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Preparation of tripyrrane analogues from resorcinol and 2-methylresorcinol for applications in the synthesis of new benziporphyrin systems†

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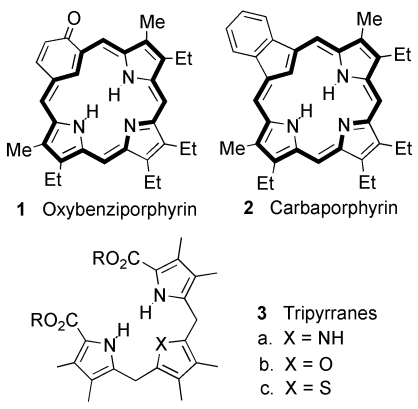
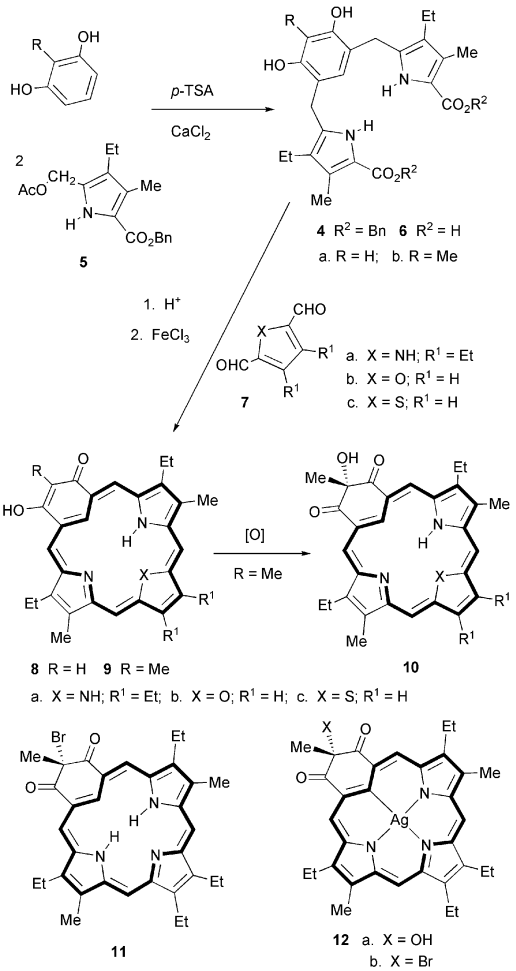
Acid catalyzed condensation of resorcinol or 2-methylresorcinol with 2 equiv. of an acetoxymethylpyrrole gave bis(pyrrolylmethyl)benzene derivatives in moderate yields; these afforded a series of novel aromatic benziporphyrins using the MacDonald "3 + 1" methodology.

The study of porphyrin analogue systems has intensified in recent years.[1] This is due in part to the unusual chemical properties exhibited by these conjugated macrocycles, which include the ability to form metal complexes with unusual oxidation levels.[2,3] In addition, these systems show potential value in the development of new catalysts[4] and as photosensitizers in photodynamic therapy.[5] Carbaporphyrinoids, where one or more of the pyrrole subunits have been replaced by carbocyclic rings, represent an important group of porphyrin analogues that exhibit unusual chemical and spectroscopic properties.[6,7] These systems, which include oxybenziporphyrins **1**[7] and benzocarbaporphyrins **2**,[8] are generally synthesized by condensing tripyrrane intermediates **3a** with carbocyclic dialdehydes using the MacDonald "3 + 1" methodology.[9] This approach is limited in that only one of the pyrrole rings can easily be replaced with a carbocyclic subunit. Tripyrrane analogues with furan (**3b**) or thiophene rings (**3c**) replacing the central pyrrole units have been known for some time,[10] but the synthesis of related systems with carbocyclic rings has proven to be fraught with difficulties.[11] Recently, we reported that azulene could undergo electrophilic substitution with acetoxymethylpyrroles to afford tripyrrane analogues and this facilitated the synthesis of novel azuliporphyrin products.[12] We now report the successful application of this strategy to tripyrrane-like intermediates from resorcinol and 2-methylresorcinol, and their use in the synthesis of novel aromatic benziporphyrin derivatives.

