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Novel Approach to Chlorins and Bacteriochlorins: [8π+2π] Cycloaddition of Diazafulvenium Methides with Porphyrins

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New and unprecedented [8π+2π] cycloaddition of diazafulvenium methides with porphyrins and chlorins is reported. The synthetic methodology allowed the access to a new type of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused chlorins and bacteriorins in a selective fashion.

Introduction

Porphyrin-type macrocycles were selected by nature as the main class of molecules to successfully interact with sunlight with the higher expression seen in the photosynthetic processes.[1] They have a rich pattern of absorption bands particularly at red and NIR (near infrared region) portion of the spectra that can be correlated to the degree of macrocycle aromaticity and symmetry.[2] Hence, a strong interest exists in employing chlorins (dihydroporphyrins) and bacteriochlorins (tetrahydroporphyrins) in light-energy conversion processes such as the mimicking of the photosynthetic process[3] or electric energy production by dye sensitized solar cells.[4] In medicine the more relevant applications are the use in cancer treatment by photodynamic therapy (PDT) and the use in cancer diagnosis. In fact, the strong fluorescence abilities at NIR of the reduced form of porphyrin macrocycles is essential to use these molecules as fluorescence markers for cancer lesions, making them valuable for tissue imaging processes.[5] On the other hand, these macrocycles, when excited by light, are excellent singlet oxygen superoxide ion producers that can destroy the diseased tissue. In PDT[6] light penetration of tissues is of great importance since deep tissue damage can be achieved. The light absorption by tissue chromophores restricted the efficient light diffusion to a narrow range of 600 to 1200 nm, which truthfully is a much narrowed window since radiation with wavelenghts higher than 850 nm do not have enough energy to produce singlet oxygen.[7] This requirement for light absorptions at the red region of the visible spectra makes chlorins[8] and bacteriochlorins[9] attractive molecules for PDT.

Strictly analyzing the photophysical properties, bacteriochlorins with strong absorptions around 750 nm will be the best choice. However, the lack of efficient synthetic processes[10] and specially the ease of oxidation and photobleaching[11] limit their practical use. One strategy to minimize these problems is the dialkyl geminal β-substituted bacteriochlorins approach proposed by Lindsey.[9a,12] The presence of a geminal dimethyl group in each reduced pyrrole ring blocks dehydrogenation leading to bacteriochlorin derivatives with considerable stability.

Nevertheless, a simpler way to get the chlorin or bacteriochlorin macrocycles is by addition reactions over the porphyrin nucleus or in some cases from controlled porphyrinogen oxidation.[13] The cycloaddition approach has been explored successfully to originate saturated positions on the macrocycle. It has been demonstrated that porphyrins can act as dienophiles in Diels–Alder reactions[10] and as dipolarophiles in 1,3-dipolar cycloadditions.[14] Furthermore, "locked" chlorins with increased stability can also be obtained by 1,3-dipolar cycloaddition of porphyrins bearing two vicinal electron-withdrawing groups in β positions.[14g] In general, chlorins are formed as the main products and bacteriochlorins or isobacteriochlorins as side products.

The study of pericyclic reactions of aza- and diazafulvenium methide systems **1** and **2** as an approach to the synthesis of functionalized pyrroles and pyrazoles is one of our current research interests.[15–18] These reactive intermediates can be considered "higher-order" azomethine ylides and azomethine imines, respectively.[19] They can act as 4π 1,3-dipoles or as 8π 1,7-dipoles although the typical reactivity pattern is that expected for 1,7-dipoles. In fact, only with 5-(trifluoromethyl)azafulvenium methides did we observe evidence of azafulvenium methides acting as a 1,3-dipole.[18] Thus, 1,7-dipoles **5** or **6**, generated from 2,2-dioxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **3** or 2,2-dioxo-1*H*,3*H*-pyrazolo-[1,5-*c*]thiazoles **4** by thermal extrusion of sulfur dioxide, participate in pericyclic reactions, namely sigmatropic [1,8]-

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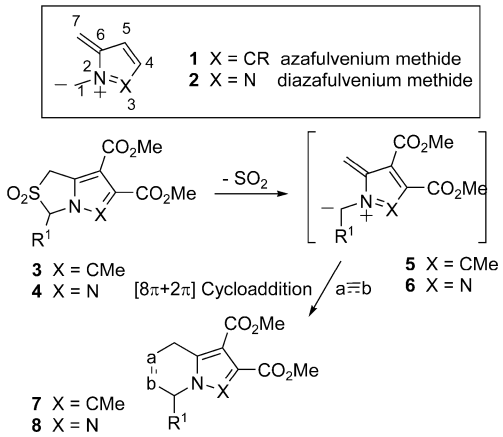
H shifts and 1,7-electrocyclizations, giving *N*-vinyl- or *C*-vinylpyrroles and -pyrazoles.[15–17,19] Azafulvenium methides **5** generated under microwave irradiation can be intercepted in [8π+2π] cycloadditions.[17] Diazafulvenium methides **6** also behave as 8π 1,7-dipoles either under microwave irradiation or conventional heating, affording the corresponding 1,7-cycloadducts **8**[16,17,19] (Scheme 1).



