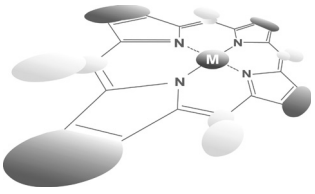
Journal of Porphyrins and Phthalocyanines
J. Porphyrins Phthalocyanines 2015; **19**: 1–7
DOI: 10.1142/S1088424615500844

Published at http://www.worldscinet.com/jpp/



Synthesis of phthalonitrile derivatives by photoinduced reactions. New unsymmetrical substituted zinc phthalocyanines

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Received 30 April 2015
Accepted 16 July 2015

ABSTRACT: The synthesis of new phthalonitrile derivatives by photoinduced reaction is described. Novel unsymmetrically substituted Zn(II) phthalocyanine bearing an aryl alcohol group (ArZnPc) was synthesized by the ring expansion reaction of boron(III) subphthalocyanine chloride with an appropriated phthalonitrile. The spectroscopic and photodynamic properties of these ArZnPc were studied.

KEYWORDS: phthalonitrile, phthalocyanine, photodynamic properties, hydroxyaryls, $S_{RN}1$.

INTRODUCTION

Phthalocyanines (Pc) are used as conventional dyes and pigments. A number of other applications such as efficient photosensitizers in photodynamic therapy (PDT) have also been found [1]. These photosensitizers exhibit a high absorption coefficient in the visible region of the spectrum, mainly in the phototherapeutic window (600–800 nm) [2]. The PDT utilizes visible light to active a photosensitizer which can react with molecules by the electron or hydrogen transfer, leading to the production of radicals (type I reaction), or it can transfer its energy to oxygen, generating the highly reactive singlet molecular oxygen, $O_2(^1\Delta g)$ (type II reaction). Both pathways can cause cell damages [3]. However, the photosensitizing ability of the phthalocyanines can be affected by its aggregation tendency due to large π conjugated systems. In particular bulky substituents (such as *tert*-butyl groups) decrease macrocycle aggregation [4].

Many of these new applications require the modification of the phthalocyanine macrocycle. The symmetrically substituted phthalocyanines have been largely investigated; only minor attention has been devoted to the preparation of asymmetrical phthalocyanines (A_3B type) [5]. The presence of a different group is particularly interesting because it may provide additional features such as increased solubility and reactivity, and may facilitate enhanced applications [6]. Different strategies have been employed for the preparation of A_3B structures. Statistical condensation is the most widely used. This non-selective method is based on the reaction of two differently substituted phthalonitriles and it affords a mixture of products which complicate the purification process [7]. However, the most efficient selective approach involves ring expansion reaction of subphthalocyanine [8]. Good yields have been obtained when the subphthalocyanine [9] derivative is treated with a phthalonitrile in the presence of a strong base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and a metal salt.

On the other hand mono and multi hydroxy-substituted Pc have been reported and shown to be promising photosensitizers for PDT (*in vitro*, the 2-hydroxy ZnPc was the most active) [10]. The synthesis of substituted phthalocyanines is related to the preparation of the new phthalonitriles. Much effort has been geared towards different synthetic strategies in order to increase the range of phthalonitriles.

The radical nucleophilic substitution can be considered an alternative route for the formation of carbon–carbon bonds [11]. This type of reactions finds increasing application in the synthesis of complex organic molecules [12], particularly, since such reactions are generally carried out under mild conditions and the substrates tolerate many functional groups. It is well-known that in

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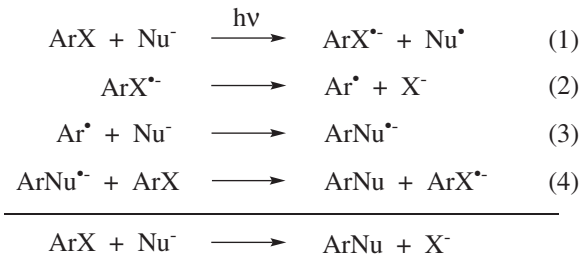


Scheme 1 $S_{RN}1$ reaction

a $S_{RN}1$ reaction (Scheme 1), a nucleophile is combined with an aryl radical to provide the corresponding coupling product. Traditionally, aryl halide substrates give the aryl radical in the photoelectron transfer reaction from the nucleophile (Equations 1 and 2). The radicals thus formed can react with the nucleophile to give the radical anion of the substitution product (Equation 3).