The construction of simple tripyrrane structures **3a** relies upon the reactivity of simple pyrroles towards electrophilic substitution at the two α-positions.[13] Resorcinol is similarly activated towards electrophilic substitution at the equivalent 4- and 6-positions (the 2-position is less accessible due to steric constraints) and this consideration suggests that this feature should allow the construction of tripyrrane analogues **4** (Scheme 1). However, this strategy proved to be surprisingly challenging. Reactions of resorcinol with 2 equiv. of acetoxymethylpyrrole **5** were carried out under many different conditions, but in most cases the required tripyrrane analogue **4a** was obtained in very low yields. Acid catalyzed reactions gave superior results to base catalyzed condensations. When Montmorillonite clay in acetic acid was used, the "benzitripyrrane" **4a** was isolated in 6% yield, but this was increased to 15% in diethyl ether and 17% in dichloromethane. *p*-Toluenesulfonic acid in dichloromethane gave 12% yield but addition of $CaCl_2$ to the reaction mixture gave a synergistic improvement to afford yields of 24%. The major problem encountered in this type of chemistry is the self-condensation of the acetoxymethylpyrroles to produce dipyrrolic by-products. In an attempt to limit these self-condensation reactions, a solution of **5** in dichloromethane was added using a syringe pump over a 10 h period to a stirred mixture of resorcinol, *p*-toluenesulfonic acid and $CaCl_2$ in the same solvent. This protocol gave the best yields and following chromatography on silica eluting with 15% ethyl acetate–toluene and recrystallization from $CHCl_3$–hexanes, the benzitripyrrane was obtained in 33%





Scheme 1

† Part 31 of the series 'Conjugated Macrocycles Related to the Porphyrins'. Part 30: J. T. Szymanski and T. D. Lash, *Tetrahedron Lett.*, 2003, **44**, 8613–8616.

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yield. Using the same conditions, 2-methylresorcinol reacted with 2 equiv. of **5** to give the related tripyrrane analogue **4b** in 30% yield.

Hydrogenolysis of benzitripyrranes **4** in THF–methanol over 10% Pd/C cleaved the benzyl ester protective groups to afford the related dicarboxylic acids **6** in quantitative yields. These were reacted with dialdehydes **7** in the presence of TFA–CH_2Cl_2, and following oxidation with dil. aq. $FeCl_3$ solutions the macrocyclic products **8–10** were isolated. Reaction of **6a** with pyrroledialdehyde **7a**, followed by oxidation, chromatography on silica eluting with 5% MeOH–$CHCl_3$ and recrystallization from $CHCl_3$–hexanes, gave the hydroxyoxybenziporphyrin **8a** as brown crystals in 37% yield.‡ The proton NMR spectrum in TFA–$CDCl_3$ showed the presence of a strong diatropic ring current with the external *meso*-protons resonating at 8.9 and 10.0 ppm, while the internal CH was observed at −2.5 ppm. The UV-vis spectrum of **8a** in 1% TEA–$CHCl_3$ was also porphyrin-like, showing a Soret band at 419 nm ($\log_{10}\varepsilon$ = 5.15) and a series of weaker Q bands at 526, 569, 619 and 681 nm. A similar hydroxyoxybenziporphyrin was previously obtained by treating a dimethoxybenziporphyrin with HBr in refluxing acetic acid.[7c] Reaction of **6a** with furan dialdehyde **7b** or thiophene dialdehyde **7c** also gave good yields of the related porphyrinoids **8b,c** but these products proved to be very insoluble and could not be fully characterized.

