Pergamon

Tetrahedron Letters 39 (1998) 4619–4622

TETRAHEDRON LETTERS

Syntheses of Chlorins Possessing Fused Nitrogen-Containing Rings

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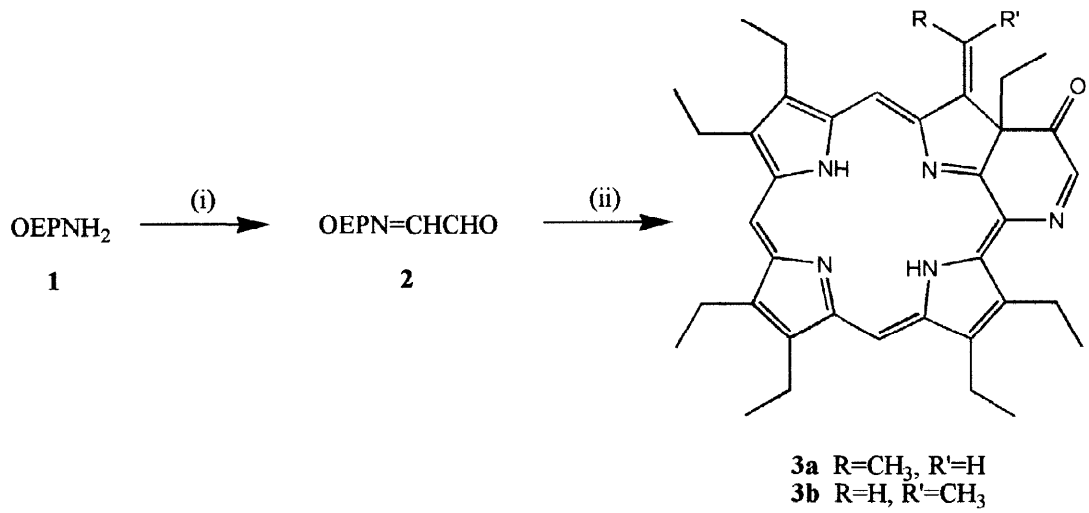
Received 9 February 1998; revised 7 April 1998; accepted 17 April 1998

Abstract: Two novel chlorins with fused nitrogen-containing rings were synthesized *via* a formylmethylimine-substituted octaethylporphyrin. The outcome of the ring-forming reaction was dependent on whether the intermediate was metallated or metal-free.

In the field of photodynamic therapy tetrapyrrolic macrocycles are often used as photosensitizers. A strong absorption in the red region of the visible spectrum is a highly desirable characteristic for an effective photosensitizing drug as this enables treatment of thicker tumours. For this reason, tetrapyrroles such as chlorins, bacteriochlorins and benzochlorins are preferred over the structurally simpler porphyrins which absorb at shorter wavelengths.[1] Our search for potential new photosensitizers led us to attempt to synthesize a benzochlorin analogue, with a fused pyridine ring in place of a fused benzene ring. These studies resulted in the preparation of two novel chlorins possessing fused nitrogen-containing rings.

Octaethylbenzochlorin is synthesized *via* intramolecular cyclization of the metallated *meso*-acrylaldehyde substituted porphyrin under acidic conditions.[2] It seemed logical to follow a similar route to prepare octaethylpyridochlorin. *Meso*-aminooctaethylporphyrin **1**[3] was condensed with glyoxal in refluxing 1:1 THF/ethanol. After 24 hours the formylmethylimine product **2** was obtained in 69% yield. Intramolecular cyclization of **2** was achieved by overnight reflux in toluene in the presence of Montmorillonite K10 acidic clay. The two isomeric chlorins **3a**[4] and **3b**[5] were isolated in 31% total yield, in addition to a substantial quantity of the hydrolysis product, **1**. The chlorin product consisted of a 4:1 mixture of the two isomers, which were separable by preparative chromatography. The major component was examined by NOE spectroscopy, which revealed it to be the Z-isomer **3a** (irradiation of the CH_3 signal at 2.81 ppm led to enhancement of the *meso*-H signal at 9.31 ppm and of the ethylidene CH signal at 7.45 ppm). The isomeric mixture was treated with acid, in an attempt to bring about a 1,2-alkyl shift and hence form the desired pyridochlorin **4**. However, this reaction was unsuccessful, leading to decomposition of the chromophore. Experiments intended to hydrogenate the ethylidene double bond of the isomeric mixture to give a single diastereomer also failed.

