A New Method for the Synthesis of Porphyrin-α-diones that is Applicable to the Synthesis of Trans-annular Extended Porphyrin Systems

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Porphyrin-α-diones can be prepared by photooxidation or SeO_2-oxidation of β-hydroxyporphyrins, which are in turn readily synthesized from the corresponding copper(II) or nickel(II) 2-halo- and 2-sulphinyl-porphyrins by reaction with the anion of *E*-benzaldoxime; the efficient conversion of the porphyrinoquinoxaline **6** into the diquinoxalino[2,3-*g*, 2,3-*q*]porphyrin **9** illustrates the usefulness of the new methodology for the synthesis of trans-annular extended porphyrin systems.

We have previously described the synthesis of porphyrin-α-diones by the photooxidation of the corresponding 2-amino-porphyrin and hydrolysis of the resultant α-keto-imine,[1] and we have shown that laterally bridged fully conjugated bis-porphyrin systems can be prepared by condensation of two equivalents of the porphyrin-α-dione with 1,2,4,5-benzenetetramine.[2] In work directed towards the synthesis of laterally bridged polyporphyrins using this condensation to assemble the system,[3] it became necessary to develop an alternate methodology for the introduction of the α-dione functionality onto the porphyrin periphery. This need arose because appropriate diaminoporphyrin precursors for the synthesis of linearly extended systems were not readily accessible. We have previously reported the synthesis of 2-hydroxyporphyrin **2** by reaction of nickel(II) 2-nitroporphyrin **1a** with the anion of α-benzaldoxime (Scheme 1).[4] We now report extension of the scope of this methodology to include nucleophilic substitution of halo and sulphinyl substituents, which can be introduced specifically into antipodal rings utilizing the strategy reported in the previous communication,[5] and we describe methods by which the resultant hydroxyporphyrins can be oxidized to porphyrin-α-diones. The efficient conversion of the porphyrinoquinoxaline **6** into the linearly annelated diquinoxalino[2,3-*g*, 2,3-*q*]porphyrin **9** illustrates the usefulness of the new methodology.

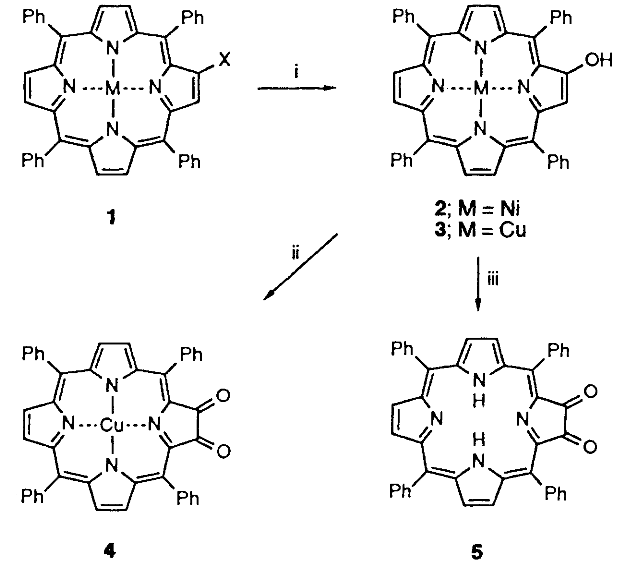
To extend the methodology for synthesis of β-hydroxyporphyrins by nucleophilic substitution, a range of nickel(II) and copper(II) β-substituted 5,10,15,20-tetraphenylporphyrins were treated with the sodium salt of *E*-benzaldoxime in Me_2SO at 80 °C for 2 h; the results are presented in Table 1. This reaction allows introduction of an oxygen functionality into the β-pyrrolic position of a porphyrin in a single step from readily accessible starting materials. With the exception of the reaction on the copper(II) chloroporphyrin **1e**, which was incompletely dissolved in the reaction solvent, the reaction proceeded smoothly in each case, in accordance with the expectation that an S_NAr-like reaction meachanism was operating[4] and that phenylsulphinyl and halo substituents would be good leaving groups. The fact that the reaction proceeds so readily on these porphyrin systems compared with the inertness of halo- and phenylsulphinyl-benzenes is no doubt a consequence of two factors. First, the Meisenheimer-like intermediate in porphyrin reactions can be achieved without loss of the aromaticity of the macrocycle as a whole and, therefore, should involve much lower energies of activation than reactions on simpler arenes. Secondly, the electronegative coordinated metal ion protects the porphyrin inner periphery against deactivating acid–base reactions without donating much additional electron density to the porphyrin outer periphery; by contrast, when the coordinated metal ion is the relatively electropositive zinc(II) ion, greater electron density is placed on the outer periphery,[6] and these substitution reactions fail to proceed.[4]

