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Nitrogen extrusion from pyrazoline-substituted porphyrins and chlorins using long wavelength visible light

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Protoporphyrin reacts with diazomethane to give pyrazolines which at long wavelength (~ 630 nm) extrude nitrogen to give the corresponding cyclopropyl derivatives.

The search for novel photosensitizers for use as drugs in photodynamic therapy (PDT), and basic research interests, have led to the synthesis of derivatives of both naturally occurring and synthetic porphyrins and chlorins.[1] A characteristic of PDT drugs is their ability to accumulate preferentially in target tissues. Photosensitizers that accumulate exclusively in diseased tissues would have great advantages as PDT agents.

We report here on the synthesis of the novel pyrazoline derivatives (**1–3**) of protoporphyrin dimethylester (PP-DME), methylpyropheophorbide (MePPP), and tetrakis(pentafluorophenyl)porphyrin (pFTPP) using a 1,3-dipole cycloaddition reaction of diazomethane.[2] These compounds were then subjected to thermal and photochemical extrusion of N_2, which produced the cyclopropane derivatives **4**, **5** and **6**. It is thought that the pyrazoline functionality might be used as a photocrosslinking group. The photosensitizer could then be bound to specific regions of human tissue.

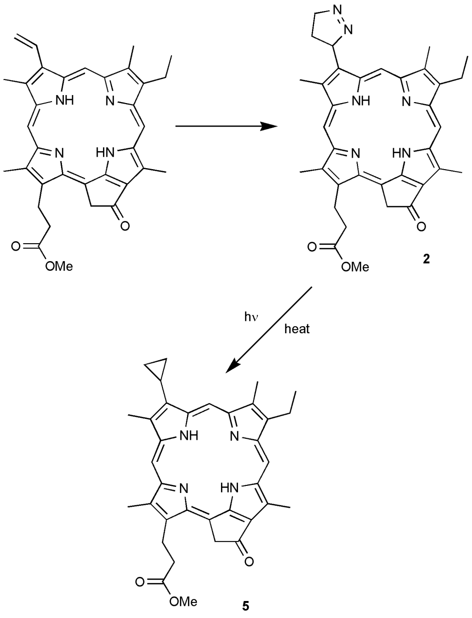
To synthesize **1a–c**, PP-DME was dissolved in CH_2Cl_2, and an excess (50:1 w/w) of diazomethane as a solution in ether, was condensed directly into the reaction flask.[2] The solution, under positive N_2 pressure, was then allowed to react overnight. 78% conversion to the three products **1a–c** was achieved (Scheme 1).[3]

It was anticipated that the compounds would undergo thermal cyclo-elimination through the extrusion of nitrogen (Scheme 1).[4] The three compounds (**1a–c**) were refluxed in toluene until complete conversion to the corresponding cyclopropanes **4a**, **4b** and **4c** was observed.[5] Both **1a** and **1b** required 24 h to completely convert, while **1c** required 47 h.

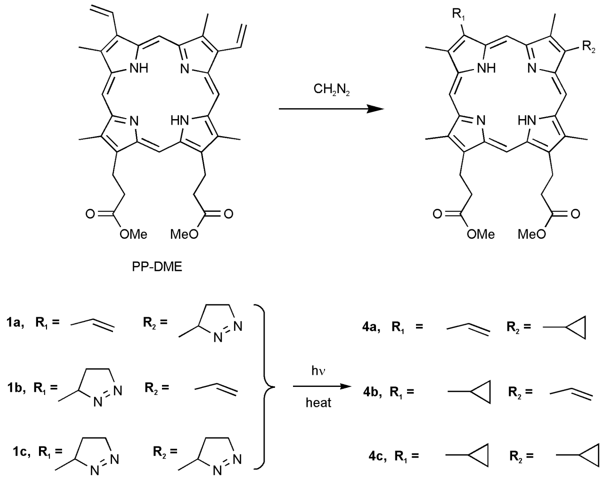
Irradiation of degassed, dilute solutions [3×10^{-4} M] of the pyrazolines with 350 nm light was then attempted.[6] It is known that pyrazolines photo-extrude nitrogen at this wavelength (Scheme 1).[7] This photoreaction produced **4a**, **4b** and **4c** in 82% (23 h), 52% (52 h) and 50% (50 h) yields respectively.

