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Stepwise Syntheses of Core-modified, meso-Substituted Porphyrins

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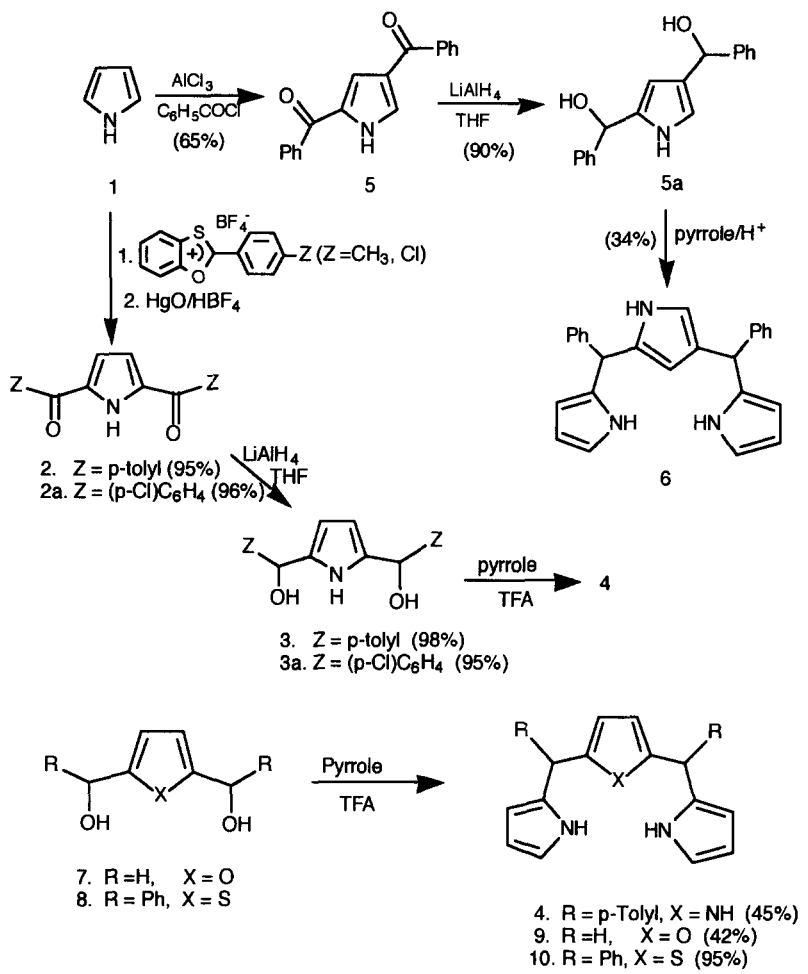
Simple conditions are discovered to afford modified tripyrrin derivatives by condensation of 2,5-bis(α-hydroxymethyl)pyrrole, thiophene and furan derivatives with pyrrole in the presence of acid catalyst. The core-modified porphyrins were synthesized by acid catalyzed 3 +1 condensation of modified tripyrrins with 2,5-bis(α-hydroxymethyl)-substituted pyrrole, thiophene or furan. This new process gives a single porphyrin isomer and overcome the synthetic problems associated with separation and purification of regioisomeric mixtures.

We recently developed an one-flask solventless synthesis of 1,9-unsubstituted, meso-substituted dipyrromethanes by acid-catalyzed condensation of an aldehyde with excess pyrrole.[1] This simple synthesis has provided the formulation for a stepwise synthesis of porphyrins bearing four different meso-substituents.[2] and prompted us to investigate a related method for synthesizing various tripyrrins for application in the syntheses of porphyrins bearing meso-substituents in a regiospecific manner. Here we report such a preparation of modified tripyrrins and their application to the synthesis of core-modified porphyrins with selective replacement of one or two nitrogen atoms with oxygen, carbon or sulfur. We found that modified tripyrrins such as **4**, **6**, **9** and **10** can be synthesized easily by reacting bis(α-hydroxymethyl)-substituted pyrroles (**3**), furan (**7**) or thiophene (**8**) with excess pyrrole in the presence of Lewis acid catalysts. The results are shown in Scheme 1. The best results were obtained when pyrrole itself was used as solvent.

