

Direct *meso*-alkylation of *meso*-formylporphyrins using Grignard reagents

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Direct *meso*-alkylation of zinc(II) or metal-free 5-formyloctaethylporphyrin is achieved by use of Grignard reagents (such as MeMgBr, EtMgBr and PhCH₂MgCl); regioselective attack at the 15-position of the porphyrin macrocycle is observed, and affords the unexpected 5-formyl-15-alkylporphyrins by way of a phlorin intermediate.

Whereas electrophilic *meso*-substitution reactions in porphyrin systems have been subjected to intensive investigation,¹ nucleophilic *meso*-substitutions have been far less frequently observed. In 1980, Setsune *et al.*² reported that though nucleophilic attack of organolithium reagents upon rhodium(III) 2,3,7,8,12,13,17,18-octaethylporphyrin (OEP) occurred initially at the *meso*-position of the porphyrin macrocycle to form an air-sensitive rhodium-phlorin complex; formation of the phlorin complex was facilitated by a strongly electronegative metal in a high oxidation state. Segawa *et al.*³ described the direct nucleophilic addition of hydroxide to gold(III) porphyrins to afford hydroxyphlorins, and Dolphin *et al.*⁴ reported the reaction of zinc(II) 5-nitro-OEP with sodium methoxide to give zinc(II) 5-methoxy-15-nitro-OEP via the autoxidation of a porphodimethene intermediate. Nucleophilic substitution reactions on metalloporphyrin π -cation radicals⁵ and π -dications⁶ have been more thoroughly investigated.

Johnson and co-workers⁷ reported that the reaction between nickel(II) 5-formyl-OEP 1 and methylmagnesium iodide gave, as expected, nickel(II) 5-(1-hydroxyethyl)-OEP 2, from which nickel(II) 5-vinyl-OEP 3 was obtained. Here we report the highly unusual, but general, reactions of zinc(II) and metal-free 5-formylporphyrins to give *meso*-alkylated products.

When zinc(II) 5-formyl-OEP⁸ 4 was treated with MeMgBr, and then treated with acid, the main product, surprisingly, was 5-formyl-15-methyl-OEP 5 [δ (CDCl₃) 12.44 (5-CHO); 9.85 (10,20-H); 4.43 (15-Me)]. No 5-(1-hydroxyethyl)-OEP 6 was detected. We were thus prompted to further investigate the reaction between zinc(II) OEP and Grignard reagents. Reaction of zinc(II) 5-formyl-OEP 4 with EtMgBr, followed by demetallation, gave 15-ethyl-5-formyl-OEP 7 in 31% yield [δ (CDCl₃) 12.45 (5-CHO); 9.89 (10,20-H); 4.97 (15-CH₂)]; Fig. 1 shows the molecular structure of 7, determined by X-ray diffraction.‡ Use of phenylmagnesium bromide and zinc(II) 5-formyl-OEP 4 gave a complex mixture of products, from which only a low yield of 5-(1-hydroxybenzyl)-OEP 8 was isolated.

Treatment of metal-free 5-formyl-OEP 9 with EtMgBr at 0 °C for a short period, without subsequent acid treatment, gave

