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ONE-POT SYNTHESIS OF REGIOCHEMICALLY PURE PORPHYRINS FROM TWO DIFFERENT PYRROLES

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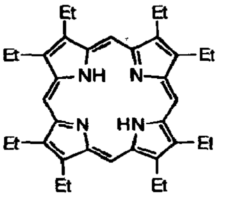
Abstract: Treatment of 2,5-di-unsubstituted pyrroles (e.g. **10**) with excess of Eschenmoser's reagent (N,N-dimethylmethyleneammonium iodide) affords 2,5-bis-(N,N-dimethylaminomethy)pyrroles (e.g. **7**); reaction with a second 2,5-di-unsubstituted pyrrole (e.g. **8**) gives pure porphyrin (e.g. **9**) with identical substituents on opposite pyrrole sub-units.

Numerous advances in porphyrin synthetic methodology have been reported in the last several years.[1,2] It still remains a fact, however, that if the target porphyrin is highly symmetrical (e.g. octaethylporphyrin **1** or tetraphenylporphyrin **2**) a one-pot monopyrrole "tetramerization" approach can be used, but if assymmetry is required in the porphyrin product and extensive chromatographic purification is to be avoided, more elaborate routes via dipyrroles, tripyrroles, and open-chain tetrapyrroles must be used.[3]



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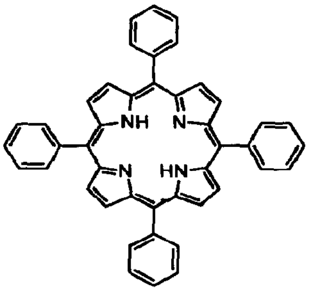

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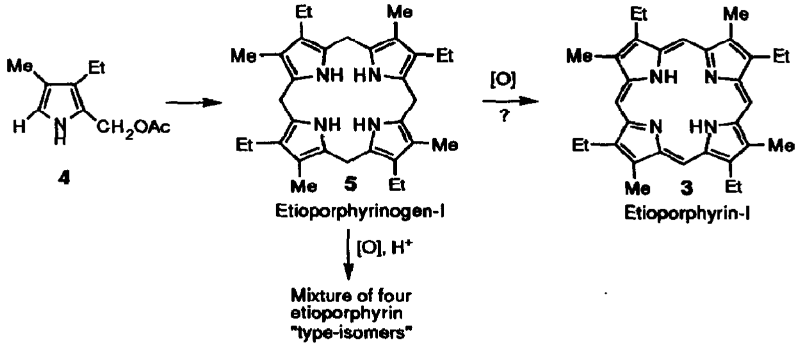
In principle, it should be possible to obtain a "type-I" porphyrin[4] 3 by acid catalyzed self-condensation of a pyrrole such as **4**, bearing a 2-substituent with a good leaving group at the benzylic carbon.[5] However, this is not the case presumably due to the fact (Scheme 1) that the intermediate porphyrinogen **5** suffers acid catalyzed "scrambling" of the pyrrole subunits.[6,7] The product is invariably a mixture of all four porphyrin type isomers.[7]



Scheme 1: Synthesis of Etioporphyrin(s) via Monopyrrole Polymerization

Nevertheless, it should be possible to avoid the formation of mixtures in such reactions if (i) the pyrrole **4** possesses a 2-substituent with a leaving group which is so reactive that it can be displaced without acid catalysis, and (ii) the intermediate porphyrinogen **5** is oxidized in situ to porphyrin **3** rapidly. An ideal 2-substituent, capable of fulfilling the above requirements due to the ready displacement of the leaving group (NMe_2) from the benzylic carbon under virtually neutral conditions, or after quaternization with methyl iodide, is dimethylaminomethyl. Moreover, it occurred to us that it should also be possible, in principle, to obtain a regiochemically pure porphyrin product (with like pyrrole rings opposite each other)[8] if one were to react two pyrroles together under neutral conditions, provided that one of those pyrroles (e.g. **7**) possessed all of the future meso-carbons of the porphyrin product, while the second pyrrole (e.g. **8**) contained none of them. In this paper we show that a one-pot reaction can indeed be used to obtain regiochemically pure porphyrins (e.g. **9**) from two different monopyrroles.

Treatment of 3,4-diethylpyrrole[9] **10** with excess of Eschenmoser's reagent[10] (N,N-dimethylmethyleneammonium iodide; Aldrich) in nitromethane afforded an 86% yield of the 2,5-bis(N,N-dimethylaminomethyl)pyrrole **7**.[11] When **7** was first treated with 3,4-dimethylpyrrole[9] **8** in acetic acid at reflux in presence of oxygen, as expected, a mixture of porphyrin products was obtained [^1H NMR (300 MHz, in $CDCl_3$), meso proton signals at 10.03, 10.07, and 10.10 ppm]; this is presumably a result of acid catalyzed scrambling of the initially formed porphyrinogen prior to aerobic oxidation to porphyrin.[6,7] Similar results were obtained when **7** and **8** were heated together in acetic acid containing potassium ferricyanide as oxidant.[12] However, reaction of pyrroles **7** and **8** in methanol in the presence of $K_3Fe(CN)_6$ gave a 19% yield of the required isomerically pure porphyrin **9**.[13] Figure 1 shows the X-ray structure[14] of the bis-perchlorate salt of **9**, clearly establishing the regiochemistry of the substituent array.