Photolysis of an oxygenated CH_2Cl_2-solution of copper(II) 2-hydroxy-5,10,15,20-tetraphenylporphyrin **3** in Pyrex using fluorescent light left the porphyrin unchanged; evidently the porphyrin **3** is not a singlet oxygen sensitizer. When Rose Bengal was added to the solution and photolysis was continued for 50 min, the desired α-dione **4** was produced in 39% yield; over-oxidation products and unchanged starting material was also obtained. Oxidation of **3** with SeO_2 in refluxing dioxane to the dione **4** proceeded in somewhat higher (58%) yield. When the copper hydroxyporphyrin **3** was first demetallated by treatment with concentrated sulphuric acid and then oxidized with SeO_2, the free-base dione **5** was

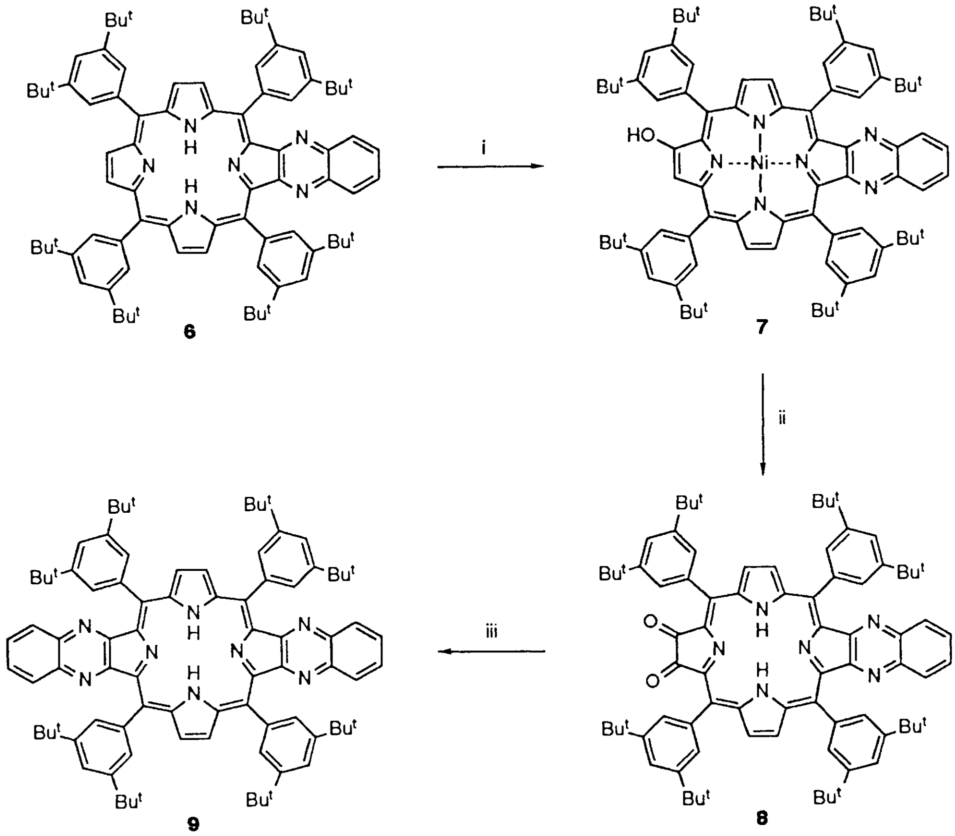
Table 1 Product and yield from treatment of metallo-2-substituted-5,10,15,20-tetraphenylporphyrins with the sodium salt of *E*-benzaldoxime[a]

Substrate		Product	Yield %
1a	M = Ni, X = NO_2	**2**	93
1b	M = Ni, X = Cl	**2**	76
1c	M = Ni, X = Br	**2**	83
1d	M = Ni, X = SOPh	**2**	96
1e	M = Cu, X = Cl	**3**	22[b]
1f	M = Cu, X = SOPh	**3**	100

[a] *E*-benzaldoxime (15 equiv.) and NaH (10 equiv.) warmed together in Me_2SO (15–25 ml) for 30 min and then added to the substrate (0.2–0.3 mmol) under nitrogen and the mixture heated at 80 °C for 2 h. The product was diluted with CH_2Cl_2–diethyl ether and washed well with water. The product obtained by evaporation of the organic layer was crystallized from CH_2Cl_2–light petroleum (60–80 °C). [b] The substrate was poorly soluble in the solvent and unchanged starting material (65%) was also recovered; the yield based on converted starting material was 63%.