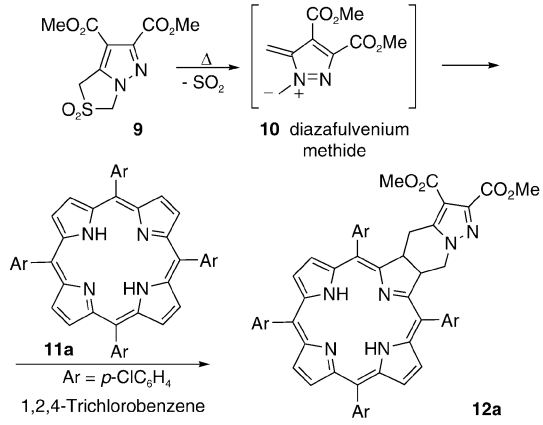
Scheme 1. [8π+2π] cycloaddition of aza- and diazafulvenium methides.

In this context, and considering our long standing interest in porphyrin chemistry[20] we decided to investigate the reactivity of porphyrins as dipolarophiles in [8π+2π] cycloaddition, aiming to find a new route to chlorin and bacteriochlorin type macrocycles.

Results and Discussion

The chemical behaviour of diazafulvenium methide **10**, generation from 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole[19] **9**, in the presence of *meso*-tetra(4-chlorophenyl)-porphyrin[21] (**11a**) was studied. Using an excess of **9** (4 equiv.) a mixture of chlorin and bacteriochlorin was obtained. The cycloaddition was then carried out under various reaction conditions aiming to achieve the selective formation of chlorin (Table 1). Under microwave irradiation at 250 °C for 20 min, using one equivalent of porphyrin **11a** and 1,2,4-trichlorobenzene as solvent, the target cycloadduct **12a** was obtained in 15% yield (Entry 1). Carrying out the reaction with excess of porphyrin **11a** (2 equiv.) the microwave induced reaction at 250 °C led to chlorin **12a** in 18% yield after 10 min (Entry 2). A more efficient process was achieved with a longer reaction time, allowing the isolation of **12a** in 30% yield and recovering 65% of the starting porphyrin (Entry 3). These proved to be the best reaction conditions to obtain chlorin **12a** since the increase of the reaction time (Entry 4), performing the reaction at lower temperature (Entry 5) or the use of 3 equiv. of porphyrin **11a** (Entry 6) did not lead to improvements. On the other hand, changing the solvent from 1,2,4-trichlorobenzene to sulfolane affords chlorin **12a** in very low yield (Entry 7). Finally, the synthesis of chlorin **12a** was carried out under conventional heating (Entry 8). Porphyrin **11a** was treated with 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole **9** in refluxing 1,2,4-trichlorobenzene for six hours giving chlorin **12a** in 22% yield. The UV/Vis spectrum of chlorin **12a** shown in Figure 1, exhibits a typical absorption band with a maximum peak at 649 nm.

Table 1. Synthesis of chlorin **12a** by [8π+2π] cycloaddition of diazafulvenium methide **10** with porphyrin **11a**.



Entry	**11a** (equiv.)	Reaction conditions	Chlorin **12a**, yield (%)	Porphyrin recovered (%)
1	1	MW, 250 °C. 20 min	15	–[b]
2	2	MW, 250 °C,10 min	18	44
3	2	MW, 250 °C, 20 min	30	65
4	2	MW, 250 °C, 40 min	18	34
5	2	MW, 230 °C, 20 min	15	47
6	3	MW, 250 °C, 20 min	22	67
7	2	MW, 250 °C, 20 min[a]	3	58
8	2	230 °C, 6 h	22	–[b]

[a] Reaction carried out in sulfolane. [b] Not determined.

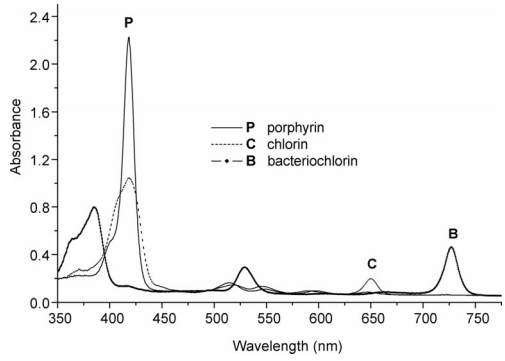
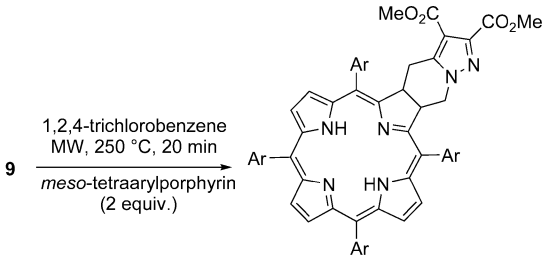


Figure 1. UV/Vis absorption spectra of porphyrin **11a**, chlorin **12a** and bacteriochlorin **13** (5 μM) in dichloromethane.

