"One pot" Microwave assisted synthesis of 5,10,15-Tri(4-Methoxyphenyl)-20-(4-Chlorophentyl)-21H,23H-Porphyrin and its Zinc (II) Complex.

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Abstract

The synthesis of new unsymmetrical A_3B porphyrin, 5,10,15-tri(4-methoxyphenyl)-20-(4-chlorophenyl)-21H, 23H-porphyrin, **1**, and its Zinc(II) complex, 5,10,15-tri(4-methoxyphenyl)-20-(4-chlorophenyl)-21, 23- Zinc(II)-porphine, **2,** was accomplished using both conventional and "one pot" solventless microwave assisted methods with interesting comparative results. The obtained molecules were characterized by ^{1}H NMR, UV-Vis and MS. These molecules are considered to represent new compounds with potential application as photosensitizers in photodynamic therapy.

Keywords: one pot synthesis, unsymmetrical porphyrin, microwave irradiation.

1. Introduction

Tetrapyrrolic groups and their coordination compounds with diverse metal ions are molecules that play important roles in biological processes, for example: hemoglobin which has a porphyrinic macrocycle coordinated with iron, is used to transport oxygen in the blood, and chlorophyll which is a tetrapyrrolic coordination compound with magnesium, and has an important role in the photosynthesis process.[1] In recent years, the synthesis of porphyrin compounds and their related metal complexes, has attracted too much attention because of their diverse potential aplications in catalysis[2], in chemical sensors[3], and in medicine[4 - 6]. In particular and related to medicinal chemistry, the most common cancer therapies used against it (surgery, radiotherapy and chemiotherapy) are non-selective to cancer tissue, which generates therefore many side effects[7]. Based on these collateral effects, the development of new and effective treatments capables of discriminate between normal and cancer tissue and also to eliminate the latter is essential and very important. Photodynamic therapy (PDT) is a binary therapy for treatment of solid tumors, based on the selection by agregation of a photosensitizing agent in tumor tissues [8, 9]; the irradiation of neoplasic regions with light at an specific wavelength, results on the activation of the photosensitizer, which generates cytotoxic species such as singlet oxygen that destroys abnormal tissues without any damage to normal one. In several cases, amphiphilic porphyrin derivatives have shown their potential to be used in the treatment of tumors by PDT [10].

In the last decade[11 - 16], the research had been directed towards obtaining new photosensitizers according to the following requirements: a simple and high purity synthesis under laboratory conditions, photoactivity at wavelengths higher than 630 nm, high solubility in biological fluids for an easy localization at the cellular and subcellular level, great selectivity for the damaged tissue, minimal toxicity in the absence of the exciting light, rapid elimination from the body after the treatment and non-toxic metabolites. Additionally, the research was centered on the synthesis of new unsymmetric porphyrins, their corresponding metal complexes and the investigation of their structure-activity relationships. Porphyrins and metalloporphyrins could be obtained by the classical methods, but microwave-assisted reactions had been proven as an interesting alternative because of the inherent advantages of microwave heating, which is selective, direct, rapid, internal, and controllable.

This paper presents our results on the synthesis and characterization of new unsymmetrical porphyrin compounds, which were designed based on some structural needs of potential photosensitizers, 5,10,15-tri(4-methoxyphenyl)-20-(4-chlorophenyl)-21H, 23H-porphyrin, **1**, and its metal complex, 5,10,15-tri(4-methoxyphenyl)-20-(4-chlorophenyl)-21, 23-Zinc(II)-porphine, **2**. The synthesis were made using classical methods and also by the "one pot" microwave assisted method, which presented some advantages as described below.

2. Experimental section

2.1 General Information

UV-Vis measurements were performed with a Perkin Elmer Lambda-12 Spectrometer. NMR spectra were recorded on a 500MHz Varian-NMR System, 1H NMR spectra at 500 MHz with CDCl3 as solvent and tetramethylsilane as internal standard. Coupling constants (J) are given in Hz. Dichloromethane was dried by distillation over lithium aluminum hydride. All other solvents were used after distillation at normal pressure. All reactants were of reagent grade used as purchased from Sigma-Aldrich and Merck as it

corresponds. Silica gel_{60} (230-400 mesh) was heat dried before used as solid support. The prepared solutions were kept in dark to prevent photodegradation. Microwave assisted reactions were performed in a commercial microwave oven (Westinghouse WMMD171D1PW) having a maximum output power of 700W.

