomeric fractions were collected, which after concentration gave a dark purple solid **2d** (62 mg, 11.5%). All the four fractions obtained contain the same compound. The first fraction was isolated as a single isomer. Mp : > 300 °C .Anal. calcd. for C₆₀H₃₈N₈O₄Cl₄ : C, 66.92; H, 3.56; N, 10.41. Found: C, 66.98; H, 3.64; N, 10.35%. FAB-MS m/z 1077 (M+1)⁺, requires 1076. UV: λ_{max} nm (CHCl₃) (log ξ): 430 (5.50), 520(4.41), 601 (4.21), 661 (4.00). ¹H NMR (CDCl₃ + DMSO -d₆) δ ppm : 9.05 (m, 8H, pyrrole β-protons), 8.63 (s, 4H, quinoline C₄-H), 7.84 (d, 4H, quinoline C₅-H), 7.37 (s, 4H, quinoline C₈-H), 7.27 (d, 4H, quinoline C₆-H), 3.98 (s, 12H, 4x O-CH₃), -2.60 (s, 2H, porphyrin N-H). IR (KBr) cm⁻¹: 3430 (w, porphyrin N-H stretch), 1620, 1585, 1492, 1464 (m, aromatic C=C, C=N ring stretch), 968, 958 (m, porphyrin macrocyclic bend), 832, 798 (s, aromatic C=C-H out-of plane bend).

Conclusions

meso-Tetrakis (-2-chloroquinolin-3-yl) porphyrins (**2a-2d**) were obtained in 10-12% yields when propionic acid is used in proportions of 25-30 ml for 1 mmol of quinoline aldehyde. These porphyrins may be useful for molecular recognition of carbohydrates.

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