Scheme 1 *Reagents and conditions*: i, sodium salt of *E*-benzaldoxime see Table 1; ii, (*a*) Rose Bengal (0.1 equiv.) in CH_2Cl_2, O_2, *hν*, 50 min or (*b*) SeO_2 (10 equiv.) in dioxane, reflux 30 min; iii, H_2SO_4–CH_2Cl_2, 5 min, then H_2O wash and neutralisation, then SeO_2 (10 equiv.) in dioxane, reflux 30 min



Scheme 2 *Reagents and conditions*: i, *N*-bromosuccinimide (1.14 equiv.) in $CHCl_3$, 1 h reflux, then $Ni(OAc)_2 \cdot 2H_2O$ in DMF, 2 h reflux, then PhSH (10 equiv.) and LiOH (5 equiv.) in DMF, 22 h at 55–60 °C, then $MeCO_3H$ in dry toluene, 1.5 h at 25 °C, then sodium salt of *E*-benzaldoxime in Me_2SO, 2.5 h at 113 °C; ii, H_2SO_4–CH_2Cl_2, 4 min, then H_2O wash and neutralisation, then O_2, *hν*; iii, *o*-phenylenediamine (3 equiv.) CH_2Cl_2, 20 min

produced in 27% overall yield; in this case the demetallation was complicated by side reactions and the desired 2-hydroxyporphyrin was itself rather unstable. While these oxidations have not been optimized and the yields obtained on this parent porphyrin system are modest, application of the methodology to more complex porphyrin systems has proved to be relatively straightforward.[3,7]

The efficient conversion of the porphyrinoquinoxaline **6** to the diquinoxalinoporphyrin **9** (Scheme 2) illustrates the utility of the new methodology for ring annelation of trans-annular (antipodal) positions on the porphyrin periphery. First, the porphyrinoquinoxaline **6** was monobrominated using 1.14 equiv. of *N*-bromosuccinimide (NBS) in refluxing ethanol-free chloroform, and then converted by metallation with $Ni(OAc)_2$ to the nickel(II) 17-bromoporphyrinoquinoxaline in 52% overall yield. Attempts to directly displace the bromo substituent using the anion of *E*-benzaldoxime were unsuccessful due to the insolubility of nickel bromoporphyrin in Me_2SO over the temperature range 70–110 °C. In order to confer the required solubility on the system, the nickel(II) bromoporphyrin was converted into the corresponding phenylsulphinylporphyrin in overall 61% yield by treatment with benzenethiolate ion in *N*,*N*-dimethylformamide (DMF) followed by oxidation of the resultant phenylthioporphyrin with peracetic acid in toluene. Reaction of the nickel(II) phenylsulphinylporphyrin with an excess of the anion of *E*-benzaldoxime gave a 98% yield of hydroxyporphyrinoquinoxaline **7**. Demetallation of **7** with concentrated H_2SO_4 followed by photooxidation gave the α-dione **8** [ν_{max} 3395, 1722 cm^{-1}; D_{2h} symmetry in ^1H NMR spectrum; λ_{max} (log ε) 420 (5.16), 488sh (4.30), 624 (3.70), 679 (3.76) and 724 nm (3.79)] in 54% overall yield. The α-dione **8** was converted smoothly by reaction with *o*-phenylenediamine to the diquinoxalino[2,3-*g*, 2,3-*q*]porphyrin **9** in 92% yield.

In summary, a new methodology for incorporation of α-dione units into porphyrins has been developed. This methodology allows the new functionality to be introduced into an antipodal ring with respect to existing functionality and should, therefore, be of use for the synthesis of linear laterally bridged polyporphyrin systems. The successful use of the new methodology in the synthesis of a linear tetrakisporphyrin and related compounds is described in the following communication.[3]

This research was funded by an Australian Research Council research grant to M. J. C. We also thank the Australian Government for the award of post-graduate research scholarships to P. L. B., S. J. L. and S. M. P.

Received, 27th June 1991; Com. 1/03226G

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