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Controlled porphyrinogen oxidation for the selective synthesis of *meso*-tetraarylchlorins

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ABSTRACT

Chlorins have been synthesized through the reduction of the corresponding porphyrins although theoretically they can be obtained from reduced macrocycle forms as porphyrinogens. A new method for the oxidation of *meso*-tetraarylporphyrinogens was developed generating a substantial amount of chlorin relatively to porphyrin. The structure of the porphyrinogen, particularly the presence of substituents on the *meso*-phenyl groups, is decisive for the final yield of chlorin. In the case of *meso-tetrakis*(2,6-dichlorophenyl)porphyrinogen, 92% of the corresponding chlorin is obtained.

Chlorins (dihydroporphyrins) are very important tetrapyrrolic macrocycles due to the biological importance of their photophysical properties, particularly the long wavelength absorption band which is also relevant for their applications in medicinal chemistry[1] and material science.[2] Due to the fact that the porphyrins have a higher intrinsic stability than chlorins, any process to prepare chlorins[3] must be designed to avoid the oxidation to porphyrins. Besides the biosynthetic processes leading to chlorins or other tetrapyrrolic macrocycle reduced forms, there are three major synthetic strategies to obtain chlorins.

Reaction of two dipyrromethanes or dipyrromethene structures originating peculiar chlorin structures which are not oxidized to porphyrin as suggested by Battersby–Monforts,[4] Lindsey[5] or Jacobi.[6]

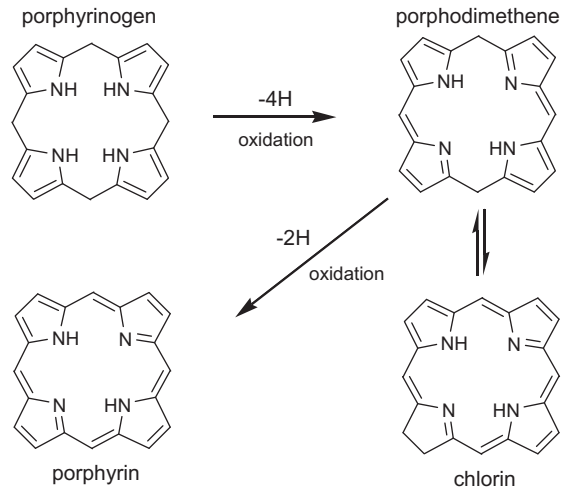
Specific addition reactions at the porphyrin β-positions originate a saturated position on the macrocycle. This is the more explored strategy with construction of carbon–hydrogen, carbon–carbon, or carbon–heteroatom bonds. Some leading examples: dihydroxylation with OsO_4,[7] hydrogenation by diimide,[8] reaction of β-nitroporphyrins with activated methylene compounds,[9] Diels–Alder reactions,[10] dipolar cycloadditions,[11] and alkylation of porphyrins with organolithium reagents.[12]

Rearrangement of metallated porphodimethenes, a method limited to *meso*-unsubstituted metallochlorins.[13]

Another interesting approach is the selective oxidation of the porphyrinogen to the chlorin stage avoiding the additional oxidation step to porphyrin. The advantages of such a procedure would be enormous considering that porphyrinogens can be easily obtained through the condensation of pyrrole and aldehydes using Lindsey conditions (Scheme 1).[14]

Very few examples in the literature exploit this possibility. Ibers claims to have obtained metallochlorins preferentially in the pyrrole–alkylacetal condensations in the presence of certain metal salts[15] albeit in very poor yields. Smith oxidized a crowned porphyrinogen selectively to the corresponding chlorin using iodine or DDQ as an oxidant.[16]

Some years ago we disclosed a method to synthesize tetraarylporphyrins from pyrrole and benzaldehydes using a mixture of



Scheme 1.