On the other hand, a special regiochemistry has been determined in the reactions of radicals with anions able to show ambident behavior [13]. The anion of the 2-naphthol have been reported to react with aryl radicals to give C_1-substitution at their naphthyl moiety [14].

In this paper we propose a selective arylation approach, based on the radical nucleophilic substitution mechanism, for the generation of 4-(hydroxyaryl)phthalonitriles from commercially available reactants. Then, we used these to synthetize a novel unsymmetrical phthalocyanines bearing either one or two hydroxy groups, as well as bulky *tert*-butyl groups. The spectroscopic and photodynamic characteristics of Pcs synthetized were also studied.

EXPERIMENTAL

All starting materials were purchased from Sigma-Aldrich. They were used without further purification. DMSO was stored under molecular sieves (4 Å). ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz a nuclear magnetic resonance spectrometer with $CDCl_3$ as solvent. Gas chromatographic analyses were performed on a cromatograph with a flame-ionization detector and using a HP-5 capillary column (30 m × 0.32 mm × 0.25 μm film thickness). The GS/MS analyses were carried out on a Shimadzu GC-MS QP 5050 spectrometer, using a Vf-5ms 30 m × 0.25 mm × 0.25 μm column. Irradiation was conducted in a reactor equipped with two 400-W lamps emitting maximally at 350 nm (Philips Model HPT, air and water refrigerated). Potentiometric titration of halide ions was performed in a pH meter using an Ag/Ag^+ electrode. Melting points were not corrected. Column chromatography was performed on silica gel (70–270 mesh ASTM). IR spectra were obtained by a Nicolet-510 FT-IR spectrometer. UV spectra were performed on an UV-1800 Shimadzu spectrophotometer. Microwave monomode CEM-Discovery reactor.

General synthesis procedure of phthalonitrile derivatives

The reactions were carried out in a 50 mL three-neck round bottomed flask equipped with a nitrogen inlet and a magnetic stirrer. To 10 mL of dry and degassed DMSO under nitrogen were added potassium *tert*-butoxide (KOBu-*t*) and then the corresponding phenol. After 5 min 4-iodophthalonitrile was added and the reaction mixture was irradiated for 180 min. The reaction was quenched with an excess of ammonium nitrate and water (30 mL). The mixture was extracted three times with methylene chloride (20 mL); the organic extract was washed twice with water, dried magnesium sulfate ($MgSO_4$). The iodide ions in the aqueous solution were determined potentiometrically. All products are unknown and they were isolated by column or radial chromatography [CH_2Cl_2:CH_3OH (95:5)] and characterized by ^{1}H NMR and ^{13}C NNR and mass spectrometry.

4-(4-Phthalonitryl)-2,6-di-*tert*-butylphenol (4). mp 214–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm 1.50 (s, 18H), 5.52 (s, 1H, OH), 7.37 (s, 2H), 7.81 (d, 1H), 7.86 (dd, 1H), 7.94 (d, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ_C, ppm 42.69, 114.29, 114.53, 114.89, 117.12, 125.16, 134.06, 134.44, 142.00, 142.95, 150.15, 150.84. CG-MS: *m/z* (%) 55 (11); 57 (32); 137 (11); 289 (21); 317 (100); 318 (21); 332 (31). IR (AgBr disc): ν, cm^{-1} 2871–2956 (C-H), 2231 (C≡N), 3619 (O–H).

4-(1,3-Dihydroxi-4-phenyl)phthalonitrile(6). mp139–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm 6.58 (t, 1H), 6.62 (dd, 1H), 6.78 (dd, 1H), 7.22–7.32 (m, 2H), 7.72 (d, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ_C, ppm 108.1, 108.8, 112.4, 113.5, 114.9, 115.4, 117.6, 121.6, 131.3, 135.4, 154.7, 157.9, 161.6. CG-MS: *m/z* (%) 63 (17); 64 (11); 65 (57); 179 (18); 208 (22); 235 (18); 236 (100); 237 (13). IR (AgBr disc): ν, cm^{-1} 2231 (C≡N), 3334–3415 (O–H).

Synthesis procedure of SubPc

1,2-Dicyanobenzene (110 mg, 0.86 mmol), boron trichloridein heptane 1 M (250 μl), and 1-chloronaphthalene (4 mL) were taken in a microwave tube. The contents were irradiated in a commercial microwave oven at 100 W and 200 °C for 10 min. After cooling, the reaction mixture was poured onto a hexane solvent. The residue was purified by column chromatography (hexane/CH_2Cl_2, (98:2)) to give SubPc (103 mg, 85%), characterized by UV and ^{1}H NMR.