Benzitripyrrane **6b** also reacted with pyrroledialdehyde **7a** under the same conditions, but in this case two macrocyclic products, **9a** and **10a**, were generated. 2-Methyloxybenziporphyrin **9a** was the anticipated product for this chemistry while **10a** represents an oxidized version with the same carbon skeleton. Mixtures of the two products could be isolated in good yields (*ca.* 40%). Following chromatography on silica and recrystallization, **9a** and **10a** were obtained in 27% and 5% yield, respectively. However, oxybenziporphyrin **9a** proved to be unstable in solution and in the presence of air afforded additional **10a**. Unfortunately, this conversion gave poor yields of **10a** and led to considerable decomposition. Different oxidation conditions were investigated, and the best results were obtained when the crude mixture of **9a** and **10a** was treated with K_2CO_3 and $PhI(OCOCF_3)_2$ in MeOH–CH_2Cl_2. Under these conditions, 3-hydroxy diketone **10a** could be isolated in pure form in overall 26% yield from benzitripyrrane **6b**. Alternatively, treatment of purified **9a** with 1 equiv. of Br_2 in acetic acid afforded the related 3-bromo derivative **11** in 44% yield. Condensation of diformylfuran **7b** with **6b** gave a mixture of **9b** and **10b**, and following oxidation of the crude mixture with $PhI(OCOCF_3)_2$, the novel oxabenziporphyrin **10b** was isolated in 20% yield. Thiophenedicarbaldehyde **7c** similarly afforded the related thiabenziporphyrins, and following oxidation the 3-hydroxy derivative **10c** was isolated in 6% yield.

The oxidized macrocycles **10a–c** were highly diatropic, and their proton NMR spectra in TFA–$CDCl_3$ showed the internal CH protons between −6.4 and −7.0 ppm.‡ Interestingly, the protonated species generated from these macrocycles in 1% TFA–$CHCl_3$ all showed split Soret bands with values of 411/426, 395/430 and 422/453 nm, for **10a**, **10b** and **10c**, respectively. More significantly, these carbaporphyrinoids were fairly soluble in $CHCl_3$ and were reasonably stable in solution. These properties have allowed preliminary exploration into the chemistry of **10a**. Carbaporphyrins **2** have been shown to react with silver(I) acetate to afford the related silver(III) organometallic derivatives.[14] As **10a** has a similar arrangement of core atoms, it was of some interest to see whether this unusual metalation chemistry also occurred for this macrocycle. As it turned out **10a** reacted with AgOAc in CH_2Cl_2–MeOH at room temp. to give the silver(III) complex **12a** in 87% yield. The silver derivative gave deep orange solutions and showed a Soret-like band at 422 nm. In the proton NMR spectrum for **12a**, the *meso*-protons resonated at 9.03 and 9.83 ppm providing further evidence for this species having aromatic character. The bromoporphyrinoid **11** also reacted with AgOAc to give the related silver derivative **12b**, although in this case the yield was very poor (9%). This is almost certainly due to the high affinity of silver(I) ions for bromine as this would be expected to lead to side reactions.

In summary, the preparation of new tripyrrane analogues form resorcinol and 2-methylresorcinol has been accomplished. These are shown to be useful intermediates for the synthesis of a series of benziporphyrins that show interesting chemistry, such as the ability to generate silver(III) organometallic derivatives. In addition, this approach will allow the synthesis of many additional carbaporphyrinoid systems.

