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Selective Synthesis of Asymmetrically Substituted 5,15-Diphenylporphyrins

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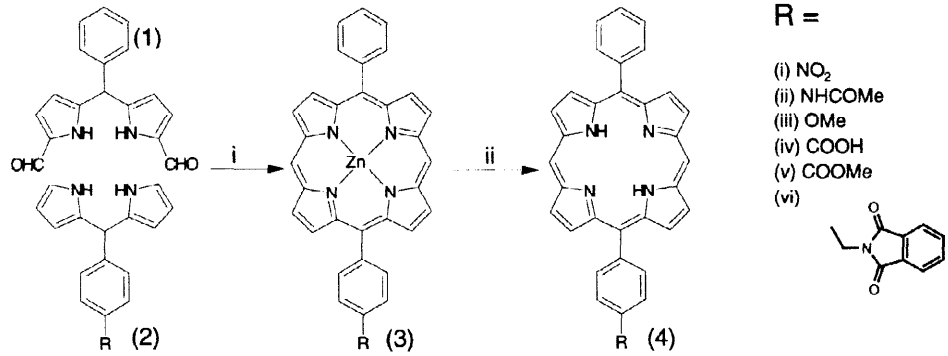
Abstract: A novel method for selectively synthesising 5,15-diphenylporphyrins bearing different substituents on the 5- and 15-phenyl rings is reported. It has been found that the presence of zinc acetate is necessary in the final step to ensure good yields of porphyrin.

The control of substitution patterns in the synthesis of *meso*-phenylporphyrins has relied largely on two methods: (1) the acid catalysed condensation of differently substituted benzaldehydes with pyrrole to give a mixture of products[1] which are then separated, (2) electrophilic substitution reactions on the pre-formed porphyrin at either the β pyrrolic positions[2] or the phenyl rings.[3] Both of these strategies, however, generate mixtures of different levels of substitution and/or regioisomers which can be difficult to separate. As part of an ongoing program in our laboratory to develop methods for conjugating porphyrins and their derivatives with biologically active molecules, we required a reliable method for controlling the number, nature and position of functional groups attached to the porphyrin macrocycle. Recently we have reported an efficient method for synthesising and purifying 5-phenyldipyrromethane in gram quantities, and the subsequent use of this compound to give the symmetrical 5,15-diphenylporphyrin in good yield.[4] We became interested in whether this methodology could be adapted and expanded to give access, without the need for mixed condensations, to 5,15-diphenylporphyrins bearing different substituents on opposing phenyl rings.

Scheme 1



Conditions: i.) *p*-Toluene sulphonic acid, CH_2Cl_2, r.t., dark, 8 hr, $Zn(OAc)_2.2H_2O$ in MeOH, stir, r.t., 17 hr
ii.) Trifluoroacetic acid, $CHCl_3$, r.t, 0.1 hr
Yields; **4(i)** 11.2%, **4(ii)** 11.1%, **4(iii)** 28.1%, **4(iv)** 13.1%, **4(v)** 8.9%, **4(vi)** 18.6%. Mp. 4(i-vi) >350°C decomp.

The MacDonald 2+2 method[5] for synthesising porphyrins from dipyrromethanes relies upon introducing the incipient 10-, 20- *meso* carbons of the porphyrin as formyl groups at the 1- and 9- positions of one dipyrromethane, and then condensing this under acid catalysed conditions with another dipyrromethane which does not bear substituents at the 1- and 9- positions. In this way the possibility for self-condensation of two identical dipyrromethanes is removed. The MacDonald method was originally developed using dipyrromethanes substituted with alkyl groups at the 2-,3- and 7-,8- positions, but no substituent at the 5- position. 5-Phenyldipyrromethane, conversely, is substituted at the 5- position with a bulky phenyl group, while the 1-,2-,3- and 7-,8-,9- positions lack substituents. A method was therefore required to introduce formyl groups regioselectively at the 1- and 9- positions of 5-phenyldipyrromethane. Using an adapted Vilsmeier[6] procedure ($POCl_3$/DMF) 1,9-*bis*formyl-5-phenyldipyrromethane (**1**) was obtained in 52% yield.

