ORGANIC
LETTERS

2011
Vol. 13, No. 1
130−133

1,3-Dioxopyrrolo[3,4-*b*]porphyrins: Synthesis and Chemistry

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Received November 8, 2010

ABSTRACT

A novel 1,3-dioxopyrrolo[3,4-*b*]porphyrin (2) has been synthesized in 70% yield following a [4 + 2] cycloaddition reaction of pyrrolo[3,4-*b*]porphyrin 1 with $^1O_2$. The new imide was used as a template to other 1,3-dioxopyrrolo[3,4-*b*]porphyrins and to the corresponding open counterparts. The UV/vis absorption spectra of the new compounds show significant red-shifts when compared with those of the nonsubstituted analogues. The structure of an imide derivative was confirmed by single-crystal X-ray diffraction.

The development of new synthetic strategies concerning the functionalization of porphyrins has attracted the interest of many research groups due to the remarkable photo- and biochemical properties of this type of compound. The structural modification of porphyrins at their β-pyrrolic positions is probably the most versatile approach to obtain new compounds with improved properties for a particular application.[1] Our research group has been particularly focused on the development of synthetic methodologies to functionalize β-pyrrolic positions of *meso*-tetraarylporphyrins by cycloaddition reactions.[2−5] In particular, we have described a novel approach to *N*-alkylpyrrolo[3,4-*b*]porphyrins via 1,5-electrocyclization of porphyrinic azomethine ylides generated from the reaction of (2-formyl-5,10,15,20-tetraphenylporphyrinato)nickel(II) with *N*-substituted glycines.[6] This methodology is an important alternative to the synthetic approach described by Smith and co-workers to obtain similar compounds.[7]

The Knapp[8] and Smith groups[9,10] found that the exocyclic pyrrole unit of the pyrroloporphyrins can act as a diene in Diels−Alder reactions with acetylenedicarboxylates. Here we describe that pyrrolo[3,4-*b*]porphyrin **1** can be converted into the corresponding 1,3-dioxopyrrolo[3,4-*b*]porphyrin **2** in excellent yield. We also show that this novel derivative can be further modified to give access to other 1,3-dioxopyrrolo[3,4-*b*]porphyrins or porphyrin-2,3-dicarboxamide derivatives.

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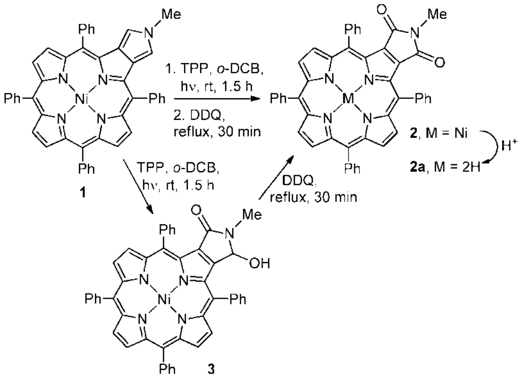
The first evidence that 1,3-dioxopyrrolo[3,4-*b*]porphyrin **2** can be obtained by oxidation of pyrrolo[3,4-*b*]porphyrin **1** occurred when we attempted the synthesis of fused diporphyrins by Diels–Alder reaction of **1** (diene) with *meso*-tetrakis(pentafluorophenyl)porphyrin (dienophile). The experiment was carried out by refluxing a toluene solution of both porphyrins. After 72 h, the TLC analysis revealed the formation of a new compound, in small amount, with an R_f value smaller than those of the starting porphyrins and with an intense green color. After the workup and purification, the mass spectrum of that compound showed a base peak with a *m/z* value at 753 not corresponding to the expected adduct. Based on the mass spectrum and NMR studies, we were able to establish the structure of the green compound as **2** (Scheme 1). The ^{1}H NMR spectrum of **2** is extremely simple, corresponding to a highly symmetric molecule: one singlet at δ 3.03 ppm ($N-CH_3$), two doublets (δ 8.56 and 8.73 ppm) and a singlet (δ 8.63 ppm) corresponding to the β-pyrrolic protons and several multiplets corresponding to the phenyl protons. The ^{13}C NMR spectrum shows a distinctive signal at δ 163.0 ppm corresponding to the two carbonyl carbons. These data are compatible with an imide-fused porphyrin. The demetalation of **2** with a mixture of sulfuric acid in dichloromethane afforded quantitatively the corresponding metal-free porphyrin **2a**. The UV/vis spectrum of compound **2a** (Figure 2) shows a broad absorption band centered at 700 nm, which makes this compound a potential candidate for PDT applications.[11]