General procedure of A_3B-phthalocyanine formation

A solution of phthalonitrile derivate (0.19 mmol) and DBU (7 μL, 0.07 mmol) in 3 mL of DMSO/1-chloronaphthalene (5:1) was added drop-wise to a suspension of SubPc (43 μg, 0.10 mmol) and zinc(II) acetate dihydrate (22 mg, 0.10 mmol) in 1 mL of DMSO/1-chloronaphthalene (5:1). The mixture was placed in a microwave reactor (100 W, 140 °C, 2 h). Then it was cooled

to room temperature and precipitated with 50 mL of water. The solid was separated by centrifugation and washed with hexane. **Pc1**, yield 40%. ESI-MS: *m/z* 781.2390 $[M + H]^+$ (781.2376 calcd. for $C_{46}H_{36}N_8OZn + H^+$). **Pc2**, yield 37%. ESI-MS: *m/z* 685.4389 $[M + H]^+$ (685.1073 calcd. for $C_{38}H_{20}N_8O_2Zn + H^+$).

Spectroscopic studies

Absorption and fluorescence spectra were recorded at 25.0 ± 0.5 °C using 1 cm path length quartz cells. The fluorescence quantum yield (Φ_F) of **Pc1** y **Pc2** were calculated by comparison of the area below the corrected emission spectrum in DMF with that of Zn(II) phthalocyanine (ZnPc) as a reference (Φ_F = 0.28) [15]. Absorbance of sample and reference were matched at the excitation wavelength (640 nm) and the areas of the emission spectra were integrated in the range 650–800 nm.

Steady state photolysis

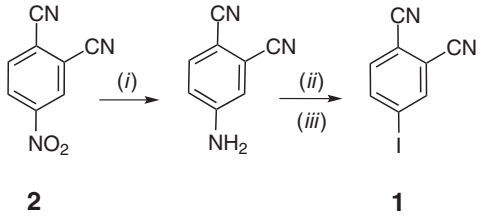
Solutions of 9,10-dimethylanthracene (DMA, 35 μM, absorbance 0.7) and photosensitizer (Q-band, absorbance 0.2) in different media were irradiated in 1 cm path length quartz cells (2 mL) with monochromatic light at λ_{irr} = 670 nm, from a LED NES110NR lamp (Red (625 nm) Lustrous-green Technology of Lightings). The kinetics of DMA photooxidation were studied by following the decrease of the absorbance (A) at λ_{max} = 378 nm. The observed rate constants (k_{obs}) were obtained by a linear least-squares fit of the semilogarithmic plot of Ln A_0/A *vs.* time. Photooxidation of DMA was used to determine $O_2(^1\Delta_g)$ production by the photosensitizer [16]. ZnPc (Φ_Δ = 0.56) was used as a reference in DMF [17]. Measurements of the sample and reference under the same conditions afforded Φ_Δ for phthalocyanines by direct comparison of the slopes in the linear region of the plots. All the experiment were performed at 25.0 ± 0.5 °C. The Pc and DMA controls do not change along the photolysis experiment (see Supplementary material). The pooled standard deviation of the kinetic data, using different prepared samples, was less than 10%.

RESULTS AND DISCUSSION

Synthesis of 4-substituted phthalonitriles

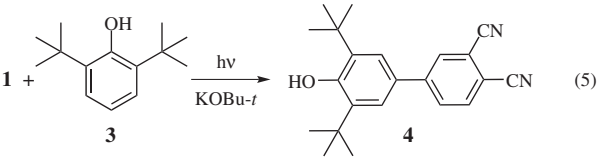
The required starting material for the radical nucleophilic substitution reaction is 4-iodophthalonitrile (**1**) which was prepared in two sequential steps from 4-nitrophthalonitrile (**2**) (Scheme 2) [18] with good yield (71%).

2,6-*Di-tert-butylphenol* (3). The photoinitiated reaction of **1** with anion of 2,6-di-*tert*-butylphenol (**3**) obtained by deprotonation with potassium *tert*-butoxide (KBuO-*t*) in DMSO, (substrate:nucleophile:base = 1:3:4) afforded 72% yield of iodide ion release (indicator of the total yield of the reaction), and the product corresponding to substitution at



Scheme 2 Synthesis of 4-iodophthalonitrile (i) Fe, methanol, HCl, Δ, 2h. (ii) $NaNO_2$, HCl, <5°C, 1.5 h. (iii) KI, H_2O, 0.5 h.

