Tetrahedron Letters No. 17, pp 1469 - 1472, 1977. Pergamon Press. Printed in Great Britain.

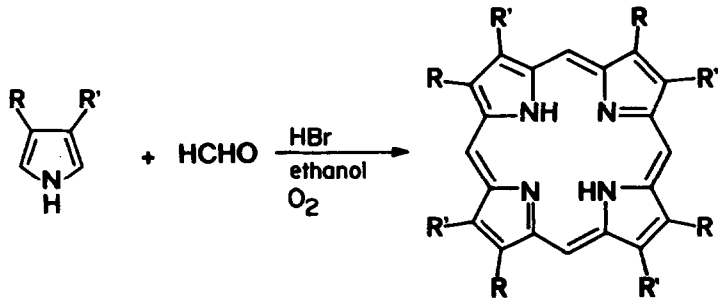
SYNTHESIS OF SUBSTITUTED PORPHYRINS

D.O. Cheng and Eugene LeGoff*
Department of Chemistry, Michigan State University
East Lansing, Michigan 48824

(Received in USA 30 November 1976; received in UK for publication 16 March 1977)

We have found that octasubstituted porphyrins having no substituents in the meso positions can be prepared in high yields by acid catalyzed condensation of formaldehyde with a variety of 3,4-disubstituted pyrroles. This improved procedure circumvents the need to prepare aldehyde, aminomethyl, or hydroxymethyl pyrrole precursors and gives higher yields than previously reported procedures involving formaldehyde and 3,4-dimethylpyrrole and 3,4-diphenylpyrrole.[1]

The reactions are carried out by refluxing for several hours an ethanolic solution of a 3,4-disubstituted pyrrole with an excess of formaldehyde and a strong acid such as hydrobromic or hydrochloric acids. The reactions mixtures are allowed to stand exposed to the air for periods of a few days to several weeks. Slow oxidation in this way gives somewhat better yields than procedures involving bubbling air through the reaction mixture.



1-7

For reactions where R ≠ R' four isomeric porphyrins are possible. In the case of tetraacetyltetraethylprophyrin, 1, we find that ∿95% of the reaction product consists of three of these isomers, 2,7,13,18-tetraacetyl-3,8,12,17-tetraethylporphyrin, 1a, 2,8,13,18-tetraacetyl-3,7,12,17-tetraethylprophyrin, 1b, and 2,8,12,18-tetraacetyl-3,7,13,17-tetraethylporphyrin, 1c, in the ratios of about 1:4:2 respectively.

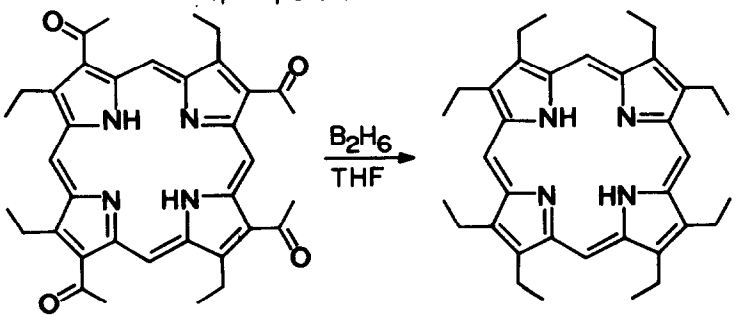
For reactions where R = R' = alkyl symmetrical porphyrins are obtained in good yields using this simplified procedure. Thus, condensing formaldehyde with 3,4-dimethylpyrrole gives after air oxidation 2,3,7,8,12,13,17,18-octamethylporphyrin, 6, in 76% while 3,4-diethylpyrrole gives 2,3,7,8,12,13,17,18-octaethylporphyrin, 7, in 65% yields.

[*Dedicated to Professor R.B. Woodward on the occasion of his 60th birthday.*]

Porphyrin, R ≠ R'	% Yield	Visible Spectrum (CH_2Cl_2), λ_{max}
1 R,R' = C_2H_5-,CH_3CO-	96	428 (Soret), 524, 560, 596, 652 nm
2 R,R' = CH_3-,CH_3CO-	64	429 (Soret), 524, 559, 596, 653 nm
3 R,R' = CH_3-,-$CO_2C_2H_5$	92	425 (Soret), 521, 556, 595, 651 nm
4 R,R' = CH_3-,-$CO_2C_8H_{17}$	52	424 (Soret), 520, 555, 593, 650 nm
5 R,R' = Ph-,-$CO_2C_2H_5$	86	433 (Soret), 525, 560, 595, 654 nm
6 R=R' = CH_3-	76	398 (Soret), 491, 530, 567, 592, 620 nm
7 R=R' = C_2H_5-	65	398 (Soret), 496, 531, 568, 594, 621 nm

The successful synthesis of these porphyrins seems to be restricted to the condition described here. Changing solvents (e.g., methanol or tetrahydrofuran) results in little or no porphyrin formation. Likewise, we have been unable to induce a variety of other aldehydes to form meso-substituted porphyrins. Instead visible spectral data suggest that the reactions are giving mainly dipyrrylmethene salts.

