First syntheses of fused pyrroloporphyrins

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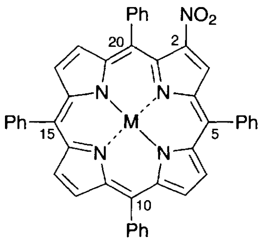
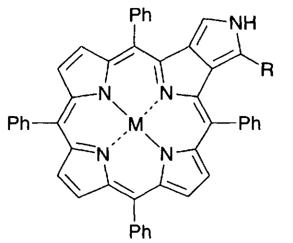
(2-Nitro-5,10,15,20-tetraphenylporphyrinato)nickel(II) reacts with α-isocyanoacetic esters in the presence of DBU to give the first β-fused pyrroloporphyrins, the pyrrole ring in the fused system being shown to undergo typical pyrrole-type chemistry; the corresponding zinc(II) complex affords a novel cyclopropanochlorin (characterized by X-ray crystallography), when treated with an α-isocyanoacetic ester.

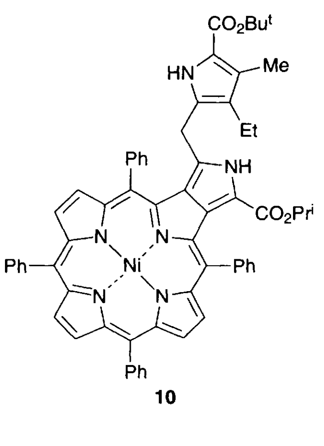
A recent publication detailing an unsuccessful attempt to convert a porphyrin amino ester derivative into a fused pyrroloporphyrin,[1] prompts us to report the first syntheses of pyrroloporphyrins *via* the Barton–Zard[2] condensation of 2-nitro-5,10,15,20-tetraphenylporphyrin (2-NO_2TPP) and isocyanoacetates. Examples of porphyrins containing an aromatic ring fused to one or more porphyrin pyrrole subunits are mainly limited to the benzo-,[3] naphtho-, phenanthro- and phenanthrolino-fused porphyrins,[4] and naphtho-fused chlorins.[5] Syntheses of novel porphyrins bearing fused arene units often depend upon the availability of, for example, isoindoles or phenanthropyrroles. Lash showed that the Barton–Zard approach might be extended to the reaction of certain nitroaromatic compounds, such as 9-nitrophenanthrene, which exhibit extensive nitroalkene character.[6] Crossley *et al.* have shown that 2-nitroporphyrins possess many similaries to simpler nitroalkenes in their reaction profiles, and might be advantageously used for functionalization at the β-pyrrolic position of tetrapyrroles.[7] In light of these findings, the readily available nickel(II) 2-NO_2TPP **1**[8] was heated with 2 equiv. of ethyl isocyanoacetate (or methyl isocyanoacetate) in the presence of the non-nucleophilic base DBU in refluxing THF–isopropyl alcohol (10/1). The β-fused pyrroloporphyrin **4** was formed as its isopropyl ester derivative (as a result of a transesterification reaction with isopropyl alcohol), together with some of the corresponding ethyl ester. The green nickel(II) pyrroloporphyrin **4** was isolated as a purple powder in 40% yield. In the absence of isopropyl alcohol and in presence of methanol, no pyrroloporphyrin was formed. When benzyl alcohol was used as co-solvent, the pyrroloporphyrin benzyl ester **5** was obtained (36% yield). When *tert*-butyl alcohol and methyl isocyanoacetate were used, no transesterification occurred, permitting the pyrroloporphyrin methyl ester **6** to be isolated in 38% yield. Because Grignard reactions upon copper(II) nitroporphyrins have been shown to give better yields of alkylporphyrins than do the corresponding reactions with the nickel(II) nitroporphyrins,[7] the Barton–Zard reaction on copper(II) 2-NO_2TPP **2**[8] was attempted (THF–Bu^{t}OH) and gave the methyl ester derivative **7** in 37% yield [λ_{max} 434 nm (ε 244 000), 544 (14 400), 562 (16 700) and 610 (17 800)].



1 M = Ni
2 M = Cu
3 M = Zn



4 R = CO_2Pr^i; M = Ni
5 R = CO_2Bn; M = Ni
6 R = CO_2Bn; M = Ni
7 R = CO_2Me; M = Cu
8 R = CO_2Pr^i; M = 2H
9 R = H; M = Ni



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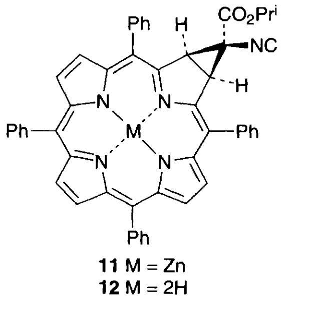

