Efficient Synthesis of 2-Oxy-5,10,15,20-tetraphenylporphyrins from a Nitroporphyrin by a Novel Multi-step Cine-substitution Sequence

Maria M. Catalano, Maxwell J. Crossley,* and Lionel G. King

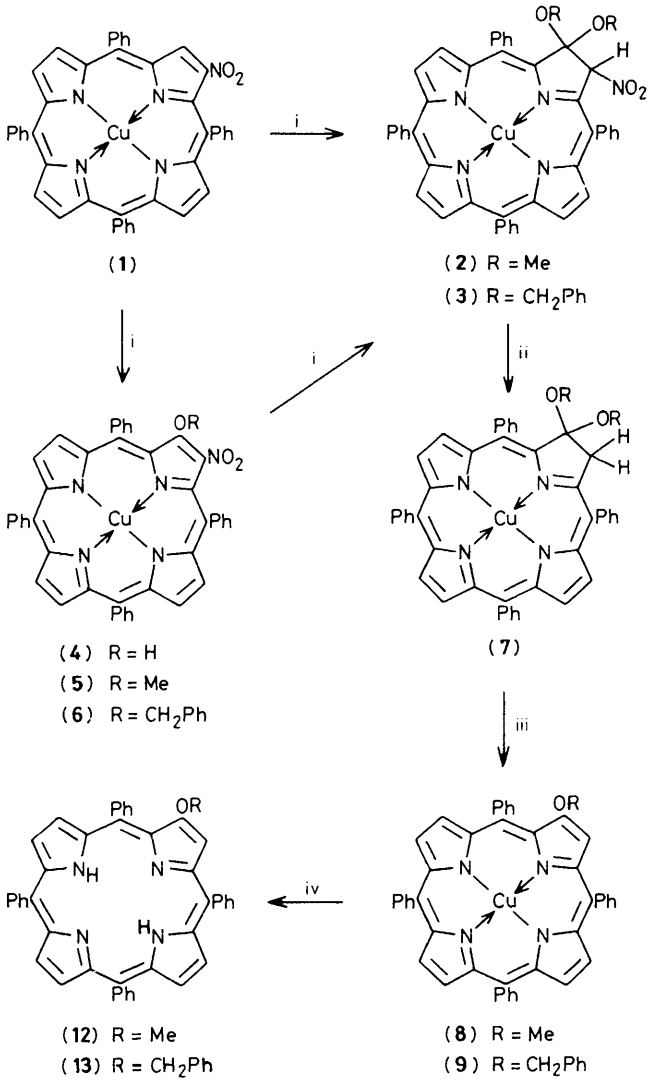
Department of Organic Chemistry, The University of Sydney, N.S.W. 2006, Australia

(2-Nitro-5,10,15,20-tetraphenylporphyrinato)copper(II) (**1**) reacts with sodium benzylate or sodium methoxide in dimethylformamide by a novel aromatic nucleophilic substitution–nucleophilic addition sequence in which hydrogen is the leaving group to give the corresponding 2,2-dialkoxy-3-nitro-2,3-dihydroporphyrins which are efficiently converted into 2-alkoxyporphyrins in two steps; the overall sequence accomplishes a cine-substitution.

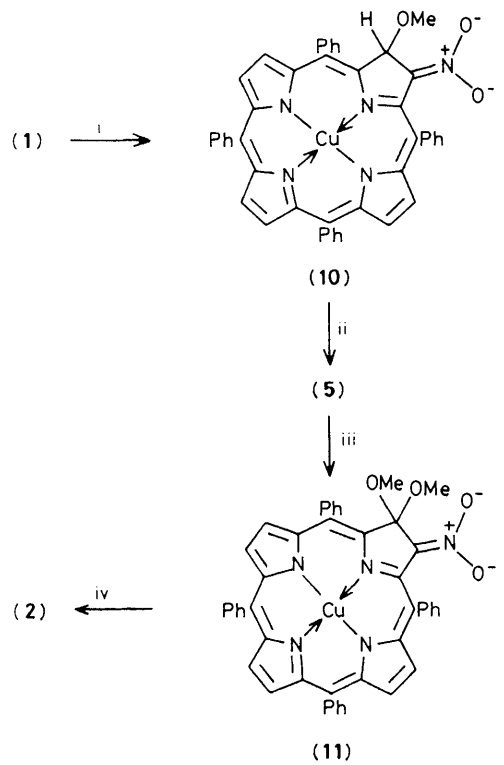
Very few methods have been developed for functionalization of porphyrins at a β-pyrrolic position.[1] While there are at least ten methods for the synthesis of *meso*-oxyporphyrins and their oxophlorin tautomers,[1,2] a convenient route to β-oxyporphyrins has been lacking. Apart from total synthesis from oxygenated-pyrrole precursors,[3] the only reported synthesis of such compounds has involved a low-yielding radical benzoyloxylation of 5,10,15,20-tetraphenylporphyrin.[4] In the preceding communication we reported an efficient synthesis of 2-nitro-5,10,15,20-tetra-arylporphyrins[5] and we now report some new porphyrin chemistry which we have developed into a convenient synthesis of 2-oxy-5,10,15,20-tetraphenylporphyrins, *i.e.* β-oxyporphyrins, based on the reaction of oxygen nucleophiles with (2-nitro-5,10,15,20-tetraphenylporphyrinato)copper(II) (**1**).