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Notes and references

‡ Selected spectroscopic data: **4a**: mp 216–217 °C; ^{1}H NMR (d_6-DMSO): δ 0.67 (6H, t, J = 7.6 Hz), 2.07 (4H, q, J = 7.6 Hz), 2.11 (6H, s), 3.57 (4H, s), 5.20 (4H, s), 6.16 (1H, s), 6.34 (1H, s), 7.28–7.41 (10H, m), 9.16 (2H, s), 10.70 (2H, br s); ^{13}C NMR (d_6-DMSO): δ 10.4, 15.2, 16.7, 24.9, 64.3, 69.3, 102.2, 115.6, 116.4, 123.1, 126.2, 127.7, 127.8, 128.5, 129.8, 133.6, 137.2, 153.3, 160.6. Anal. calcd for $C_{38}H_{40}N_2O_6$: C, 73.53; H, 6.49; N, 4.51. Found: C, 73.66; H, 6.44; N, 4.53%. **4b**: mp 161–163 °C; ^{1}H NMR (d_6-DMSO): δ 1.03 (6H, t, J = 7.4 Hz), 1.90 (3H, s), 2.27 (6H, s), 2.44 (4H, q, J = 7.6 Hz), 3.76 (4H, s), 5.24 (4H, s), 5.37 (2H, br s), 6.66 (1H, s), 7.27–7.38 (10H, m), 8.95 (2H, br s); ^{13}C NMR (d_6-DMSO): δ 8.6, 10.8, 15.7, 17.4, 27.3, 65.7, 111.4, 117.6 (2), 124.2, 127.4, 128.1, 128.7, 128.9, 132.2, 136.9, 151.6, 161.9. Anal. calcd for $C_{39}H_{42}N_2O_6$: C, 73.79; H, 6.67; N, 4.41. Found: C, 73.43; H, 6.65; N, 4.47%. **10a**: mp > 300 °C; UV-vis (1% Et_3N–$CHCl_3$): λ_{max} ($\log_{10}\varepsilon$) 384 (infl., 4.90), 417 (5.11), 509 (4.14), 544 (4.08), 593 nm (3.75); UV-vis (1% TFA–$CHCl_3$): λ_{max} ($\log_{10}\varepsilon$) 411 (5.32), 426 (5.32), 533 (4.08), 569 (3.93), 584 nm (4.08); ^{1}H NMR ($CDCl_3$): δ −7.99 (1H, s), 0.07 (3H, s), 1.76 (12H, m), 3.54 (6H, s), 3.83 (4H, m), 4.03 (4H, m), 9.54 (2H, s), 10.33 (2H, s); ^{13}C NMR ($CDCl_3$): δ 11.2, 17.5, 18.5, 19.9, 20.0, 30.2, 86.2, 94.9, 103.2, 119.7, 120.1, 130.4, 131.3, 138.4, 143.5, 145.1, 154.3, 201.4; HRMS (FAB): calcd for $C_{33}H_{37}N_3O_3$ + H: m/z 524.2913. Found 524.2916. Anal. calcd for $C_{33}H_{37}N_3O_3$: C, 75.69; H, 7.12; N, 8.02. Found: C, 75.42; H, 6.94; N, 8.05%. **10b**: mp > 300 °C; ^{1}H NMR (TFA–$CDCl_3$): δ −6.88 (1H, s), −4.11 (1H, br s), 1.46 (3H, s), 1.68 (12H, m), 3.63 (6H, s), 4.09 (8H, m), 10.44 (2H, s), 11.05 (2H, s); ^{13}C NMR (TFA–$CDCl_3$): δ 11.7, 11.8, 17.2, 20.3, 28.5, 87.5, 95.4, 96.4, 112.1, 130.6, 134.6, 139.7, 146.9, 154.0, 201.9. **12a**: mp > 300 °C; UV-vis (1% Et_3N–$CHCl_3$): λ_{max} ($\log_{10}\varepsilon$) 388 (4.49), 422 (4.83), 508 (3.91), 542 (4.23), 580 nm (4.02); ^{1}H NMR ($CDCl_3$): δ 1.61 (3H, s), 1.62–1.69 (12H, m), 3.26 (6H, s), 3.66 (8H, m), 9.03 (2H, s), 9.83 (2H, s); ^{13}C NMR ($CDCl_3$): δ 12.0, 17.6, 18.2, 19.7, 20.1, 29.4, 82.6, 97.0, 109.1, 108.2, 111.9, 131.0, 134.9, 136.5, 137.3, 141.1, 199.6; HRMS (FAB): calcd for $C_{33}H_{34}N_3O_3Ag$ + H: m/z 628.1729. Found 628.1728.

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