For many reactions involving transformation of the peripheral substituents the use of these isomeric porphyrin mixtures proves wholly satisfactory. Thus, diborane reduction of the carbonyl groups of 1 affords octaethylporphyrin, 7, (R=R'=C_2H_5) in a 97% yield. This represents an overall yield of 55% for a four step sequence.[2]



(mixture of isomers) 97% YIELD

Heating tetracarbethoxytetraphenylporphyrin, 5, with LiI in dimethylformamide cleaves the hindered ester[4] affording the tetracarboxylic acid 8, (R,R'=Ph or -CO_2H) [λ_{max} (5% aq. Na_2CO_3): 413 (Soret), 512, 548, 574, 624] in 85% yield. Hydrolysis of tetracarbethoxytetramethylporphyrin, 3, with KOH in H_2O/THF gives the tetracarboxylic acid 9, (R,R'=CH_3 or -CO_2H) [λ_{max} (5% aq. Na_2CO_3): 403 (Soret), 504, 542, 568, 620] in 93% yield. This same acid, 9, can be prepared in low yields via a prebiotic type synthesis by condensing 4-methyl-3-pyrrolecarboxylic acid with formaldehyde in dilute aqueous hydrochloric acid.

Reesterification of the tetracarboxylic acid 9 with dodecyl iodide in the presence of triethylamine[5] gives a 32% yield of the hexane soluble tetracarbododecoxytetramethylporphyrin, 10, (R,R'=CH_3 or -$CO_2C_{12}H_{25}$) [λ_{max} (CH_2Cl_2): 424 (Soret), 522, 556, 602, 665]. In non-polar solvents

(hexane) the Soret bands of the tetraesters 10 (λ_{max} 409 and 423 nm) and 5 (λ_{max} 408 and 421 nm) are split into a concentration dependent doublet. We attribute this to aggregation of these non-polar porphyrins a phenomenon observed in other porphyrin systems.[6]

These new high yield porphyrin syntheses and their transformation products will allow the preparation of a large variety of customized porphyrins having a substitution pattern more like those which occur naturally (i.e., unsubstituted in the meso-positions). The following represent general procedures for the synthesis of these porphyrins.

3-acetyl-4-ethylpyrrole: A solution of 3.9 g (20 mmol) of toluenesulfonylmethyl isocyanide[7] and 2.0 g (20 mmol) of 3-hexen-2-one (prepared in 70% yield from acetylmethyltriphenylphosphorane and propionaldehyde) in 100 ml of 2:1 ether-dimethylsulfoxide is added to an ether suspension of 2.0 g (44 mmol) of 51% NaH. After 15 min 400 ml of H_2O was added. The ether layer was separated and the aqueous layer extracted with 3 x 50 ml portions of ether. The combined ether extracts were freed of ether, taken up in CH_2Cl_2 and chromatographed on alumina yielding 2.5 g (91% yield) of 3-acetyl-4-ethylpyrrole, mp 60.5-62°C; pmr ($CDCl_3$): δ7.3 (m, 1H, pyrrolic-H), 6.5 (m, 1H, pyrrolic-H), 2,75 (q, 2H, $\underline{CH_2}$), 2.38 (s, 3H, $\underline{CH_3}CO$), 1.2 (t, 3H, $\underline{CH_3}$).

The following 3,4-disubstituted pyrroles were prepared using this same general procedure[8]: (R,R', % yield), CH_3, CH_3CO-, 84; CH_3-, -$CO_2C_2H_5$, 70; CH_3-, -$CO_2C_8H_{17}$, 91; Ph-, -$CO_2C_2H_5$, 60.

Tetraacetyltetraethylporphyrin, 1: A mixture of 2 g (15 mmol) of 3-acetyl-4-ethylpyrrole, 60 ml of 40% aqueous formaldehyde and 24 ml of 48% hydrobromic acid in 600 ml of ethanol were refluxed for 10 hr. This mixture was allowed to stand in an open beaker for 10 days. Filtering the reaction mixture gave 532 mg of 1. The filtrate was neutralyzed with dilute aqueous NaOH then extracted with methylene chloride. The methylene chloride extract was evaporated and the residue chromatographed on alumina affording an additional 1.54 g of 1 (total yield 96%); λ_{max} (CH_2Cl_2): 428nm (3.1×10^5), 524 (2.5×10^4), 560 (1.1×10^4), 596 (1.0×10^4), 652 (4.6×10^3). HPLC on silica gel-eluent 0.5% CH_3OH in CH_2Cl_2) gave in order of elution: isomer 1a, pmr ($CDCl_3$); δ10.30 (s, 1H, meso-H), 9.93 (s, 2H, meso-H), 9.03 (s, 1H, meso-H), 4.03 (m, 8H, $\underline{CH_3}$), 3.30 (s, 6H, $\underline{CH_3}CO$), 3.23 (s, 6H, $\underline{CH_3}CO$), 1.70 (m, 12H, $\underline{CH_2}$), -4.97 (s, 2H, N-$\underline{H}$); isomer 1b: 10.58 (s, 1H, meso-H), 10.22 (s, 2H, meso-H), 9.43 (s, 1H, meso-H), 4.13 (m, 8H, $\underline{CH_2}$), 3.33 (2 singlets, 6$\underline{H}$, CH_3CO), 3.23 (2 singlets, 6$\underline{H}$, CH_3CO), 1.80 (m, 12H, $\underline{CH_3}$) -4.45 (s, 2H, N-$\underline{H}$); isomer 1c: 10.76 (s, 2H, meso-H), 9.76 (s, 2H, meso-H), 4.18 (q, 8H, $\underline{CH_2}$), 3.33 (s, 12H, $\underline{CH_3}CO$), 1.86 (t, 12H, $\underline{CH_3}$), -4.37 (s, 2H, N-$\underline{H}$).