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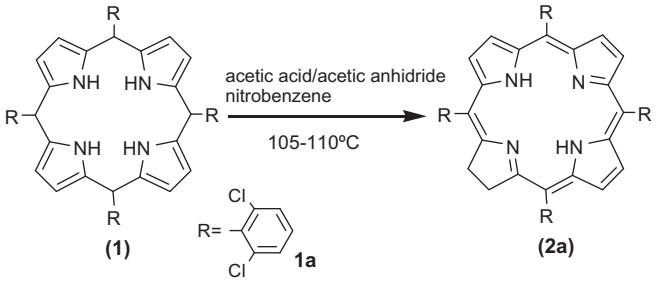


Scheme 2.

Table 1
Results of the porphyrinogen **1a** oxidation in the presence of carboxylic acids

Carboxylic acid	Product yield (%)	Chlorin/porphyrin (%)
Acetic	32[a]	63/37
Propionic	12[a]	92/8
Butyric	11[b]	76/24
Isobutyric	9[b]	62/38
Formic	c	—

[a] Precipitates from reaction mixture.
[b] Isolated by chromatography.
[c] No chlorin or porphyrin formation.

nitrobenzene/acetic acid as the solvent.[17] The advantage of this one-step method is that in many cases the porphyrins precipitate from the reaction mixture. In this case nitrobenzene plays the role of an efficient and selective oxidant[18] generating porphyrin free of chlorin contamination, a frequent problem in the Rothemund type reaction conditions.[19] Being the tetraarylporphyrinogens accessible from pyrrole–aldehyde condensation using Lindsey conditions,[14] we considered the possibility of the replacement of the expensive quinones, generally the usual oxidant to convert to porphyrins, by a mixture of acetic acid–nitrobenzene as the oxidant, which proved to be effective in the pyrrole–aldehyde porphyrin synthesis. We firstly observed that, following this procedure, chlorin appears in small amounts jointly with the predominant porphyrin product,[20] contrary to what occurs in the one-step reaction. With this observation it was decided to change the reaction conditions aiming at a selective oxidation of porphyrinogen to chlorin. After preparing the *meso*-(2,6-dichlorophenyl) porphyrinogen **1a**, evaporation of the dichloromethane over a mixture of acetic acid/acetic anhydride with a small amount of nitrobenzene at 105–110 °C during 3 h was carried out. After cooling we isolated 32% of a mixture of *meso*-tetra(2,6-dichlorophenyl) chlorin **2a** (63%) and the corresponding porphyrin (37%) (Scheme 2).

Using the same procedure to prepare porphyrinogen **1** the effect of using different carboxylic acids on the chlorin yield was studied and is quoted in Table 1.

The structure of the carboxylic acids does not greatly influence the overall yields, but has a great influence on the relative amount of chlorin in the mixture. Propionic acid proved the most convenient for this oxidation step originating the highest yields of chlorin. In addition, product isolation is easier with propionic and acetic acids because they promote direct crystallization of the product. With other acids, removal of the acid and nitrobenzene can be a cumbersome operation.

The possibility of replacing nitrobenzene by several nitroaromatics was also studied and the results are shown in Table 2.

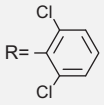
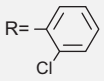
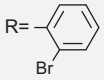
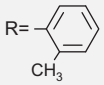
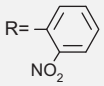
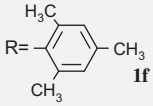
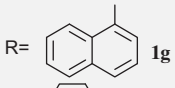
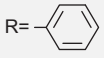
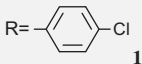
The nitroaromatic compound significantly affects the final oxidative state of the product as shown by the chlorin/porphyrin ratio. With nitroaniline the same yield and the same amount of chlorin are obtained as in the case of nitrobenzene. Nitroanisole gives a

Table 2
Results of the oxidation of porphyrinogen **1** in the presence of propionic acid and nitroaromatic compounds

Nitroaromatic	Product yield (%)	Chlorin/porphyrin (%)	Reduction potential[21] (mV)
Nitrobenzene	12[a]	92/8	−486[c]
4-Nitroaniline	11[a]	91/9	−509[d]
4-Nitroanisole	13[a]	80/20	−784[e]
1-Nitronaphthalene	4[b]	45/55	−600[e]
None	9[b]	68/32	—

[a] Isolated by chromatography.
[b] Precipitates from reaction mixture.
[c] E_{ref} = −380 mV.
[d] Vs SCE.
[e] Vs Ag/AgI, 0.1 M I^-.