C_4 of the anion, 4-(4-phthalonitryl)-2,6-di-*tert*-butylphenol [19] **4** (36%) (Equation 5, Table 1, Exp. 1).



(5)

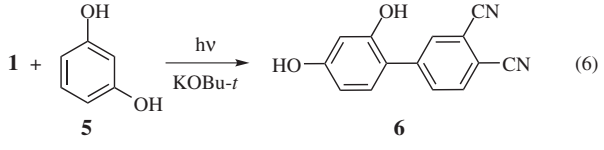
The by-products observed correspond to decomposition of phthalonitrile. No reaction was observed in the absence of light irradiation (Table 1, Exp. 2). In order to confirm the electron transfer mechanism, inhibition reactions were performed by adding amounts of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or *para*-dinitrobenzene (*p*-DNB), commonly used as inhibitors in the mechanistic study (Scheme 1) [11]. Inhibition of the synthesis of **4** was observed in both reactions (Table 1, Exps. 3 and 4). These effects provide good evidence of the $S_{RN}1$ mechanism in the C_4-arylation.

Subsequently, solvent and the number of equivalents of **3** or base were tested to identify optimal conditions. The formation of **4** was favored by increasing the equivalents of **3** and decreasing the excess of base (Table 1, Exps. 5 and 6).

By changing the solvent from DMSO to NH_3 accompanied by a decrease in the concentration of the reactants, **4** was the main product formed (65%) accompanied by decrease of decomposition of ArH (Table 1, Exp. 7). The small change in the yield does not justify the use of this solvent.

Thus, the best C-substitution yield was obtained using 3 equivalents of **3**, defect of base, DMSO and 180 min of irradiation (Table 1, Exp. 8).

***Resorcinol* (5).** The best conditions developed during the study with anion of **3** were applied to resorcinol (**5**) reactions. The reaction of **5**, base and **1** (Equation 6) gave the substitution product **6** in good yield (Table 1, Exp. 9).



(6)

When the crude product was purified by direct crystallization the yield increased to 77% (Table 1, Exp. 10). In this reaction, we observed that the yield of product decreased with excess base.

Table 1. Photoinitiated reactions of 4-iodophthalonitrile **1** with nucleophiles in DMSO[a]

Exp.	**1** M × 10^3	Nucleophile M × 10^3	Base M × 10^3	X^-, %[b]	Products (% yields)[c]
1	32	**3**, 95	128	72	**4**, 36
2[d]	32	**3**, 95	128	<5	—
3[e]	31	**3**, 91	122	35	**4**, 13
4[f]	32	**3**, 93	122	58	**4**, —
5	30	**3**, 149	204	81	**4**, 34
6	31	**3**, 303	323	94	**4**, 53
7[h]	9.4	**3**, 50	51	70	**4**, 65
8	50	**3**, 148	144	69	**4**, 49[g]
9	79	**5**, 234	234	89	**6**, 48[g]
10	79	**5**, 252	240	88	**6**, 77[i]
11	79	**5**, 218	245		**6**, 27[i]

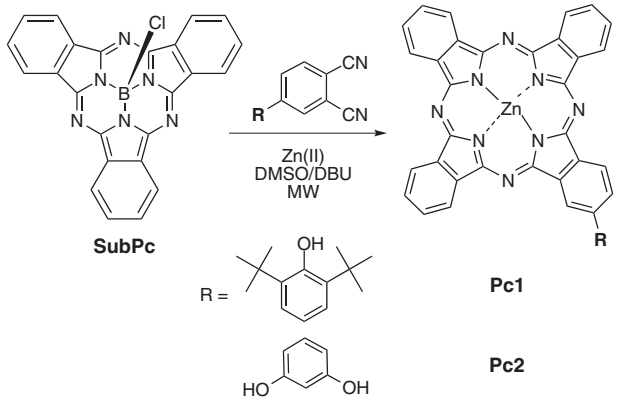
[a] Photoinitiated reactions (unless indicated) carried out under nitrogen. Reaction time = 180 min. [b] Potentiometrically determined on the basis of the ArX concentration. [c] Determined by GLC and the internal standard method on the basis of the ArX concentration. [d] Reaction carried out in the dark. [e] *p*-dinitrobenzene (40 mmol.%). [f] TEMPO (41 mmol.%). [g] Isolated yield by chromatography column. [h] Solvent = NH_3(l). T = -33 °C. [i] Purified by direct crystallization.