2.2 Synthesis of 5,10,15-tri(4-methoxyphenyl) 20-(4-chlorophenyl)-21H, 23H-porphyrin, 1.

Method A. Porphyrin 1 was synthesized according to Lindsey and co-workers [17], via condensation of the corresponding aromatic aldehydes and pyrrole under mixed-acid catalysis. $BF_3.Et_2O$ (1.2 mL, $9.72x10^{-3}$ mmol) and trifluoroacetic acid, TFA (0.35 mL, 4.57 mmol) were added to a solution of 4-methoxybenzaldehyde (0.45 mL, 3.75 mmol), 4-chlorobenzaldehyde (176 mg, 1.25 mmol) and freshly distilled pyrrole (0.35 mL, 5 mmol) in dichloromethane; the mixture was kept at room temperature for 2 h. Then 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DDQ (570 mg, 0.251 mmol) was added, and the mixture was kept at room temperature for 2 h. The solvent was evaporated and the reaction mixture was purified by silica gel column chromatography using as eluent dichloromethane-hexane (1-1), fractions were collected and solvent was evaporated to give 138.4 mg (15% yield) of porphyrin 1 as a purple solid. ^{1}H NMR ($CDCl_3$) -2.77 (s, 2H), 4.09 (s, 9H), 7.28 (d, J = 8.6, 6H), 7.73 (d, J = 8.3, 2H), 8.12 (d, J = 8.5, 6H), 8.14 (d, J = 8.3, 2H), 8.80 (d, J = 4.7, 2H), 8.87 (s, 4H), 8.88 (d, J = 4.9, 2H); UV(CH_2Cl_2) max 421, 519, 555, 595, 649 nm; MS (FAB) m/z: 740.0 (M+1)

Method B. A mixture of 4-methoxybenzaldehyde (0.39 mL, 3.20 mmol), 4-chlorobenzaldehyde (150 mg, 1.07 mmol) and freshly distilled pyrrole (0.3 mL, 4.27 mmol) were dissolved in dichloromethane at room temperature; silica gel was added and the solvent was removed under vacuum. The adsorbed reaction mixture was irradiated in a microwave oven at 420W, for 10 min. After cooling, the reaction mixture was purified by silica gel column chromatography using as eluent dichloromethane-hexane (7-3), fractions were collected, solvent evaporated and the porphyrin **1** produced was recrystallized in methanol to give 19.4 mg (2.5% yield). Porphyrin **1** was also synthesized by a modification of the method described formerly but changing the silica gel by propionic acid/silica gel which was prepared as described in the literature [18], to give 33.9 mg (4.3%) of porphyrin **1** after purification by column chromatography and recrystallization in methanol.

2.3 Synthesis of 5,10,15-tri(4-methoxyphenyl)-20-(4-chlorophenyl)-21, 23- Zinc(II)-porphine, 2.

Method A. A mixture of porphyrin **1** (121.0 mg, 0.164 mmol) in dichloromethane and $Zn(OAc)_2 2H_2O$ (72.1 mg, 0.328 mmol) in methanol was stirred at room temperature for 3 h. After removal of solvent under reduced pressure conditions the residue was washed out with methanol, to remove excess of metal salt, and dried under vacuum. The purple solid was purified by silica gel column chromatography using as eluent dichloromethane-hexane (7-3), fractions were collected and solvent was evaporated to give 70.1 mg (57.7% yield) of metalloporphyrin **2**. ^{1}H NMR ($CDCl_3$) 4.13 (s, 9H), 7.31 (d, *J* = 8.5, 6H), 7.73 (d, *J* = 8.2, 2H), 8.10 (d, *J* = 8.9, 6H), 8.12 (d, *J* = 8.2, 2H), 8.81 (d, *J* = 4.5, 2H), 8.82 (s, 4H), 8.90 (d, *J* = 4.7, 2H); UV(CH_2Cl_2) max 421, 550, 590.5 nm.

Method B. 4-methoxybenzaldehyde (1.29 mL, 10.7 mmol), 4-chlorobenzaldehyde (500 mg, 3.56 mmol), fresh distilled pyrrole (1 mL, 14.2 mmol), $Zn(OAc)_2 2H_2O$ (780 mg, 3.56 mmol) and pyridine (0.57 mL, 7.12 mmol) were dissolved in methanol at room temperature; anhydrous silica gel (8g) was added and the solvent was removed under vacuum. The adsorbed reaction mixture was irradiated in a microwave oven at 560W, for 11 min. After cooling, the reaction mixture was purified by silica gel column chromatography using as eluent dichloromethane-hexane (7-3), fractions were collected and solvent was evaporated to give 30.6 mg (1.1% yield) of metalloporphyrin **2**.