Scheme 1. Synthesis of Porphyrins **2**, **2a**, and **3**



The unusual structure of porphyrin **2**, and the anticipated possibility of using the imide function for the construction of novel porphyrin derivatives, prompted us to study new experimental conditions in order to improve the yield of such compound. In fact, after some modifications on the experimental conditions, we were able to obtain compound **2** in 70% yield (Table 1). As shown in Table 1 (entries i–iii), the oxidation of **1** to **2** is strongly dependent on the reaction temperature.

Table 1. Formation of Compounds **2** and **3** using Different Reaction Conditions[a]

	conditions	recovered **1** (%)	yield of **2** (%)	yield of **3** (%)
i	toluene, reflux, 72 h	60	5	–
ii	*o*-dichlorobenzene, 150 °C, 72 h	27	28	–
iii	*o*-dichlorobenzene, reflux, 72 h	19	34	–
iv	*o*-dichlorobenzene, rt, irradiation, 1.5 h	65	6	21
v	TPP, *o*-dichlorobenzene, rt, irradiation, 1.5 h	–	15	35
vi	1. TPP, *o*-dichlorobenzene, rt, irradiation, 1.5 h; 2. reflux, 16 h	–	53	–
vii	1. TPP, *o*-dichlorobenzene, rt, irradiation, 1.5 h; 2. DDQ, reflux, 30 min	–	70	–
viii	*o*-dichlorobenzene, reflux, N_2	99	–	–
ix	*o*-dichlorobenzene, reflux, shielded from light	99	–	–

[a] All reactions were exposed to air, except viii.

Refluxing a toluene solution of **1** for 3 days, in an open system, affords **2** in 5% yield only (60% of **1** is recovered). However, in *o*-dichlorobenzene (*o*-DCB), at 150 °C, the yield increases to 28% while in refluxing *o*-DCB (180 °C) it reaches 34%. In a control experiment, an *o*-DCB solution of porphyrin **1** was heated at reflux under a nitrogen atmosphere. After 3 days porphyrin **1** was totally recovered, confirming that oxygen is the oxidant in this reaction. Suspecting that singlet oxygen ($^1O_2$) could have an important role in the oxidation process, an additional experiment was carried out. An *o*-DCB solution of pyrroloporphyrin **1** was heated at reflux for 3 days, in an open system, but protected from ambient light. Also in this case, pyrroloporphyrin **1** was completely recovered. This result confirms that singlet $^1O_2$ is the ultimate oxidant. Based on this result, it is expected that the yield of **2** may be greatly improved if the experimental conditions used favor the $^1O_2$ formation.[12] The role of $^1O_2$ as dienophile in Diels–Alder reactions is well established, leading to dioxetane adducts. Usually these adducts are unstable and convert to carbonyl derivatives.

An efficient $^1O_2$ production requires, in addition to molecular oxygen, visible light and a photosensitizing agent (PS). Because porphyrins are excellent PS,[12] probably when porphyrin **1** is exposed to ambient light, it converts molecular oxygen ($^3O_2$) into $^1O_2$ which then reacts with the porphyrin itself affording imide **2**. This reasoning prompted us to carry out the two following experiments: (i) irradiation of an *o*-DCB solution of **1** with artificial white light and (ii) irradiation of an *o*-DCB solution of **1** containing an additional PS, namely *meso*-tetraphenylporphyrin (**TPP**). This last strategy was adopted because our pyrroloporphyrin **1** is a Ni(II) complex and this type of complexes are usually associated to an inadequate