Synthesis of phthalocyanine derivatives

The 4-(hydroxyaryl)phthalonitrile derivatives were employed to synthesize the A_3B-phthalocyanine by ring expansion of SubPc (Scheme 3). SubPc was obtained from an appropriate phthalonitrile fused with boron trichloride in 1-chloronaphthlene by conventional heating [9] or microware irradiation [19]. In our procedure, the SubPc was prepared using microware irradiation (100 W, 200 °C, 10 min) with 85% yield.

The reaction of SubPc and phthalonitriles **4** and **6** were performed in the presence of DBU and Zn(II) acetate dehydrate in DMSO/1-chloronaphthalene using microwave irradiation. Under such conditions, only one phthalocyanine was obtained facilitating the purification process.

After heating the mixture of SubPc and **4** for 2 h, **Pc1** afforded with a 40% yield (Scheme 3). The SubPc was also ring expanded with **6** to afford **Pc2** (37%).



Scheme 3 Synthesis of phthalocyanine

Spectroscopic studies

The absorption spectra of the **Pc1** and **Pc2** were studied in different solvents (Fig. 1). These show the typical Soret and Q-bands characteristic of zinc(II) phthalocyanine derivatives, in the visible region at *ca.* 600–750 nm (Q-band) attributed to the π–π* transition [15]. A sharp absorption bands were obtained indicating that there was no aggregation of these phthalocyanines [20]. Organic solvents are known to reduce aggregation whereas aqueous solvents result in highly aggregated complexes and the peripheral substituents increase the distance between the planar macrocycle rings thereby making solvation easier.

By varying the solvent polarity, a small effect is observed on the location of Q-bands. The main Q-band for the unsubstituted ZnPc shows similar values to those observed for **Pc1** and **Pc2** in the different solvents used [15].

In all organic solvents, **Pc1** and **Pc2** are soluble (~2×10^{-6} M). The spectrum of **Pc2** has similar intensity in all these. However, the intensity of **Pc1** spectrum decreased in methanol as a consequence of the increase in the lipophilic (two *tert*-butyl groups) character of macrocycle.

Both Pcs were very poorly solubilized in water, as shown by the broadening and low signal intensity.

Figure 2 shows the **Pc2** spectrum in water at different pHs. It can be seen that solubility increases with increasing pH, *i.e.* with the deprotonation of the hydroxyl group.

The spectroscopic properties of **Pc1** and **Pc2** were compared with that of ZnPc in DMF, see Table 2. The Q-bands of **Pc1** and **Pc2** present a ~2 nm bathochromic