The work was extended to the reactivity of *meso*-tetraphenyl-, *meso*-tetratolyl-, *meso*-tetra(4-methoxyphenyl)- and *meso*-tetra(4-fluorophenyl)porphyrin (**11b**–**11e**[21]). Using the previously optimized reaction conditions chlorins

12b–**12e** were selectively obtained (Table 2). The cycloaddition of diazafulvenium methide **10** was more efficient with *meso*-tetraphenylporphyrin affording chlorin **12b** in 31% yield (Entry 1) whereas the cycloaddition of *meso*-tetra(4-fluorophenyl)porphyrin **11e** afforded chlorin **12e** in only 10% yield (Entry 4). The microwave induced [8π+2π] cycloadditions of porphyrin **11c** and **11d** led to the corresponding chlorins in 26% and 20% yield, respectively (Entries 2 and 3). The chlorins exhibited similar UV/Vis absorption spectra with an absorption band at ca. 649 nm.

Table 2. Synthesis of chlorins by [8π+2π] cycloaddition of diazafulvenium methide **10** with porphyrins.



11b Ar = Ph
11c Ar = Tol
11d Ar = *p*-$MeOC_6H_4$
11e Ar = *p*-FC_6H_4

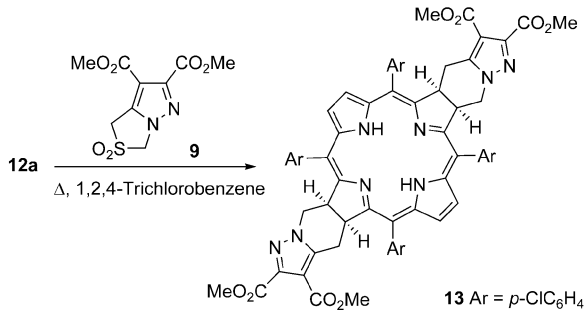
12b Ar = Ph
12c Ar = Tol
12d Ar = *p*-$MeOC_6H_4$
12e Ar = *p*-FC_6H_4

Entry	Porphyrin	Chlorin, yield (%)	Porphyrin recovered (%)
1	**11b**	31	58
2	**11c**	26	51
3	**11d**	20	48
4	**11e**	10	34

It should be emphasized that this synthetic methodology leads to chlorin derivatives in a selective fashion and in fact under the optimized reaction conditions the formation of bisadducts (bacteriochlorins) was never detected.

Having established a route to chlorins fused to a 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine ring system, it was strategicaly important to explore the use of the [8π+2π] cycloaddition of diazafulvenium methides for the preparation of bacteriochlorins. Thus, the reactivity of chlorin **12a** towards diazafulvenium methide **10** generated in situ from 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole **9** was studied (Table 3). Carrying out the reaction under microwave irradiation at 250 °C for 20 min and using 1.1 equiv. of 1,7-dipole percursor bacteriochlorin **13** was obtained in 8% with the recovery of 50% of the starting chlorin (Entry 1). Using the same reaction conditions but increasing the amount of **9** to 10 equiv. only a slightly improvement of the yield was observed (Entry 2). The same result was obtained performing the microwave induced reaction at 250 °C for 10 min with 4.4 equiv. of compound **9** (Entry 3). In this case the conventional heating proved to be more efficient than the microwave methodology. In fact, carrying out the reaction in refluxing 1,2,4-trichlorobenzene for four hours the target bacteriochlorin **13** could be isolated as single product in 36% yield (40% calculated based on the chlorin consumed) (Entry 4). The recovery of chlorin from these reactions is an indication of the considerable stability of this macrocycle.

Table 3. Synthesis of bacteriochlorin **13** by [8π+2π] cycloaddition of diazafulvenium methide **10** with chlorin **12a**.



13 Ar = *p*-ClC_6H_4

Entry	**9** (equiv.)	Reaction conditions	**13**, yield (%)	**12a** recovered (%)
1	1.1	MW, 250 °C, 20 min	8 (16[a])	50
2	10	MW, 250 °C, 20 min	12	–[b]
3	4.4	MW, 250 °C, 10 min	12	–[b]
4	4.4	225 °C, 4 h	36 (40[a])	12

[a] Calculated, based on the chlorin consumed. [b] Traces.