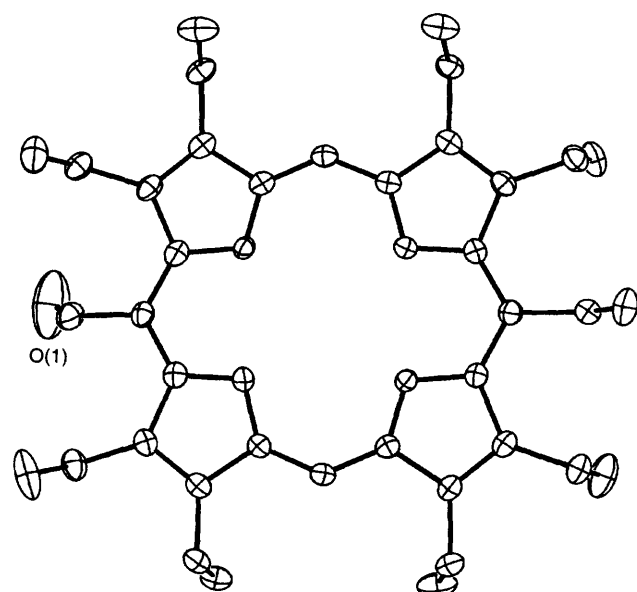
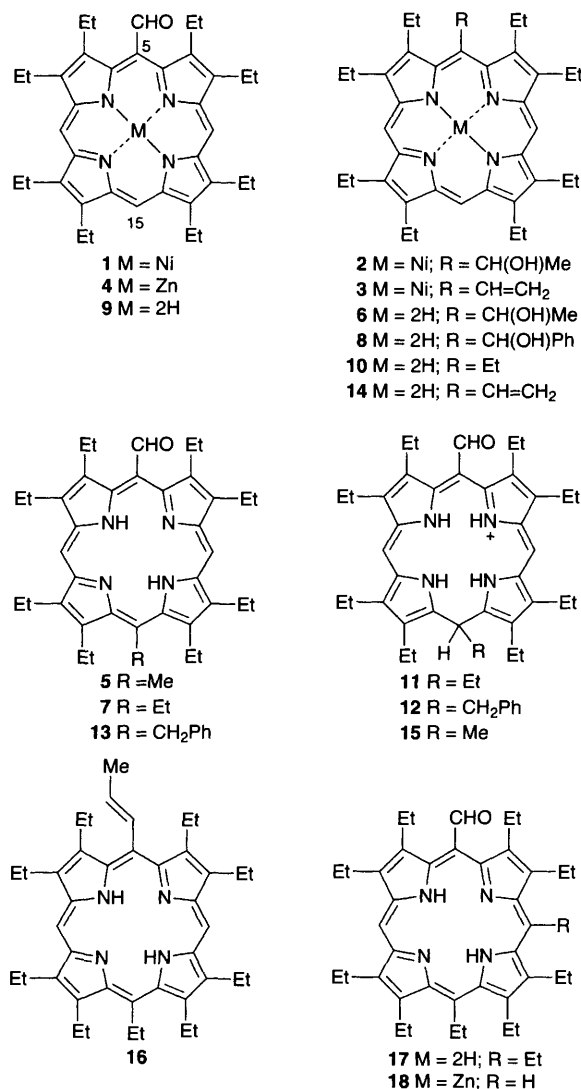


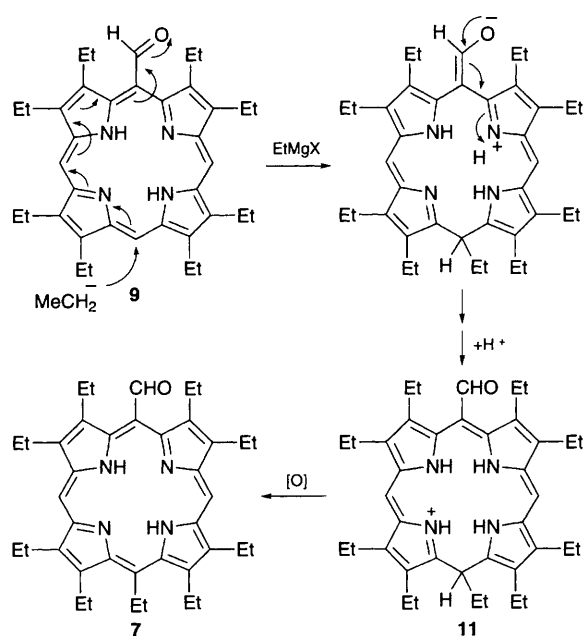
Fig. 1 Molecular structure‡ of 2,3,7,8,12,13,15,17,18-nonaethyl-5-formylporphyrin 7. Atomic positions are represented with 50% probability thermal ellipsoids.



a very polar green compound (32% yield), along with some 15-ethyl-5-formyl-OEP **7** (9%) and a small amount of 5-ethyl-OEP **10** (3%). The visible absorption spectrum of the green compound [λ_{max} (CH_2Cl_2) 440 nm (ϵ 89000) and 702 (11500)] is characteristic of the phlorin monocation **11** and compared well with those in the literature¹⁰ as did acid-base optical transformations of the intermediate. The phlorin structure **11** was also confirmed by high resolution mass spectrometry (found: 593.4246; $\text{C}_{39}\text{H}_{53}\text{N}_4\text{O}$ requires: 593.4219) and by its ready conversion into 15-ethyl-5-formyl-OEP **7** upon acid treatment in air. Phlorin **11** was reasonably stable during column chromatography and only a small portion of it was converted to porphyrin **7**.