0040-4039/98/$19.00
PII: S0040-4039(98)00853-3



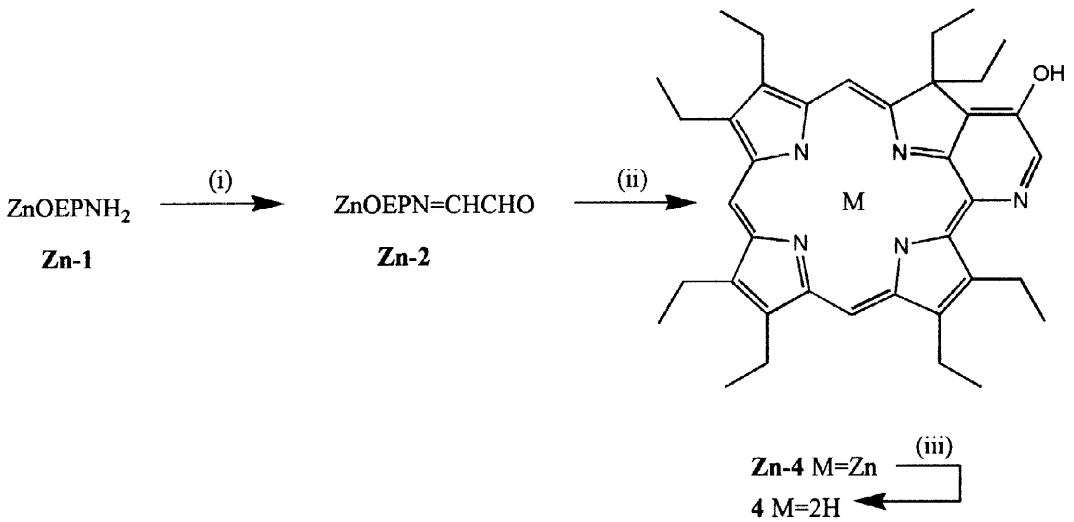
(i) CHOCHO, THF/EtOH, Δ; (ii) Montmorillonite K10, toluene, Δ

Scheme 1. Synthesis of the isomeric chlorins **3a** and **3b**

The presence or absence of a centrally-complexed metal can have a marked effect on the outcome of intramolecular cyclization reactions of porphyrins.[2] Therefore the cyclization of the zinc complex of **2** was studied. **Zn-2** was prepared by condensation of the zinc aminoporphyrin **Zn-1** with glyoxal (metallation of **2** with zinc acetate led to hydrolysis of the imine, resulting in isolation of **Zn-1**). The cyclization was performed using the conditions described above (toluene, Montmorillonite K10, heat), and did indeed proceed differently to that of the free base **2**. In this case, reaction was much slower, little change being discernable until refluxing had continued for 3 or 4 days. At this point only a trace amount of the expected product (the zinc complex of **3a/3b**)[4,5] was seen on TLC. A more polar green compound appeared to be the major product of the reaction (in addition to unreacted starting material, **Zn-2**, present as approximately 80% of the mixture). After work-up this compound was isolated in 20% yield and NMR analysis showed it to be the zinc complex of **4**. Demetallation with trifluoroacetic acid gave the free base **4**.[6]