The structure of bacteriochlorin **13** was unambiguously established by X-ray crystallography.[22] This bisadduct has the typical UV/Vis absorption spectra of bacteriochlorins with an absorption band with a maximum peak at 727 nm (Figure 1). No evidence for the formation of isobacteriochlorin could be observed. Thus, the reaction occurs with site selectivity as well as with regioselectivity. On the other hand, the process is also stereoselective leading to a macrocycle with the two 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine rings with *cis* configuration.

The ^{1}H NMR spectrum of bacteriochlorin **13** shows the NH protons at –1.80 and –1.76 ppm with a 75:25 ratio, which is an evidence of the NH tautomerism. In fact, in the absence of this porphyrin inner proton exchange, the two NH protons should give rise to one singlet since the chemical environment of these protons would be the same due to the symmetry of bacteriochlorin **13**.[14e] Several reports on the NH tautomeric processes observed for porphyrins, chlorins and bacteriochlorins are known.[23] Furthermore, the NH tautomerization in bacteriochlorins is energetically less favorable and is usually observed at room temperature[23a,23b] which is in agreement with our observation.

Conclusions

Herein, the [8π+2π] cycloaddition of diazafulvenium methides with porphyrins and chlorins is reported for the first time. Porphyrins react as the 2π component affording new 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused chlorin derivatives in a selective fashion. These type of chlorins also participate in the cycloaddition with diazafulvenium

methides to give 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused bacteriochlorins with site-, regio- and stereoselectivity.

Experimental Section

General Procedure for the Preparation of Chlorins by [8π+2π] Cycloaddition of Diazafulvenium Methide with Porphyrins: A solution of dimethyl 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*][1,3]thiazole-6,7-dicarboxylate (**9**) (19 mg, 0.07 mmol) and pophyrin (0.14 mmol) in 1,2,4-trichlorobenzene (1 mL) was flushed with argon and irradiated in the microwave reactor with the temperature set to 250 °C for 20 min. After cooling to room temperature, the mixture was purified by flash chromatography (CH_2Cl_2/ethyl acetate, 95:5%) affording unreacted porphyrin and chlorin.

Chlorin 12a: Yield 30% (20 mg), m.p. > 300 °C (from CH_2Cl_2/methanol) (65% unreacted porphyrin recovered, 68 mg from 105 mg). IR (KBr): $1/\lambda_{max}$ = 3356, 2949, 1743, 1559, 1516, 1489, 1472, 1394, 1360, 1213, 1176, 1056, 1090, 1016, 995, 969, 848, 722, 706, 488 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, J = 4.9 Hz, 1 H, β-H pyrrolic), 8.57 (d, J = 4.9 Hz, 1 H, β-H pyrrolic), 8.40 (s, 2 H, β-H pyrrolic), 8.29 (d, J = 4.8 Hz, 1 H, β-H pyrrolic), 8.22 (d, J = 4.8 Hz, 1 H, β-H pyrrolic), 8.17–8.14 (m, 2 H, Ar), 8.10–8.03 (m, 2 H, Ar), 7.97–7.95 (m, 3 H, Ar), 7.85–7.84 (m, 3 H, Ar), 7.70–7.65 (m, 6 H, Ar), 5.70–5.64 (m, 1 H, reduced β-H pyrrolic), 5.42–5.36 (m, 1 H, reduced β-H pyrrolic), 4.44 (dd, J = 13.6, 7.4 Hz, 1 H, CH_2 fused ring), 3.99 (dd, J = 13.6, 8.9 Hz, 1 H, CH_2 fused ring), 3.84 (s, 3 H, CO_2Me), 3.78 (s, 3 H, CO_2Me), 3.54 (dd, J = 15.9, 6.8 Hz, 1 H, CH_2 fused ring), 2.73 (dd, J = 15.9, 9.3 Hz, 1 H, CH_2 fused ring), –1.72 (s, 2 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 162.4, 162.2, 161.9, 153.1, 152.9, 143.4, 142.9, 140.9, 140.8, 139.9, 139.8, 139.4, 136.4, 135.7, 135.6, 135.4, 135.3, 135.0, 134.9, 134.4, 133.2, 133.1, 132.6, 132.5, 129.2, 128.9, 128.7, 128.3, 128.2, 128.1, 127.2, 124.5, 124.3, 122.5, 122.2, 111.4, 111.2, 110.8, 52.5, 51.7, 49.3, 48.0, 45.5, 26.0 ppm. ESI-HRMS found 961.1629 calcd. 961.1625 ($C_{53}H_{37}Cl_4N_6O_4$ [M + H]$^+$). UV/Vis (CH_2Cl_2): λ_{max} /nm (logε) = 418 (5.26), 518 (4.18), 545 (4.13), 596 (3.83), 649 (4.44).

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and characterization data and NMR spectra for compounds **12** and **13**. Crystallographic data for bacteriochlorin **13**.

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