Use of 5-formyl-OEP **9** and PhCH_2MgCl at 0°C likewise afforded the benzyl phlorin **12** (14% yield) and 15-benzyl-5-formyl-OEP **13** (8%). Benzyl phlorin **12** was easily converted into 15-benzyl-5-formyl-OEP **13** in acidic media. However, when free base 5-formyl-OEP **9** was treated with MeMgBr at room temperature the major product was 5-vinyl-OEP **14** (42% yield). Methyl phlorin **15** was only a minor product (11% yield), and this could be converted into 5-formyl-15-methyl-OEP **5** by treatment with TFA. Similar, but less satisfactory results were obtained using lithium alkyls; the reaction of methyl lithium with metal-free 5-formyl-OEP **9** gave mainly 5-(1-hydroxyethyl)-OEP **6**, but the reaction between methyl lithium and zinc(II) 5-formyl-OEP **4** afforded 5-formyl-15-methyl-OEP **5** in low yield, along with some free base 5-formyl-OEP **9** (after treatment with TFA).

Scheme 1 shows a possible mechanistic explanation for our results; the nucleophilic attack at the 15-position is presumably promoted by anion stabilization afforded by the electronegative formyl group, to afford the phlorin **15**. Phlorins are readily oxidized in air to give porphyrins, e.g. **7**.¹¹ We also explored the possibility of bis-alkylation by use of EtMgBr and 15-ethyl-5-formyl-OEP **7**. After acid treatment, only a small amount of 15-ethyl-5-(1'-propenyl)-OEP **16** was obtained, with no evi-



Scheme 1

dence of 10,15-diethyl-5-formyl-OEP **17** being produced. The reaction between zinc(II) 15-ethyl-5-formyl-OEP **18** and EtMgBr also failed to give 10,15-diethyl-5-formyl-OEP **17** or its zinc(II) complex. Reactions between zinc(II) and metal-free porphyrins bearing other electronegative groups at *meso*-positions are in progress, and will be reported in a full paper.

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Footnotes

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‡ *Crystal Data*: A single large crystal of **7** ($\text{C}_{39}\text{H}_{50}\text{N}_4\text{O}$) was grown by the slow diffusion of MeOH into a solution of the porphyrin dissolved in CH_2Cl_2 . The crystal was cut to dimensions of $0.60 \times 0.40 \times 0.18$ mm for cell determination and data collection. The unit cell was monoclinic $P2_1/c$ with cell dimensions $a = 8.7782(12)$, $b = 13.539(2)$, $c = 28.054(3)$ Å, $\beta = 96.324(10)$, $V = 3313.9(7)$ and $Z = 4$ (FW = 590.83). X-Ray diffraction data were collected on a Siemens P4 diffractometer with a rotating anode [$\lambda(\text{Cu-K}\alpha) = 1.54178$ Å] at 130(2) K in $\theta/2\theta$ scan mode to $2\theta_{\text{max}} = 112^\circ$. Of 4837 reflections measured ($+h,+k,\pm l$) 4336 were independent ($R_{\text{int}} = 0.0228$) and 3602 had $I > 2\sigma$ ($T_{\text{min}} = 0.83$, $T_{\text{max}} = 0.92$, $\rho_{\text{calc}} = 1.184$ g cm^{-3} , $\mu = 0.547$ mm^{-1}). The structure was solved by direct methods and refined (based on F^2 using all independent data) by full-matrix least-squares methods with 411 parameters (Siemens SHELXTL V. 5.03). Core hydrogens (50% occupancy for each nitrogen) were located on a difference map and allowed to refine freely. All other hydrogen atom positions were located by idealized geometry and refined using a riding model. An absorption correction was applied using XABS2.⁹ The final difference map had a largest peak of 0.378 $\text{e}\text{\AA}^{-3}$ and a largest hole of -0.565 $\text{e}\text{\AA}^{-3}$. Final R factors were $R1 = 0.0522$ (based on observed data) and $wR2 = 0.1272$ (based on all data). Much like other reported free base OEPs, the porphyrin macrocycle displayed only minimal deviations from planarity. The molecule displayed a formyl $\text{C}=\text{O}$ bond length of $1.227(4)$ Å. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and reference number 182/131.

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