11 M = Zn
12 M = 2H

The proton NMR spectrum of **4** showed the characteristic patterns of a pyrrole unit with a broad NH singlet at δ 9.47 (exchangeable with D_2O) and an α-proton doublet (*J* 2.7 Hz) at δ 5.98. The electronic absorption spectra showed a 20 nm red shift of the Soret band [λ_{max} 434 nm (ε 169 000)] compared with Ni^{II} TPP, and three Q bands at 534 nm (ε 8800), 556 (9600) and 604 (13 700). Fast atom bombardment mass spectrometry of **4** confirmed the presence of the fused pyrrole ring and transesterification to have occurred [*m/z* 795 (100%); 734 (50%, M − Pr^iO)]. The nickel(II) complex **4**, stable in neat TFA, was demetallated using TFA/1%H_2SO_4, and showed increased basicity *versus* Ni^{II} TPP (which is demetallated with conc. H_2SO_4). The metal free pyrroloporphyrin **8** was obtained in 85% yield [λ_{max} 440 nm (ε 203 000), 482 (25 000), 526 (17 300), 606 (7400) and 662 (4300); δ ($CDCl_3$) 9.40 (s, NH, pyrr), 6.03 (d, *J* 2.7 Hz, 2 H, pyrrole α-H) and −2.24 (s, 2 H, porphyrin NH)].

Attempts to apply standard saponification and decarboxylation methodology (ethylene glycol, NaOH, 180 °C) to pyrroloporphyrin **4** were unsuccessful. However, S_N2 demethylation with lithium chloride and subsequent decarboxylation in Me_2SO[9] was successful on **6**. The 2′,5′-diunsubstituted pyrroloporphyrin **9** was formed in 80% yield. A significant blue shift of its Soret band is observed, presumably due to relief of steric interactions between the 2′-ester function and the adjacent meso-phenyl ring [λ_{max} 430 nm (ε 161 000), 526 (12 900), 552 (11 300) and 614 (20 700)]. Compound **9** displays a C_2 symmetric proton NMR spectrum [δ ($CDCl_3$) 8.70 (s, NH pyrr), 8.62, 8.54, 8.51 (each d, *J* 4.8 Hz, 2 H, β-H) and 6.06 (d, *J* 2.4 Hz, 2 H, pyrrole α-H] and a molecular peak at *m/z* 710. The pyrroloporphyrin **9** was found to be unstable to the acidic conditions used previously to demetallate **4**.

The fused pyrrolo-ring was found to undergo typical pyrrole chemistry; acid catalyzed condensation of *tert*-butyl 5-acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate with **4** afforded the fused dipyrromethane **10** in 65% yield. Compound **10** displayed the expected ^1H NMR spectrum [*e.g.* δ ($CDCl_3$) 8.80, 8.35 (each 2 H, NH) and 3.00 (s, 2 H, CH_2 bridge)], and mass spectral peaks [*m/z* 1017 (100%), 961 (17%) and 943 (11%)]; a significantly red shifted optical spectrum was also observed [λ_{max} 444 nm (ε 129 000), 540 (10 100), 566 (10 700) and 616 (12 600)].

Variation of the central coordinated metal has a profound effect on reaction pathway to pyrroloporphyrin. It has previously been shown that relatively electronegative metal ions [*e.g.* copper(II) and nickel(II)] can be seen as activating groups for nucleophilic reactions at the porphyrin periphery, whereas Zn^{II} 2-NO_2TPP **3** was found to be unreactive or else yielded preferential attack at the meso position.[7] When **3**[10] was submitted to the Barton–Zard synthesis ($CNCH_2CO_2Et$–THF–Pr^iOH), a major new green compound, identified as **11**, was isolated [δ ($CDCl_3$) 8.54, 8.41, 8.32 (each d, *J* 4.5 Hz, 2 H, β-H), 4.80 (s, 2 H); molecular peak at *m/z* 800]. Compound **11** exhibits a visible absorption spectrum typical of chlorins [λ_{max} 422 nm (ε 240 000), 520 (8200), 560 (8700), 584 (11 700) and 608 (34 900)]. An X-ray crystallographic study of **11** showed it to be a cyclopropanyl annulated chlorin with an *exo* configuration with regard to the isopropyl ester function (Fig. 1),‡ consistent with the presence of a single stereoisomer as indicated by its ^1H NMR spectrum. The compound crystallizes as a centrosymmetric dimer with isocyanide axially coordinated to the zinc; we suspect that production of the cyclopropane product **11** when the zinc(II) complex is used as starting material is related to this coordination phenomenon which, in an appropriate intermediate or transition state, apparently diverts the isocyano function from its usual role[2] in pyrrole synthesis. Cyclopropano-chlorins have previously been prepared *via* a thermal rearrangement of nickel homoporphyrins,[12] from the reaction of zinc(II) tetraphenylporphyrin with carbenes,[13] and from reactions of porphyrin diols with zinc(II) acetate and acetylacetone.[14] Reaction of **11** in methylene chloride containing 1% TFA gave the metal-free compound **12** [Q band shifted to 646 nm; δ −2.11 (s, 2 H, NH)].