Table 3
Results of the oxidation of several porphyrinogens in the presence of propionic acid and nitrobenzene[a]

Porphyrinogen (**1**)	Product yield[a] (%)	Chlorin/porphyrin (%)
 **1a**	28	92/8
 **1b**	39	26/74
 **1c**	10	70/30
 **1d**	33	65/35
 **1e**	20	70/30
 **1f**	8	55/45
 **1g**	39[b]	75/25
 **1h**	28	37/63
 **1i**	39[b]	55/45

[a] Isolated yields (see Supplementary data).
[b] Precipitates from reaction mixture.

little more final product but more amount of porphyrin appears. Without any nitroaromatic, the chlorin is favored but higher amounts of porphyrin appear in the final product. These results can be related to the reduction capacity of the nitroaromatic compounds. The presence of a methoxy group turns the nitroaromatic a weaker oxidant and the presence of an amino group (protonated in reaction medium) functions as an electron-withdrawing group, making the nitroaromatic a more powerful oxidant.[22] This last statement seems contradictory because better oxidants will give higher yields of porphyrin which is the more oxidized macrocycle.

However, it seems clear that chlorins are not intermediates in the oxidative steps that lead to porphyrin. Instead they are at the same oxidative level as porphodimethenes and the isomerization is favored with some nitroaromatics relative to others. Nitronaphthalene, with almost the same reduction potential as the nitroben-

zene, originates a far smaller amount of chlorin stressing the importance of the nitroaromatic structure. The role of nitroaromatics in the origin of higher amounts of chlorin is certainly related to these particular reaction conditions with large amounts of porphyrinogen to be oxidized relatively to the existing oxidant species. In one-pot pyrrole/aldehyde condensation carried out in the presence of the nitrobenzene[17] the amount of porphyrinogen at each moment is small and no chlorin is detected. This fact finds support in Dolphin's hypothesis[23] stating that one reason to favor chlorin formation can be oxidative disproportionation of the macrocycle in different oxidative states.

Temperature also seems to be an important factor, the oxidation with propionic acid/nitrobenzene of the porphyrinogen **1a** at the lower temperature of 70–80 °C yields 9% of a mixture having only 76% of chlorin.

In a further development for the oxidative step a more concentrated solution of propionic acid/acetic anhydride/nitrobenzene at 105–110 °C was used. In this case we obtained 190 mg of a precipitate of **2a** (17% yield) with 92% of chlorin. From the chromatographic isolation of the mother liquid more porphyrin/chlorin mixture was obtained in a total yield of 28%. The visible spectrum showed a small band at 736 nm which is probably due to the presence of a small amount of bacteriochlorin macrocycle. Following this improvement several porphyrinogens were oxidized to mixtures of chlorins and porphyrins (Table 3).

The propionic acid/acetic anhydride/nitrobenzene mixture efficiently oxidizes *meso*-tetraarylporphyrinogens originating substantial amounts of chlorins. The effect of phenyl substitution on the chlorin selectivity is not easy to rationalize. In the absence of substituents, porphyrin is the major oxidative product (**1h**). The presence of electron-withdrawing groups tends to favor the chlorin oxidation state with the exception of (**1b**). Interestingly, the same chlorine atom at *para* position favors the chlorin (**1i**). In general however, steric effects by substituents at the *ortho* position of the phenyl group seem to favor the chlorin as in the case of **1c–e,** and also in the case of the 1-naphthyl derivative (**1g**). The 2,6-dichloro derivative **1a** which has two kinds of effects gives the greater amount of chlorin.

In conclusion we developed a method to efficiently oxidize porphyrinogens to a mixture of porphyrin and chlorin. In some cases the chlorin is isolated as the main product. For *meso*-tetra(2,6-dichlorophenyl) porphyrinogen **1a** the *meso*-tetra(2,6-dichlorophenyl) chlorin **2a** is obtained in relatively higher yield and purity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.010.

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