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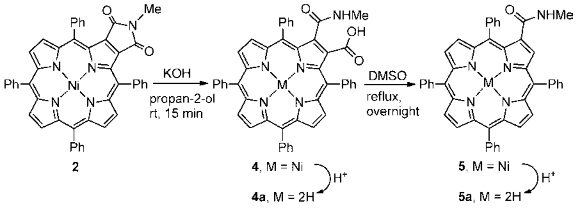
production of $^1O_2$.[12] Both experiments were carried out by stirring the solutions for 1.5 h at room temperature under artificial white light (500 W halogen lamp, 350 W m^{-2}) (Table 1, entries iv and v). In both cases an unexpected drastic change in color (from green to red) was observed. After the workup and purification compound **2** (obtained in 6 and 15% yield under conditions iv and v, respectively) was accompanied by a novel major red compound (21 and 35% under conditions iv and v, respectively) that was identified as porphyrin **3** (Scheme 1). Other minor red compounds were also observed by TLC, mainly when the reaction was carried out in the presence of **TPP**, but their characterization was not possible as a result of their instability in silica gel. Comparing the results of both experiments, the beneficial effect of the additional PS is evident. A higher conversion was obtained and the combined yield of **2** plus **3** almost doubled when compared with the reaction without **TPP**. The ^{1}H NMR spectrum of porphyrin **3** shows in the aliphatic region, in addition to the singlet at δ 3.03 ppm, a doublet at δ 5.76 ppm corresponding to the resonance of one proton. This doublet is converted into a singlet by D_2O addition. The mass spectrum of **3** (m/z = 755, two units higher than **2**) is also in agreement with the proposed structure. Refluxing the crude reaction mixture obtained under conditions v of Table 1 for 16 h resulted in the complete oxidation of **3** to **2**, which was isolated in 53% yield (Table 1, entry vi). This process is much faster and efficient if DDQ is added to the reaction mixture (Table 1, entry vii). In that way, imide **2** is obtained in 70% yield after irradiation for 1.5 h at room temperature followed by refluxing for 30 min with DDQ.

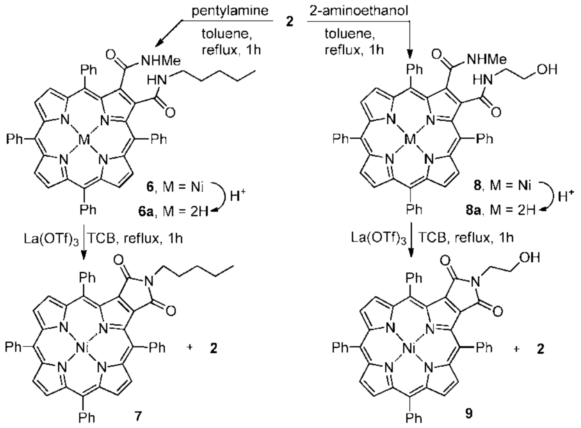
Once established a fast and efficient procedure for the conversion of pyrroloporphyrin **1** into imide **2**, we decided to use this imide as precursor for other porphyrin-2,3-dicarboxylic acid derivatives. Hydrolysis of the imide group with KOH in propan-2-ol resulted in the formation of the red 3-(methylcarbamoyl)porphyrin-2-carboxylic acid **4** in 84% yield (Scheme 2). Several attempts to obtain the porphyrin-2,3-dicarboxylic acid by complete hydrolysis of **2** or **4**, both in basic and acid conditions, and either under classical or microwave heating conditions, were all unsuccessful. When compound **2** was heated at reflux in DMSO a decarboxylation occurred affording amide **5** in 52% yield. The ^{1}H NMR spectrum of **5** shows a singlet at δ 8.90 ppm which is correlated (^3J) with a carbonyl carbon in the ^{1}H$-$^{13}C HMBC spectrum suggesting the loss of CO_2. The mass spectrum, with a peak at m/z = 727, is also consistent with structure **5**.