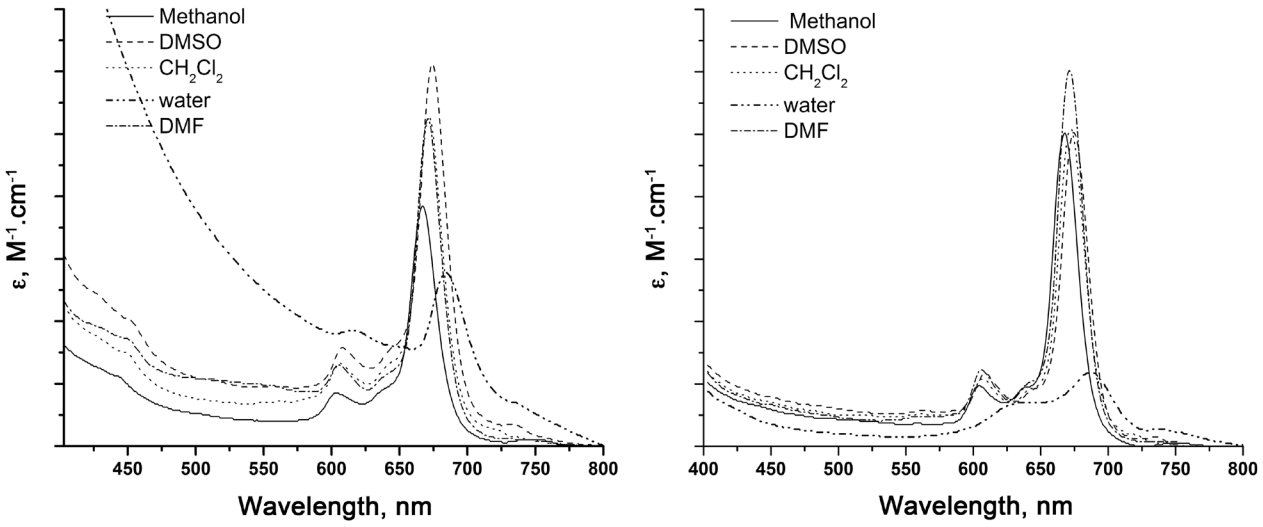


Fig. 1. Absorption spectra of (a) **Pc1** and (b) **Pc2** in different solvents. Concentrations ~2×10^{-6} M

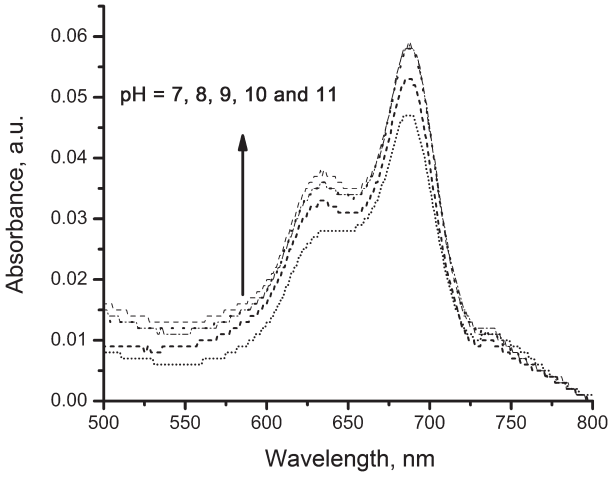


Fig. 2. Absorption spectra of **Pc2** in water at different pH. Concentrations ~2×10^{-6} M

shift with respect to ZnPc (668 nm) [21] due to the effect of the hydroxyaryl groups.

The steady-state fluorescence emission spectra of **Pc1** and **Pc2** were performed in DMF (Fig. 3b). The spectra show two bands in the red spectral region, which are characteristic for similar zinc(II) phthalocyanines [2]. A small Stokes shift (≈8 nm) was observed, indicating that the spectroscopic energy is nearly identical to the relaxed energy of the singlet state.

As expected from the absorption data, the emission maxima are bathochromically shifted with respect to that of ZnPc. By comparison with ZnPc as a Ref. [22], the values of fluorescence quantum yields (Φ_F) were calculated in DMF. The results of Φ_F are summarized in Table 2. They are appropriate values for quantification of phthalocyanine by fluorescence emission techniques.

Table 2. Spectroscopic data, fluorescence quantum yield (Φ_F), kinetic parameters (k_{obs}) for the photooxidation reaction of DMA and quantum yield of $O_2(^1\Delta_g)$ production (Φ_Δ) of Pcs in DMF

Pc	λ_{abs}, nm	λ_{ems}, nm	Φ_F	k_{obs}	Φ_Δ
ZnPc[a]	668	676	0.28		0.56
Pc1	670	678	0.23	$(1.86 \pm 0.1)10^{-4}$	0.30 ± 0.02
Pc2	671	680	0.29	$(3.83 \pm 0.1)10^{-4}$	0.62 ± 0.02

[a]ZnPc = zinc phthalocyanine (R = H). Value from Ref. 23.

Photodynamic activity in DMF solution

Taking into account that DMA quenches $O^2(^1\Delta_g)$ exclusively by chemical reaction [23], and that the typical first-order kinetic plots of the DMA absorption at 378 nm with time describing the progress of the reaction. Consequently, this substrate, DMA, can be used as a method to evaluate the ability of the photosensitizers to produce $O^2(^1\Delta_g)$ in solution [8, 24].

The quantum yield of $O_2(^1\Delta_g)$ production (Φ_Δ) was calculated by comparing the slope for the **Pc1** and **Pc2** (Fig. 4) with the corresponding slope obtained for the reference ZnPc.

The results for Φ_Δ (Table 2) follow the order **Pc2** > ZnPc > **Pc1**. Very close values of Φ_Δ were obtained for these phthalocyanines indicating that they are higher efficient photosensitizers to produce $O_2(^1\Delta_g)$ in DMF (Table 2).