Pyridochlorin **4** has a slightly red-shifted long-wavelength absorption (λ_{max} = 672 nm), compared to octaethylbenzochlorin (λ_{max} = 658 nm), and it possesses additional characteristics that might improve its performance as a photosensitizer over the latter. It is known that amphiphilic macrocycles, i.e. those bearing both hydrophobic and hydrophilic moieties, display better tumour-localizing properties than photosensitizers without these properties.[7] The presence of the polar hydroxypyridyl ring attached to the low polarity porphyrin skeleton increases the amphiphilicity of **4**. Octaethylbenzochlorin suffers from a lack of functional groups

available for further derivatization: the preparation of analogues based on this compound requires additional synthetic steps in order to introduce such a functionality.[8] In contrast, chlorin **4** possesses "built-in" sites at the hydroxypyridine ring that may allow for more direct analogue formation.



(i) CHOCHO, THF/EtOH, Δ; (ii) Montmorillonite K10, toluene, Δ; (iii) TFA

Scheme 2. Synthesis of pyridochlorin **4**

Acknowledgement:

We gratefully acknowledge the financial support of the Natural Sciences and Engineering Council of Canada.

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4. **3a**: ^{1}H NMR ($CDCl_3$) δ: -1.78 (br s, 1H, NH), -0.74 (br s, 1H, NH), 0.50 (t, J=7.3 Hz, 3H, CH_3), 1.65-1.90 (m, 18H, $6CH_3$), 2.81 (d, J=7.6 Hz, 3H, $\underline{CH_3}$=CH), 3.70-4.00 (m, 12H, $6CH_2$), 4.09-4.26 (m, 2H, CH_2), 7.45 (q, J=7.5 Hz, 1H, $\underline{CH}$=CH_3), 8.15 (s, 1H, $\underline{CH}$=N), 9.31, 9.51, 9.57 (3s, 3H, *meso*-H's); UV-Vis in $CHCl_3$, λ nm (ε): 360 (4.33), 410 (4.82), 446 (4.67), 584 (3.66), 672 (3.79), 722 (4.03); Analysis calc'd for $C_{38}H_{45}N_5O.H_2O$: C, 75.34; H, 7.82; N, 11.56: found C, 74.89; H, 7.69; N, 11.15.

5. **3b**: ^{1}H NMR ($CDCl_3$) δ: -1.14 (br s, 1H, NH), -0.74 (br s, 1H, NH), 0.10 (t, J=7.3 Hz, 3H, CH_3), 1.68-1.84 (m, 18H, $6CH_3$), 2.62 (d, J=7.5 Hz, 3H, $\underline{CH_3}$=CH), 3.70-3.95 (m, 12H, $6CH_2$), 4.04-4.25 (m, 2H, CH_2), 7.72 (q, J=7.5 Hz, 1H, $\underline{CH}$=CH_3), 7.98 (s, 1H, $\underline{CH}$=N), 9.16, 9.43, 9.53 (3s, 3H, *meso*-H's).

6. **4**: ^{1}H NMR (pyridine-d_5) δ: 0.40 (t, J=7.3 Hz, 6H, $2CH_3$), 1.63-1.81 (m, 15H, $5CH_3$), 1.88 (t, J=7.3 Hz, 3H, CH_3), 2.78-2.91 (m, 2H, CH_2), 3.49-3.71 (m, 10H, $5CH_2$), 3.85 (q, J=7.5 Hz, 2H, CH_2), 4.43 (q, J=7.3 Hz, 2H, CH_2), 8.40, 8.99, 9.58, 9.69 (4s, 4H, 3*meso*-H's and $\underline{CH}$=N), 13.06 (br s, 1H, OH); UV-Vis in $CHCl_3$, λ nm (ε): 412 (4.89), 490 (3.51), 522 (3.73), 556 (3.75), 616 (3.86), 672 (4.36); Analysis calc'd for $C_{38}H_{47}N_5O.0.5H_2O$: C, 76.22; H, 8.08; N, 11.70: found C, 75.96; H, 7.64; N, 11.67.

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