It is known that α-(hydroxymethyl) substituted pyrroles are highly reactive and condense to give porphyrins in the presence of acid catalysts.[3] The reaction proceeds by equilibrium formation of a cationic intermediate after dehydration followed by nucleophilic attack by pyrrole. This mechanism indicates the possibility of controlling the equilibrium and product distribution by adjusting reactant concentrations. This was indeed the case. When bis-(α-hydroxymethyl)pyrrole derivatives, such as **3**, **3a** and **5a** dissolved in excess pyrrole (40 equiv.) were stirred at 25 °C in the presence of trifluoroacetic acid or $BF_3{\cdot}OEt_2$, the tripyrrins **4** and **6** were formed in 95% and 34% yields respectively.[4] TLC analysis of **4** showed no other products formation except small amounts of polymeric material at the origin. In the case of **6**, the major spot was also desired product but large amount of polymeric material left in the origin. We also found the same synthetic method could be applied in the synthesis of 16-thiatripyrrin **10** and 16-oxatripyrrin **9**.[5] The yields of tripyrrins varied depending on the nature of the starting substrates but maximum yields were obtained when $BF_3.OEt_2$ was used as catalyst. Compound **5** was readily synthesized by Friedel-Craft acylation[6] of pyrrole in the presence of excess anhydrous $AlCl_3$. Diol **5a** was obtained by reduction of 2,4-diacylpyrrole **5** with $LiAlH_4$. Because the Friedel-Craft acylation of pyrrole resulted in the 2,4-diacyl substituted pyrrole, independent approaches were applied to obtain the 2,5-diacyl substituted pyrroles **2** and **2a**. We adapted alkylation method developed by Barbero etal.[7a] Compounds **2** and **2a** were readily available by alkylation of pyrrole using 1,3-benzoxathiolium tetrafluoroborate as alkylating agent and subsequent oxidative cleavage of the resulting thioketal.[7b] The yields in each steps

were quantitative. Resulting 2,5-diacyl pyrroles **2** and **2a** were reduced by $LiAlH_4$ in THF to afford diols **3** and **3a** in quantitative yields.

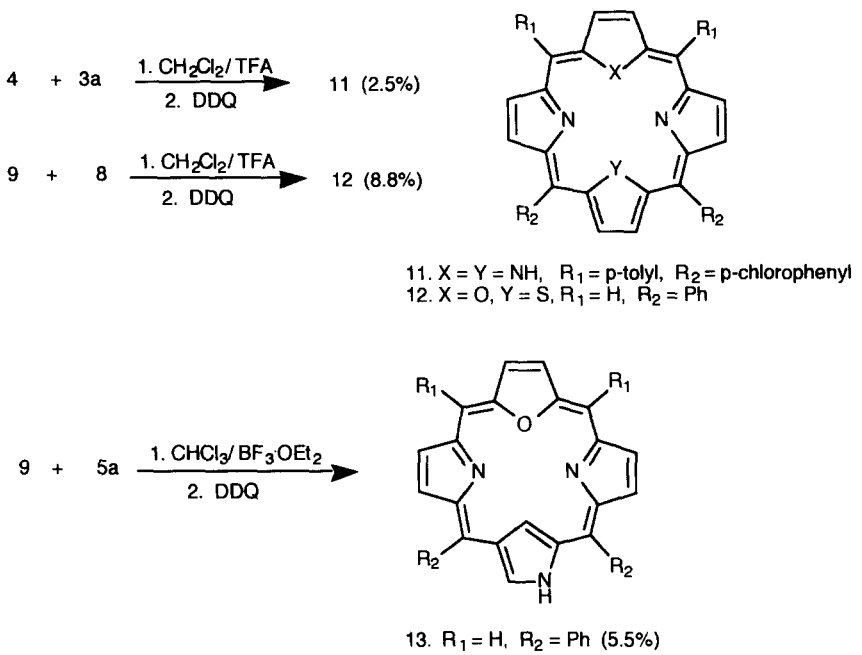
Scheme 1



The diols **3** and **3a** were rather unstable, so they were not purified extensively but IR spectra clearly indicated disappearance of the carbonyl stretching (~1630 cm^{-1}) frequency at the end of reduction and appearance of the hydroxy stretching (~3340 cm^{-1}) band. The obvious advantages of the present reactions are their wide applicability in synthesizing porphyrins having different meso-substituents in a regiospecific manner. In addition, there have been no previous examples of general synthetic methods for the preparation of 5,7-15,17-tetrahydrotripyrrins with hetero atoms (e.g. S, O) other than nitrogen at position 16. Attempted synthesis of porphyrins by the 3+1 condensation of **4**, **6** or **10** with **3**, **7** or **5a** respectively, under Lindsey condition[8] did not proceed well. But condensation of **4** with 2,5-bis[(α-(p-chlorophenyl)-α-hydroxy)]pyrrole **3a** gave porphyrin **11** (2.5% yield)[9] and condensation of **9** with **8** resulted in 22-thia-

24-oxa-5,10-diphenylporphyrin **12** in 8.8 % yield after extensive chromatographic separation.[9] Condensation of **9** with diol **5a** also resulted 22-carba-24-oxa-7-aza-5,10-diphenylporphyrin **13** in 5.5 % yield.[9]

Scheme 2



The ^1H NMR spectra of **12** indicated there were no N-H hydrogens in the cavity. The ^1H NMR spectra of **13** showed high field shift of the inner C-H at -3.20 ppm as sharp singlet due to aromatic ring current. Only a single isomeric porphyrin was observed and isolated in each reaction. It is known that replacement of the nitrogen atoms of the porphyrins with other potential ligands usually produces unique macrocycles with different cavity sizes and complexing abilities.[10] These approaches may provide novel routes to core-modified porphyrins with specific substitution patterns of hetero atoms. Currently, we are investigating the possibility of synthesizing other core-modified porphyrins and expanded porphyrins using these tripyrrins. The chemistry for preparing these new methods of porphyrin family and their metal complexes is now in hand.