Octamethylporphyrin, 6: A solution of 190 mg (2 mmol) of 3,4-diemthylpyrrole[9,10] in 20 ml of ethanol (95%) was added to a warm solution of 2 ml of 40% aqueous formaldehyde, 1 ml of 1N hydrochloric acid and 20 ml of ethanol at 50-60°C. The mixture was stirred at this temperature for 1 hr, then allowed to stand at 20°C for 3 days. Filtering the reaction mixture gave 27 mg of octamethylporphyrin. The filtrate was diluted with H_2O, neutralized with aqueous NaOH and extracted with CH_2Cl_2. Evaporation of the CH_2Cl_2 gave a residue which was washed with cold methanol. There was obtained an additional 134 mg of octamethylporphyrin (76% yield).

Octaethylporphyrin, 7: To a solution (0°C) of 175 mg (0.3 mmol) of 1 in 60 ml of freshly distilled tetrahydrofuran was added under N_2 4 ml (4 mmol) of 1N diborane-THF solution. The reaction mixture was stirred for 1 hr at 0°C then for 2 hrs at 20°. It was then cooled to 0°C and 45 ml of 5% aqueous HCl added dropwise keeping the temperature below 35°C. The resulting solution was added to 100 ml of 1M aqueous Na_2CO_3 and the whole mixture extracted with CH_2Cl_2. Removal of the solvent followed by chromatography of the residue on neutral alumina ($CHCl_3$ eluent) afforded 115 mg of octaethylporphyrin, 7, (97% yield) which proved identical to an authentic sample.

Tetramethylporphyrintetracarboxylic acid, 9: A mixture of 653 mg (1 mmol) of tetramethyltetracarbethoxyporphyrin, 9, in 45 ml of 1N KOH solution in 200 ml of distilled tetrahydrofuran was refluxed for 150 hrs (under N_2). The solvents were removed under reduced pressure and the resulting residue dissolved in 50 ml of H_2O. Acidification to pH = 1 with hydrochloric acid caused a precipitate to form. This was collected by centrifugation and washed repeatedly with H_2O. There was obtained 503 mg (93% yield) of 9; λ_{max} (5% aq. Na_2CO_3); 403 nm (ε 2.2×10^5), 507 (1.7×10^4), 542 (1.0×10^4), 568 (8.5×10^3), 620 (4.2×10^3).

Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

References and Notes

* To whom correspondence should be addressed.

1) A. Treibs and N. Häberle, Liebigs Ann. Chem., 718, 183 (1968).
2) The sequence from commercially available starting materials involves the syntheses: 3-hexen-2-one → 3-acetyl-4-ethylpyrrole → porphyrin 1 → OEP, 7. Cf ref. 3, 11.
3) H.W. Whitlock and R. Hanuer, J. Org. Chem., 33, 2169 (1968).
4) P.D.G. Dean, J. Chem. Soc., 6655 (1965).
5) R.H. Mills, M.W. Farrar, and O.J. Weinkauff, Chem. Ind., 2144 (1962).
6) H. Scheer and J.J. Katz in "Porphyrins and Metalloporphyrins," K.M. Smith, Ed., Elsevier Scientific Publishing Co., Amsterdam, 1975, pp 493-501.
7) "Organic Syntheses," Vol. 55, John Wiley & Son, Inc., NY (1976) Unchecked Procedure #1941.
8) A.M. van Leusen, H. Siderius, B.E. Hoogenboom, and D. van Leusen, Tetrahedron Lett., 5337 (1972).
9) D.O. Cheng, T.L. Bowman and E. LeGoff, J. Heterocyclic Chem., 13, 1145 (1976).
10) K. Ichimura, S. Ichikawa, and K. Imamura, Bull. Chem. Soc. Japan, 49, 1157 (1976).
11) J.B. Paine, W.B. Kirshner, D.W. Moskowitz and D. Dolphin, J. Org. Chem., 41, 3857 (1976).