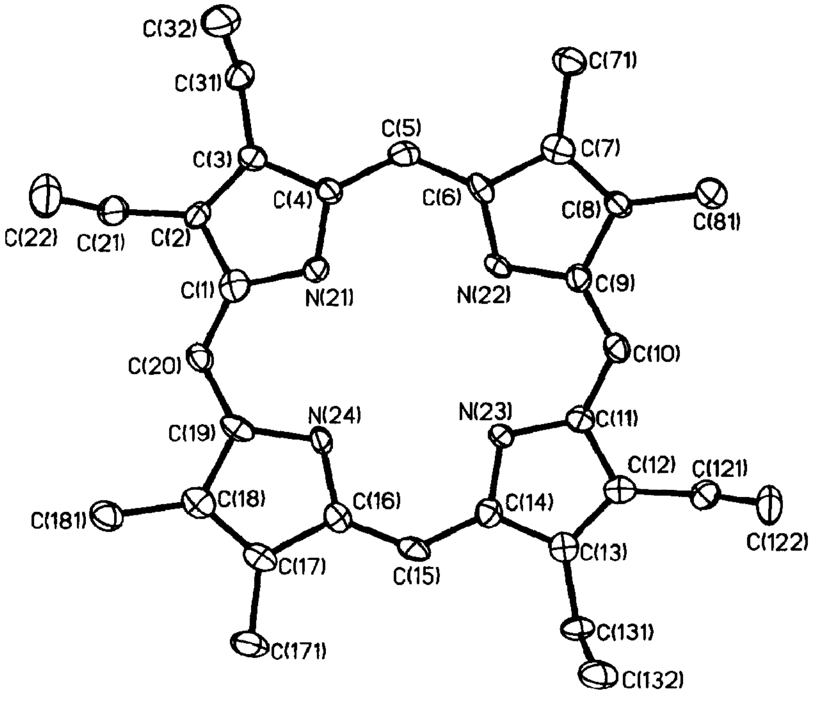
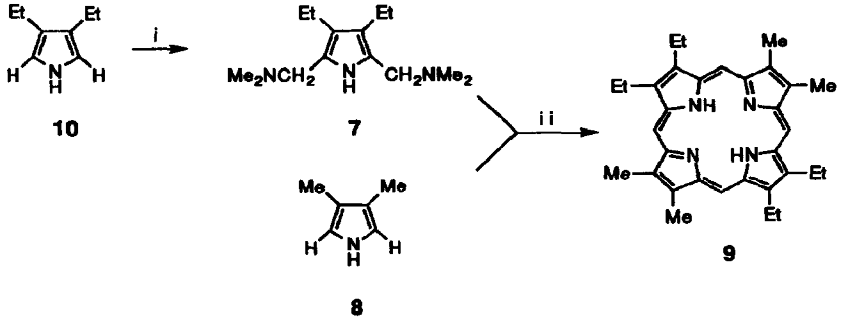
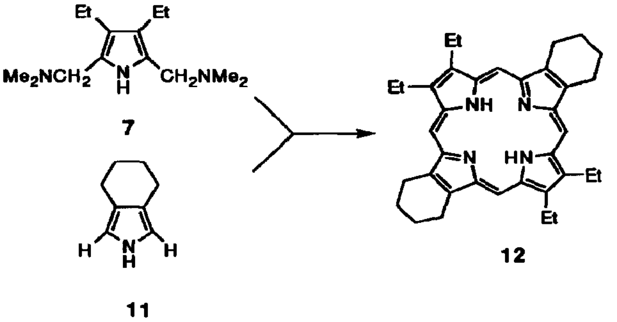


Figure 1: X-ray Structure[14] of Bis-Perchlorate Salt of Porphyrin **9** (counterions omitted for clarity)



Reagents: i, $I^- Me_2N^+=CH_2$; ii, MeOH, $K_3Fe_3(CN)_6$

Similar results were obtained using **7** and 3:4-butanopyrrole **11** to afford porphyrin **12**. Further applications of this methodology will be reported in due course.



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13. Typical procedure for synthesis of **9**: Pyrroles **7** (842 mg) and **8** (341 mg) were added to a solution of potassium ferricyanide (8.0 g) in methanol (75 mL). The mixture was heated under reflux for 3 h before being diluted with dichloromethane and washed with 5% aqueous ammonium hydroxide solution and then water. The organic phase was separated, dried (Na_2SO_4), and evaporated to dryness to give a residue which was triturated with methanol and the purple crystals were collected. Recrystallization from dichloromethane/cyclohexane gave 162 mg (19%) of **9**, mp >300°C, λ_{max} (CH_2Cl_2) 397 nm (ε 150,000), 498 (13,100), 530 (9700), 566 (6400), 618 (4900). ^{1}H NMR ($CDCl_3$), δ, 10.07 (s, 4H, meso-H), 4.10 (q *J* = 7.8 Hz, 8H, $C\underline{H}_2CH_3$), 3.61 (s, 12H, CH_3), 1.91 (t J = 7.8 Hz, 12H, $CH_2C\underline{H}_3$), -3.79 (br s, 2H, NH). See Figure 1 for X-ray structure of bis-perchlorate salt.[14]

14. Due to poor solubility of the free-base **9** the porphyrin dication diperchlorate was prepared by treatment of porphyrin **9** with 5% $HClO_4$ in CH_2Cl_2/CH_3OH. Crystal data: $[C_{32}H_{40}N_4][ClO_4]_2 \cdot CH_3OH$, M_r = 711.6, red plate, 0.15 x 0.15 x 0.016 mm, triclinic, space group P1, a = 9.377(4) Å, b = 11.538(4) Å, c = 16.406(7) Å, α = 73.96(3)°, β = 87.56(3)°, γ = 80.97(3)°, V = 1684.8(12) Å^3, Z = 2, μ = 2.244 mm^{-1}, Siemens P4(RA) diffractometer, Cu Kα radiation, λ = 1.54178 Å, $2\theta_{max}$ = 112°, R = 0.093 for 3149 observed reflections with F > 3.0 σ(F). Disorder in one perchlorate anion.

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