Treatment of (**1**) with sodium methoxide in dry dimethylformamide (DMF) (18 h, 0—25 °C) followed by an aqueous quench gave the blue-green 2,2-dimethoxy-3-nitro-2,3-dihydroporphrin (**2**)† (91%) m.p. >300 °C [$\nu_{max.}$ 1559 cm^{-1}; $\lambda_{max.}$ (log ε) ($CHCl_3$) 416(5.34), 514(3.59), 559(sh.) (3.99), 616 nm (4.33)] (Scheme 1). Similar treatment of (**1**) with sodium benzylate (DMF, 48 h, 0—25 °C) gave the corresponding 2,2-dibenzyloxy-3-nitro-2,3-dihydroporphyrin (**3**) (38%) together with the 2-benzyloxyporphyrin (**9**) (18%) [418(519), 541(3.90), 581 nm (3.41); *m/z* 781(100%)], while reaction with sodium hydroxide (DMF, 48 h, 25 °C) gave the 2-hydroxy-3-nitroporphyrin (**4**) (51%).

When the reaction of (**1**) and sodium methoxide was quenched after only 4 h the 2-methoxy-3-nitroporphyrin (**5**) (31%) [1525 cm^{-1}, 414(5.38), 541(4.20), 581 nm (3.71); *m/z* 750(100%)] was obtained together with (**2**) (23%). Treatment



Scheme 1. i, NaOR in DMF, then H_2O; ii, Bu_3SnH–AIBN; iii, aqueous oxalic acid or silica; iv, conc. H_2SO_4–CH_2Cl_2, neutralization.



Scheme 2. i, MeO^-; ii, oxidant; iii, MeO^-; iv, H^+.

† All new porphyrins have been adequately characterized by analytical and/or spectroscopic means.

of (**5**) with sodium methoxide (DMF, 24 h, 0—25 °C) afforded (**2**) (83%) in comparable yield to the same reaction on (**1**). The 2-benzyloxy-3-nitroporphyrin (**6**), obtained in 89% yield by benzylation of (**4**), reacted similarly with sodium benzylate.

The nitro group in both dihydroporphyrins (**2**) and (**3**) is secondary, pseudobenzylic, and α to two inductively electron-withdrawing groups and thus is well placed for reductive removal under radical conditions.[6]

Reductive denitration of (**2**) occurred on treatment with tributylstannane (3 equiv.) and azobisisobutyronitrile (AIBN) (0.4 equiv.) in refluxing benzene (4 h, N_2) to yield the blue–green 2,2-dimethoxy-2,3-dihydroporphyrin (**7**) which readily eliminated methanol on mild acid treatment or chromatography on silica to afford (2-methoxy-5,10,15,20-tetraphenylporphyrinato)copper(II) (**8**) (90% overall) [419(5.82), 540(4.22), 580 nm (3.73); *m/z* 705(100%)]. Similar treatment of (**3**) afforded the 2-benzyloxyporphyrin (**9**) (96%). The overall sequence from (**1**) has thus accomplished a cine-substitution in which a nitro group is displaced.

A pathway which accounts for the formation of (**2**) is proposed in Scheme 2. The initial Meisenheimer-like complex (**10**) is oxidized with loss of a hydrogen to (**5**). This step is unusual but redox processes are relatively easy in porphyrin systems.[7] Further attack by MeO^- leads to a second Meisenheimer-like complex (**11**) which is protonated to give (**2**) without loss of aromaticity in the macrocycle. Analogous addition products have not been obtained from Meisenheimer complexes in simpler arene systems since aromaticity is lost and the energy penalty is too great.

Other free-base and metallo-2-alkoxy-5,10,15,20-tetraphenylporphyrins are readily accessible from the above compounds. Thus hydrogenolysis (H_2, 10% Pd/C, 5 h, CH_2Cl_2) of (**9**) proceeded without concomitant reduction of the macrocycle to give (2-hydroxy-5,10,15,20-tetraphenylporphyrinato)copper(II) (100%) [3300—3500(br.) cm^{-1}; 423(5.12), 547(3.84), 587 nm (3.24)], methylation of which gave (**8**) (98%). The complexes (**5**), (**8**), and (**9**) were smoothly (>91%) demetallated [(**8**)→(**12**), (**9**)→(**13**)] in a two phase conc. H_2SO_4–CH_2Cl_2 system (5 min, room temp.) without competing electrophilic sulphonation of the activated porphyrin rings, and readily converted into other metal derivatives.

The sequence outlined here provides an efficient entry into 2-oxyporphyrin systems and is a further example of unusual reactivity of the porphyrin β-pyrrolic position when a chlorin-like aromatic delocalization pathway can be maintained.[8] Extension of this route to provide other 2-substituted porphyrins is under investigation.

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