3. Characterization

3.1 Absorption Spectrum

UV-Vis spectra were obtained for porpyrin **1** and zinc porphyrin **2** in dichloromethane. As we can observe in Figure 1 and Table 1, the electronic absorption spectra of free base porphyrin **1**, displays a typical pattern in visible region, with an intense Soret band and the four Q-bands: Qy(1,0), Qy(0,0), Qx(1,0), Qx(0,0). Taking into account that UV-Vis spectra of porphyrins are sensitive to metallation, it was noticed the absence of two Q-bands in Zn(II) porphyrin **2**, as expected. This behavior is due to differences in symmetry of the two compounds, in free base porphyrins, without the metal and having two hydrogen bonded to the nitrogen atoms, the symmetry is rectangular (C2 and D2h), and in metalloporphyrin, having a metal inside the porphyrine core, the symmetry is square (increases to C4 and D4h). The net result is a simpler spectra for methalloporphyrin **2** than for the free base porphyhrin **1**, owing to the symmetry effect [20].

3.2 NMR spectra

The more noticeable NMR signal when comparing free base porphyrin **1** with the corresponding Zn(II) porphyrin **2**, is the highly shielded peak around -2.8 ppm of the N-H in the porphyrin core, which is absent after complexation of porphyrin with Zn(II) because

the two H atoms are replaced by metal ion. This observation in addition to the UV-Vis data, could support the fact that the zinc atom is bonded inside the porphyrine core with nitrogen atoms and not outside with other electron releasing groups such as methoxy. Other NMR peaks corresponding to the protons of phenyl and pyrrole rings (7.28 – 8.90 ppm) and methoxy substituent groups (around 4 ppm), are consistent with the different protons of the porphyrin macrocycle of the desired products.

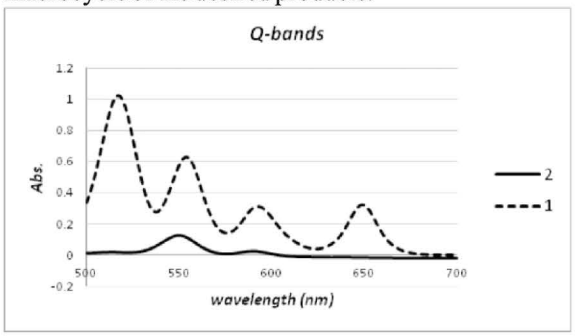


FIGURE 1. Absortion spectra of porphyrin **1** and metalloporphyrin **2**, Q-bands region.

TABLE 1. UV-Vis data of porphyrin **1** and metalloporphyrin **2**.

Compound	Soret band	Q-bands
1	421.0	519.0 555.0 595.0 649.0
2	421.0	550.0 590.5

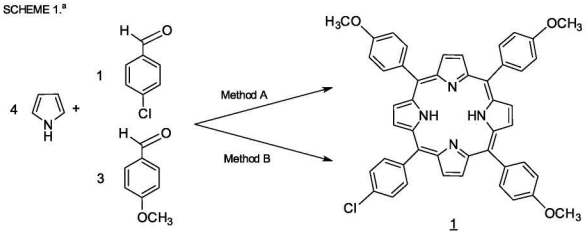
4. Results and discussion

4.1 Synthesis of Porphyrin 1.

The synthesis of the unsymmetrical A_3B porphyrin, **1**, was accomplished following the procedure described by Lindsey and co-workers (Scheme 1 – Method A), via acid-catalyzed condensation of pyrrole with two aromatic aldehydes (4-methoxybenzaldehyde and 4-chlorobenzaldehyde) [17]. After the first step, the porphyrinogen intermediate was formed and then oxidized to porphyrin **1** with DDQ. Addition of DDQ changed the color of the mixture from dark red to dark green, and finally the crude product was dark purple. The purification of this reaction mixture by chromatography column allowed us to obtain a new unsymmetrical porphyrin, **1** (15% yield). As observed, the yield is not good enough, but for this method is according to the expected values. On the other hand, there are some disadvantages of this conventional method, such as: a highly corrosive acid media, the large amounts of oxidation agent and the highly toxic halogenated solvent. Additional disadvantages are: the longer reaction times and the difficulty to purify the products, the latter mainly because of the excess of DDQ and other side products in the reaction mixture.

In order to improve the performance of the synthesis of porphyrin **1**, it was also accomplished by eco-friendly "one pot" microwave assisted synthesis, without solvent and having the reactants adsorbed in silica gel (Scheme 1 – Method B). After the irradiation, we observed formation of the desired product adsorbed on the solid support and also the recovery of 4-methoxybenzaldehyde on the internal flask wall, probably due to the high temperature (around 85°C) reached after irradiation and the lack of stirring during the reaction time. Another microwave assisted experiment was performed using propionic acid/silica gel as solid support, observing an increase of the reaction yield (4.3%) when compared to the synthesis performed using only neutral silica gel (2.5%).