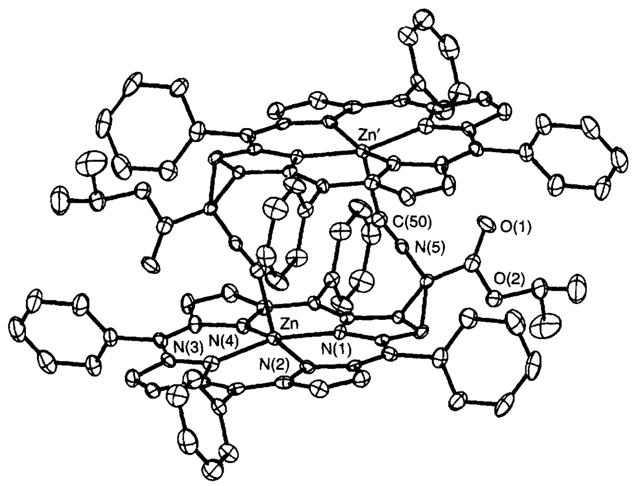

Fig. 1 Molecular structure of the centrosymmetric isocyanide-Zn ligated dimer from **11**. Atomic positions are represented with 50% probability thermal ellipsoids.

The route outlined in this communication provides a general method for efficient synthesis of fused pyrroloporphyrins and allows potential access to (pyrrolo)$_n$porphyrins (n = 1–4), fused oligoporphyrins, and cyclopropanoporphyrins.

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Footnotes

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‡ *Crystal Data* for $C_{50}H_{35}N_5O_2Zn$ **11**, M = 803.20, orthorhombic, a = 19.641(2), b = 14.937(2), c = 28.003(4) Å, U = 8216(2) Å^3 (by least-squares refinement on diffractometer angles for 50 centred reflections), λ = 1.54178 Å, space group *Pbca*, Z = 8, D_c = 1.299 g cm^{-3}, $F(000)$ = 3328. Green-purple parallelepipeds. Crystal dimensions 0.15 × 0.25 × 0.38 mm, μCu-Kα = 1.20 mm^{-1}, Syntex P2$_1$ diffractometer, scan type 2θ-θ, T = 130(2) K, 2θ_{max} = 114°, 6152 data, 5549 unique [R(int) = 0.0176], 3678 > 2$\sigma(I)$, XABS2 absorption correction, solution and refinement using Siemens SHELXTL v. 5, refinement based on F^2, wR (all data) = 0.1360, R (obsd data) = 0.0586, largest peak in final difference Fourier map = 0.29 eÅ^{-3}. 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 the reference number 182/64.

References

1 R. F. C. Brown, P. Perlmutter and H. K. Tope, *Aust. J. Chem.*, 1995, **48**, 1447.
2 D. H. R. Barton, J. Kervagoret and S. Z. Zard, *Tetrahedron*, 1990, **46**, 7587.
3 For recent examples of benzo-fused porphyrins, see P. S. Clezy and C. W. F. Leung, *Aust. J. Chem.*, 1993, **46**, 1705; R. Bonnett and K. A. McManus, *J. Chem. Soc., Chem. Commun.*, 1994, 1129; L. T. Nguyen, M. O. Senge and K. M. Smith, *J. Org. Chem.*, 1996, **61**, 998; T. D. Lash, *Energy Fuels*, 1993, **7**, 166.
4 T. D. Lash and B. H. Novak, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 683; *Tetrahedron Lett.*, 1995, **36**, 4381; T. D. Lash and C. P. Denny, *Tetrahedron*, 1995, **51**, 59; Y. Lin and T. D. Lash, *Tetrahedron Lett.*, 1995, **36**, 9441.
5 M. A. Faustino, M. G. P. M. S. Neves, M. G. H. Vicente, A. M. S. Silva and J. A. S. Cavaleiro, *Tetrahedron Lett.*, 1995, **36**, 5977; Y. V. Ishkov and Z. I. Zhilina, *Zh. Org. Khim.*, 1995, **31**, 136.
6 T. D. Lash, B. H. Novak and Y. Lin, *Tetrahedron Lett.*, 1994, **35**, 2493.
7 M. J. Crossley, M. M. Harding and C. W. Tansey, *J. Org. Chem.*, 1994, **59**, 4433. M. J. Crossley and L. G. King, *J. Org. Chem.*, 1993, **58**, 4370.
8 M. M. Catalano, M. J. Crossley, M. M. Harding and L. G. King, *J. Chem. Soc., Chem. Commun.*, 1984, 1535.
9 J. Tang and J. G. Verkade, *J. Org. Chem.*, 1994, **59**, 7793.
10 J. E. Baldwin, M. J. Crossley and J. F. DeBernardis, *Tetrahedron*, 1982, **38**, 685.
11 S. Parkin, B. Moezzi and H. Hope, *J. Appl. Cryst.*, 1995, **28**, 53.
12 H. J. Callot, Th. Tschamber and E. Schaeffer, *J. Am. Chem. Soc.*, 1975, **97**, 6178.
13 H. J. Callot, *Tetrahedron Lett.*, 1972, **11**, 1011.
14 G. V. Ponomarev and A. M. Shul'ga, *Khim. Geterotsikl. Soedin.*, 1992, 126.

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