Scheme 2. Synthesis of Porphyrins **4**, **4a**, **5**, and **5a**



Another interesting modification of **2** involved its reaction with pentylamine or 2-aminoethanol in refluxing toluene; porphyrins **6** and **8** were obtained in quantitative yields (Scheme 3). These porphyrin-2,3-dicarboxamides undergo efficient ring-closure to the corresponding imides **7** and **9** when heated at reflux in 1,2,4-trichlorobenzene in the presence of $La(TfO)_3$. These imides were isolated in 38 and 32% yields, respectively (some imide **2** is also formed in both cases). In the absence of the Lewis acid catalyst, most part of the dicarboxamides is recovered and the imides are formed in very low yields (~2%).

Scheme 3. Synthesis of Porphyrins **6**−**9**, **6a**, and **8a**



Derivative **7** was successfully crystallized from a mixture of dichloromethane and hexane, which allowed the isolation of large crystals whose structure was unveiled from single-crystal X-ray diffraction.[13] The asymmetric unit is composed of a whole molecular unit as depicted in Figure 1. The porphyrin ring is distorted with the average planes containing each pyrrole unit subtending mutual dihedral angles which vary between ca. 22.3 and 27.7° (Figure 1). Noteworthy, these distortions fall within the expected values for Ni^{2+} porphyrins, has already been observed (in several degrees of distortion) for a handful of related structures[10,14] as revealed by a search in the Cambridge Structural Database[15] and by the conformational analysis of Shelnutt.[16] Nevertheless, despite these ring distortions, the central Ni^{2+} cation has an almost regular $\{NiN_4\}$ square planar coordination geometry [Ni−N bond lengths ranging from 1.9199(15)−1.9328(14) Å; *cis* and *trans* angles in the

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[13] Crystal data: $C_{51}H_{37}N_5NiO_3$, M = 810.55, triclinic, space group $P\bar{1}$, Z = 2, a = 11.5233(5) Å, b = 12.9680(5) Å, c = 13.3977(5) Å, α = 101.394(2)°, β = 94.514(2)°, γ = 99.229(2)°, V = 1924.56(13) Å^3, red plate with crystal size of 0.18 × 0.12 × 0.04 mm^3. Of a total of 75 694 reflections collected, 10 222 were independent (R_{int} = 0.0428). Final $R1$ = 0.0413 [$I > 2\sigma(I)$] and w$R2$ = 0.1208 (all data). CCDC 780286. See Supporting Information for further details on the crystal solution and refinement.

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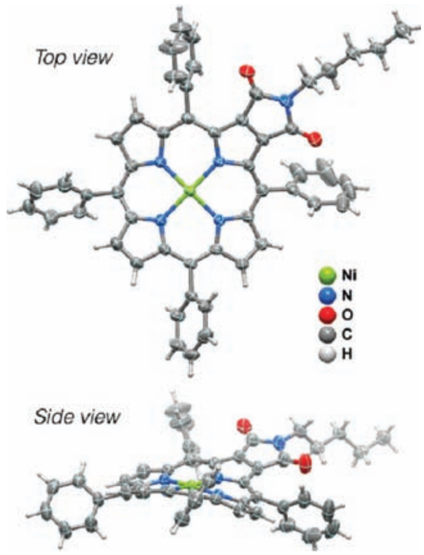

Figure 1. Schematic top and side representations of the molecular unit of compound **7**. Non-hydrogen atoms are represented as thermal ellipsoids drawn at the 80% probability level, and hydrogen atoms are represented as small spheres with arbitrary radius (see Figure S41 in the Supporting Information for a detailed atom labeling and specific bond lengths and angles of the $\{NiN_4\}$ coordination environment). For clarity, only one location of the pendant pentyl chain is represented.

89.64(6)−90.46(6)° and 174.72(6)−175.05(6)° ranges, respectively—see Figure S41 in the Supporting Information]. Crystal packing is essentially mediated by the need to effectively fill the available space (Figure S42 in the Supporting Information). Indeed, the combined effect of the high distortion degree of the ring with the steric impediment of the pendant aliphatic chain, do not allow the occurrence of significant supramolecular contacts between neighboring species.