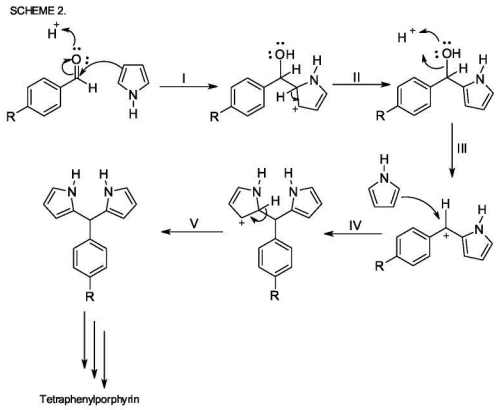
SCHEME 1.[a]



[a]Key: Method A. 1) BF_3Et_2O, TFA, CH_2Cl_2, 2h RT; 2) DDQ, 2h, RT; Method B. Silica gel (neutral or H+), MW, 420W, 10min.

This behavior could be explained based on the reaction mechanism of the formation of the tetraphenylporphyrin (Scheme 2) [19], in which the first step involves the protonation of the carbonyl oxygen of the aromatic aldehyde leaving the carbon with positive character, which is needed for the pyrrole nucleophilic attack. The results of the synthesis using propionic acid/silica gel suggested that the acid catalysis is better when an acidified solid support is used than when the reaction is performed without previous acidification of the silica gel. This acid condition is also important in step III (scheme 2), where a hydroxyl group needs to be protonated to leave as a water molecule.

SCHEME 2.

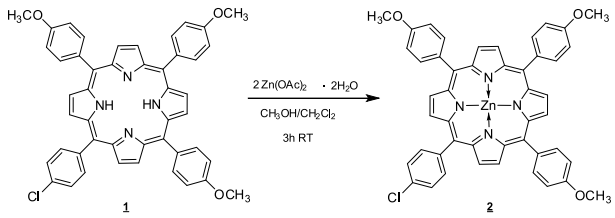


4.2 Synthesis of Metalloporphyrin 2.

The porphyrin **1** and zinc acetate were allowed to react resulting in the formation of the correspondig new zinc(II) metal complex, **2**, scheme 3 (57.7% yield). But this conventional method have some

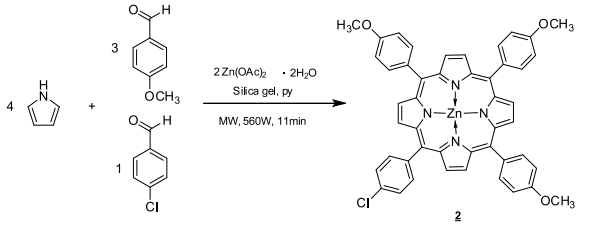
disadvantages including; use of chlorinated solvents, long reaction times and at least two steps to obtain the desired metal complex when considering first the formation of the porphyrin core and second its metallation using the metal salt.

SCHEME 3.



Based on this, the synthesis of metalloporphyrin **2**, was accomplished following the "one pot" microwave assisted method described in scheme 4. Although the yield was not good (1.1%), the method used here presented some advantages compared with the conventional one, for instance: shorter reaction time (less than 15min), absence of solvents in the reaction mixture and easier purification. The presence in the reaction mixture of the other statistically possible metalloporphyrins (A_4, A_2B_2, AB_3, B_2) and the recovery of part of the aromatic aldehydes could be the reason of the low yields Future work in our group involves some optimizations to improve the synthesis, specifically the yield.

SCHEME 4.



In order to compare the fully conventional method of synthesis of metalloporphyrin **2** with the "one pot" microwave assisted synthesis, we need to consider the yields of the two steps involved in conventional synthesis (15% and 57.7%), with a global yield of 8.4%, compared to the 1.1% yield of the one step synthesis. In this frame, we can suggest that the latter yield is better not only by itself, but also considering the advantages described above.

4. Conclusions

In this work, we have accomplished the synthesis of a new unsymmetrical porphyrin **1** and its corresponding Zn(II) complex **2** based on their characterization by UV-Vis, proton NMR and MS as it corresponds. These compounds were obtained by two different routes, which give us the possibility to compare the results of a conventional synthetic method and a "one pot" microwave assisted synthetic method. For these particular compounds, at this moment, the one pot microwave assisted synthesis had proven to have a disadvantage in terms of reaction yield, but is the easiest to purify and the fastest reaction when compared with conventional methods. Besides, the absence of any solvent because of the solid support reaction media, gives to this method additional advantages when consider Green Chemistry development. Finally, compounds **1** and **2** allow us to contribute with new molecules with potential application as photosensitizers in photodynamic therapy.

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6. References

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