These results led to the investigation of chlorins as pyrazoline adducts. The pyrazoline derivative of MePPP was synthesized in the same way as **1**, giving the pyrazoline cycloadduct **2** in 78% yield (Scheme 2).[2] Irradiation of **2** in a dilute solution [3×10^{-4} M] of oxygen purged benzene with 350 nm light produced the photoproduct **5**.[6]

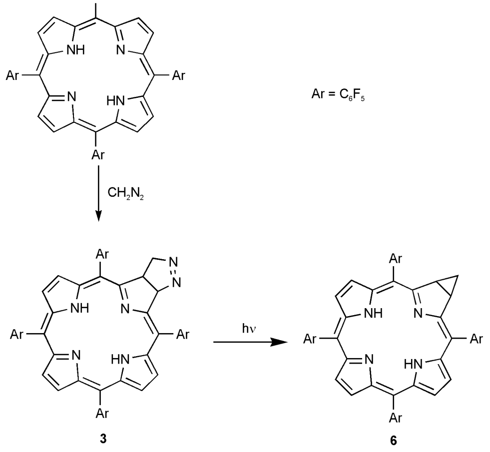
The pyrazoline derivative of pFTPP was synthesized as above.[2] The product **3** was obtained in 60% yield. Thermolysis of the pyrazoline **3** to the cyclopropane cycloadduct **6** required refluxing in mesitylene for 1 h (Scheme 3). The yield was 96%.



Scheme 2



Scheme 1



Scheme 3

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Cavaleiro's group[8] have recently reported on the reaction of diazomethane with β-nitro-*meso*-tetraphenylporphyrin to give a pyrazoline-fused chlorin which gave the corresponding cyclopropane adduct by refluxing in toluene.

One of the requirements of a photosensitizer for PDT is that it absorbs light at wavelengths where human tissue does not. Light penetration through human tissue increases significantly between 630 and 750 nm, which allows efficient excitation of a photosensitizer drug.[9] Long wavelength irradiation of the pyrazolines was then attempted. This produced the first example of such long wavelength activation of a photoreactive functionality at the porphyrin periphery. The pyrazolines **1a**, **1b**, **1c** were irradiated with filtered light with wavelengths between 550 and 650 nm (Scheme 1).[10] The products **4a**, **4b** and **4c** were observed in 35% (14 h), 52% (7 h) and 78% (38 h) yield respectively.

The chlorin **2** absorbs light more efficiently at longer wavelengths than does **1**. Compound **2** has a strong Q-band absorption at 665 nm (ε = 52,700 in benzene) which is only half as intense as its Soret-band (411 nm, ε = 107,100). Compound **2** was then irradiated at 672 nm.[11] An irradiated dilute solution [3×10^{-4} M] of **2** in oxygen purged benzene yielded almost quantitatively after 14 h a single photoproduct, which was shown to be the cyclopropane cycloadduct **5**.

Compound **3** is also a chlorin, and absorbs light strongly at 648 nm. Thus it was irradiated with filtered light at wavelengths between 550 and 650 nm.[10] After 1 h the product **6** was obtained in quantitative yield.

Pyrazolines absorb light between 300–400 nm *via* a n–π* transition, thus it would be expected that the photoextrusion would occur during irradiation at wavelengths in this region, as was observed in the initial experiments.[12] The interesting result here is the extrusion of nitrogen at longer wavelengths. It was initially thought that a photochemical reaction of this type would be unlikely. Light of 672 nm, in the case of the MePPP pyrazoline derivative (**2**), would lead to an excitation to the first excited singlet state at 42.4 kcal mol^{-1}. Nitrogen extrusion is thought to occur through S_1 or T_1 of the pyrazoline, excitation energies being 70–90 and 50–60 kcal mol^{-1} respectively.[12] This would seem to suggest that there is not enough energy absorbed by the porphyrin to transfer to the pyrazoline to cause the extrusion. The results can however be explained if one assumes that the pyrazoline is not a distinct entity from the porphyrin, but is in fact an extended part of the chromophore.[13,14] Add to this the fact that the activation energy barrier to nitrogen extrusion has been calculated at 35.2 kcal mol^{-1},[15] then it seems reasonable that the nitrogen extrusion can occur at the long wavelengths.

To conclude, we have demonstrated the first examples of long wavelength activation of an unconjugated photoreactive functionality at the porphyrin periphery. This is an interesting development as long wavelength activation of a compound is a requirement for use in PDT, and the pyrazoline functionality might be used as a cross-linker for the chlorin chromophore to enable site-specific accumulation of a drug in diseased tissue.

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Notes and references

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