The distortion due to the presence of 1,3-dioxopyrrole substituent group must be particularly relevant in the free-base series. In fact, when the UV/vis spectra of compounds **2a**, **4a**, **5a**, and **6a**, with different combinations of electron-withdrawing groups, are compared with the UV/vis spectrum of **TPP**, the most remarkable red-shift is observed for porphyrin **2a** (Figure 2, see also the UV/vis spectra of the corresponding nickel complexes in Figure S44, Supporting Information). Comparing the lower energy absorption Q-band of **TPP** with the corresponding absorption band of **5a** (one electron-withdrawing group in a β-pyrrolic position), only a 5 nm red-shift is observed. Slightly higher red-shifts (ca. 11 nm) are observed for porphyrins **4a** and **6a** (both with two electron-withdrawing groups in β-pyrrolic positions).[17] This means that the remarkable red-shift (56 nm) observed for porphyrin **2a** cannot be justified by the presence of two electron-withdrawing groups but mainly to the enhanced macrocycle distortion[18−20] caused by the presence of the 1,3-dioxopyrrole unit. The differences observed in the UV/vis spectra of the nickel derivatives (Figure S44, Supporting Information) are less relevant than those observed in the spectra of the corresponding free-base porphyrins, supporting a less pronunced distortion of the macrocycle due to the presence of the metal.

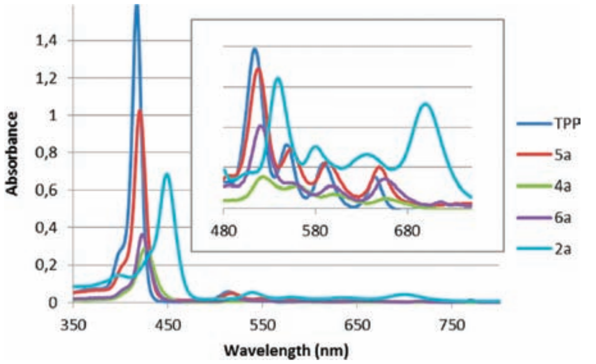

Figure 2. UV/vis spectra of the free-base derivatives (3 μM) in $CHCl_3$. The spectrum of TPP is shown as reference.

Pyrroloporphyrin **1** is unstable to acidic conditions[6] and, therefore, cannot be demetalated. However, using the data for a free-base pyrroloporphyrin reported in the literature,[7] we can see that the lower energy absorption Q-band of compound **2a** (700 nm) is 38 nm red-shifted relatively to the corresponding absorption band of that compound (662 nm). Again, this effect is not so noticeable when we compare the UV/vis spectra of the nickel complexes **1** and **2** (Q-bands at 615 and 608 nm, respectively).

In summary, a novel 1,3-dioxopyrrolo[3,4-*b*]porphyrin (**2**) was obtained in excellent yield by a new synthetic approach. The formation of **2** involves a [4 + 2] cycloaddition reaction between pyrrolo[3,4-*b*]porphyrin **1** (the diene) and $^1O_2$ (the dienophile). The novel compound exhibits spectral features (a Q-band at 700 nm) which are suitable for its potential use in PDT. Furthermore compound **2** can be used as an adequate template to other 1,3-dioxopyrrolo[3,4-*b*]porphyrins or to the corresponding open counterparts.

Acknowledgment. Thanks are due to the Universidade de Aveiro, Fundação para a Ciência e a Tecnologia (FCT) for specific funding toward the purchase of the single-crystal diffractometer and FEDER for funding the Organic Chemistry Research Unit and the Project PTDC/QUI/74150/2006. C.M.B.C. thanks FCT for the PhD grant SFRH/BD/38611/2007.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. Details on the crystal data collection, solution and refinement of compound **7**. Additional drawings of the crystal packing and asymmetric unit of **7**, showing the atomic labeling and selected bond lengths and angles of the Ni^{2+} environment. Crystal structure in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) It is well established that the presence of electron-withdrawing substituents in β-pyrrolic positions promote the contraction of the HOMO-LUMO gap that is reflected by red-shifts in absorption bands (refs 18−20).

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