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References and notes

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3. Kuroda, Y; Murase, H; Susuki, Y; Ogoshi, H. *Tetrahedron Lett.*, **30**, 2411 (1989).
4. All the tripyrromethanes were analyzed by ^1H NMR and mass spectrometry.
5. The 2,5-bis[(α-hydroxy-α-phenyl)methyl]thiophene (**8**) was synthesized[5a] and 2,5-furandimethanol was purchased from Aldrich. a). Ulman, A; Manassen, J. *J. Chem. Soc. Perkin Trans.I* ., 1066 (1979).
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9. Spectroscopic data for the new compounds are follow: ^1H NMR ($CDCl_3$) for **3** δ 8.60(br, 1H, N-H), 7.26(d, 4H, Ar-H, J = 7.6 Hz), 7.17(d, 4H, Ar-H, J = 7.6 Hz), 7.08(s, 2H, H-3, H-4), 5.74 - 5.82(m, 2H, meso-H), 3.86(s, 2H, OH), 2.34(s, 6H, methyl); **3a** δ 7.90(d, 4H, Ar-H, J = 6.7 Hz), 7.52(d, 4H, Ar-H, J = 6.7 Hz), 6.88(s, 2H, pyrrole-H), 5.66(bs, 1H, N-H); **4** δ 7.86(bs, 2H, N-H), 7.69(bs, 1H, N-H), 7.02 - 7.12(m, 8H, Ar-H), 6.64(m, 2H), 6.11(m, 2H), 5.95(bs, 2H), 5.74(2s, 2H, pyrrole-H), 5.31(s, 2H, meso-H), 2.34(s, 6H, methyl); **5a.** δ 8.40(bs, 1H, N-H), 7.25(m, 10H, Ar-H), 6.27(d, 1H, pyrrole-H), 5.78(d, 1H, pyrrole-H), 5.57(d, 1H, meso-H), 5.58(s, 1H, meso-H), 3.65(bs, 1H, OH), 2.92(bs, 1H, OH); **6** δ 7.91(m, 2H, N-H), 7.72(m, 1H, N-H), 7.33-7.15(m, 10H, Ar-H), 6.66(m, 2H), 6.33(s, 1H), 6.14(m, 2H), 5.87(m, 2H), 5.42(s, 1H, meso-H), 5.30(s, 1H, meso-H), MALDI (Matrix Assisted Laser Desorption Ionization) MS Calc. for $C_{26}H_{23}N_3$ 377.2, Found 376.2 (M^+-H^+); **9** δ 7.91(bs, 2H, N-H), 6.59-6.57(m, 2H, pyrrole-H), 6.12-6.09(m, 2H, pyrrole-H), 5.98(bs, 2H, pyrrole-H), 5.92(s, 2H, furan-H), 3.87(s, 4H, meso-H); **10** δ 7.89(brs, 2H, N-H), 7.36-7.25(m, 10H, Ar-H), 6.83(m, 2H, pyrrole-H), 6.69(s, 2H, thiophene-H), 6.15(m, 2H, pyrrole-H), 5.93(m, 2H, pyrrole-H), 5.57(s, 2H, meso-H), **11** δ 8.64(m, 8H, Ar-H), 8.12(m, 8H, Ar-H), 7.74(m, 4H), 7.56(m, 4H), 2.71(s, 12H, methyl), -2.82(s, 2H, N-H)., MALDI (Matrix Assisted Laser Desorption Ionization) MS Calcd for $C_{46}H_{32}N_4O_2$ 711.69, Found 711.9, UV-vis (CH_2Cl_2) λ_{max} (ε x 10^3); 418(497), 515(19), 550(9), 590(6), 646(4); **12** δ 10.16(s, 2H, meso-H), 9.86(s, 2H, thiophene-H), 9.78(s, 2H, furan-H), 9.09(d, 2H, pyrrole-H), 8.80(d, 2H, pyrrole-H), 8.27-8.23(m, 4H, Ar-H), 7.86-7.80(m, 6H, Ar-H), MALDI (Matrix Assisted Laser Desorption Ionization) MS Calcd for $C_{32}H_{20}N_2SO$ 480.5, Found 480.5, UV-vis (CH_2Cl_2) λ_{max} (ε x 10^3); 416(121), 498(17), 628(1), 691(3); **13** δ 10.19 (s, 1H,), 9.82(s, 1H), 9.33 (d,1H), 9.20(s, 1H), 9.16 and 8.86 (AA'BB', 2H), 8.97 (s, 1H), 8.74-8.67 (m, 3H), 8.27-8.18 (m, 4H, Ar-H), 7.86-7.75 (m, 6H, Ar-H), -3.20 (bs, 1H, inner C-H). MALDI (Matrix Assisted Laser Desorption Ionization) MS Calcd for $C_{32}H_{21}N_3O$ 463.54, Found 464.2, UV-vis(CH_2Cl_2) λ_{max}(ε x 10^3); 409(70.6), 427(45), 470(13.6), 538(5.4), 564(4.8), 691(1.0).
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