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Having successfully obtained the compound **(1)** we investigated the acid catalysed condensation of this compound with several 5-phenyldipyrromethanes bearing different substituents on the phenyl ring. Although it was expected that this reaction would proceed smoothly, it was found in all cases that only minor amounts of porphyrin (< 0.1%) could be generated using MacDonald's original conditions (HI in acetic acid). As the original conditions of the MacDonald synthesis were devised to yield porphin-1,4,6,7-tetraacetic acid-2,3,5,8-tetrapropionic acid octamethyl ester (uroporphyrin IV methyl ester), it was believed that solubility differences may have been responsible for the poor yields. Several attempts were made to perform the condensation of **(1)** with phenyl substituted 5-phenyldipyrromethanes using different organic solvents (CH_2Cl_2, $CHCl_3$, THF) and organic phase soluble acids (*p*-toluenesulphonic acid, trifluoroacetic acid, trichloroacetic acid) but this resulted in no significant improvement in yields. It seemed therefore, that factors other than the pK_a of the acid or the solubility of the dipyrromethanes in the reaction solvent were responsible for the failure of the reaction.

In order to form the immediate precursor of the porphyrin, the porphyrinogen, the formyl groups of the 1,9-*bis*formyldipyrromethane must be brought into close proximity with the 1- and 9- positions of the second dipyrromethane. Molecular modelling[7] of **(1)** and **(2)**, and comparison with similar models for the dipyrromethanes used by MacDonald in his original 2+2 synthesis, revealed a significant twisting of the two pyrrole rings for the 5-phenyldipyrromethanes after energy minimisation. The results of molecular modelling suggest that a greater amount of steric strain is involved in the formation of 5,15-diphenylporphyrinogen when compared to the formation of uroporphyrin IV methyl ester. In the synthesis of phthalocyanines[8] (tetraazatetrabenzoporphyrins) it is necessary to incorporate a metal template in the condensation process. This presumably stabilises the intermediate cyclic tetrameric structure, which is subsequently oxidised to the fully aromatic macrocycle. It was decided, therefore, to adopt a similar strategy and incorporate a metal template in the condensation of **(1)** with phenyl substituted 5-phenyldipyrromethanes.

Zinc porphyrins undergo facile demetallation using strong acids.[9] Zinc acetate was therefore selected as a template candidate due to this property, and also because of the partial solubility of this salt in organic solvents. Condensation reactions were performed by mixing **(1)** with each of the phenyl substituted 5-phenyldipyrromethanes **(2)** (i-vi) (1:1 molar ratio) in degassed (argon) dichloromethane, followed by injection of a 4-fold excess of *p*-toluenesulphonic acid in methanol. After stirring in the dark for 8 hours a saturated methanolic solution of zinc acetate dihydrate was added and the mixture was stirred for a further 17 hours (Scheme 1).

Condensation of **(1)** and **(2)** in the absence of zinc acetate gave only minor amounts (<0.01%) of porphyrin products, which were identified by UV-visible spectroscopy. Addition of the zinc salt to the reaction medium, however, resulted in a dramatic increase in yields to between 8.9 and 28% depending on the substituent present on the dipyrromethane. Demetallation of compounds **3(i-vi)** was carried out with trifluoroacetic acid in chloroform, at ambient temperature, to yield the free-base 5,15-diphenylporphyrins **4(i-vi)**. We believe that the method reported here will be of wide interest to those involved in conjugating porphyrins to biologically active molecules and solid supports for use in targeted photochemotherapy, as fluorescent probes and also in the areas of catalysis and optoelectronics.

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3 (i) *[5-(4-Nitrophenyl)-15-phenylporphyrinato]zinc II* UV-vis ($CHCl_3$) λ_{max} 412, 542. **4** (i) *5-(4-Nitrophenyl)-15-phenylporphyrin*; UV-vis ($CHCl_3$) λ_{max} 409, 505, 541, 575, 629; ^{1}H NMR (270 MHz, $CDCl_3$) δ -3.18 (br s, 2H, pyrrolic NH), 7.80-7.82 (m, 3H, *m/p*-phenyl), 8.26-8.27 (m, 2H, *o*-phenyl), 8.52-8.74 (m, 4H, *p*-substituted phenyl), 9.05-9.27 (m, 4H, β), 9.49-9.58 (d, 4H, J = 4.5 Hz, β), 10.39 (s, 2H, *meso*); MALDI, 508.4 (M-H, 100).