In summary, we describe in this work a different and direct protocol to obtain new phthalonitriles (biaryl type) using photoinduced nucleophilic substitution. We have developed a simple and versatile route for the synthesis of novel hydroxyl aryl derivates in good yields using commercial and stable starting materials.

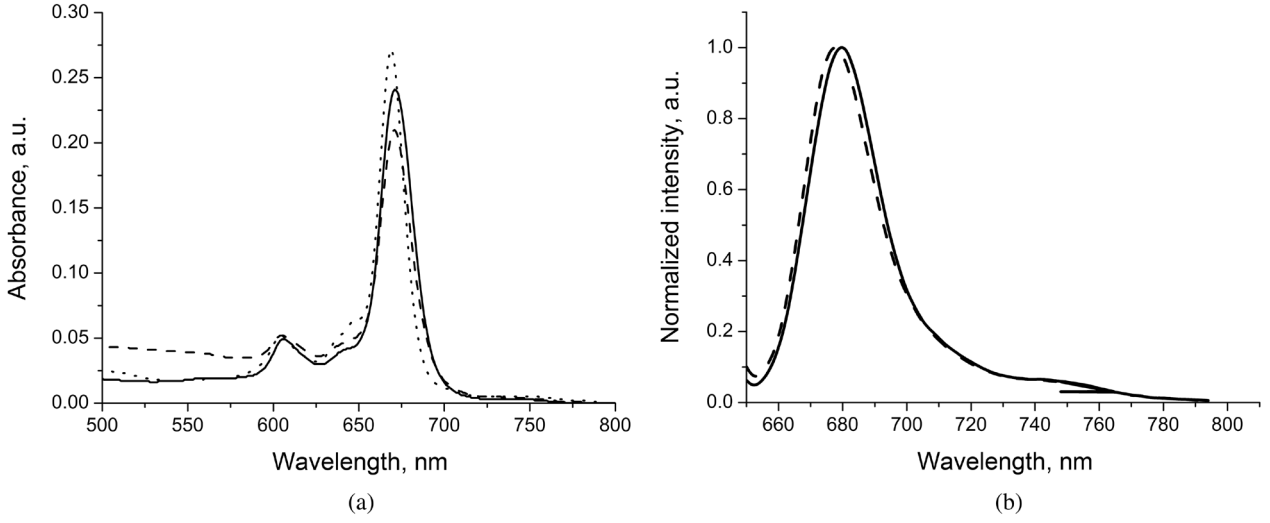


Fig. 3. (a) Absorption spectra of **ZnPc** (...), **Pc1** (---) and **Pc2** (—) in DMF. (b) Normalized fluorescence emission of **Pc1** (--) and **Pc2** (—) in DMF, λ_{exc} = 640 nm. Concentrations ~2×10^{-6} M

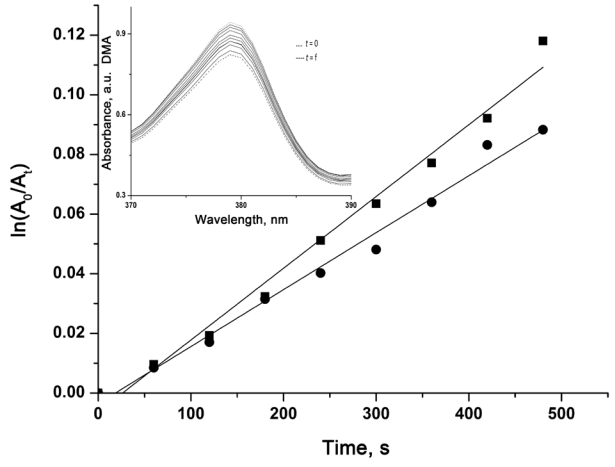


Fig. 4. First-order plots for the photooxidation of DMA photosensitized by **Pc1** (•), and ZnPc (■) in DMF. Values represent mean±standard deviation of three separate experiments. The insert plots the electronic absorption spectra of DMA at different times

These compounds were used by ring expansion reaction of SubPc in the presence of DBU and zinc(II) acetate dihydrate. This approach produces selectively asymmetric type A_3B macrocycles in moderate yields.

The new phthalocyanines presented similar spectroscopic and photodynamic properties in DMF with high values of $O_2(^1\Delta_g)$ production, indicating that they are candidate agents to produce phototoxicity in biological media.

The possibility of synthesizing unsymmetrical Pcs with substituents situated at specific positions and an OH group transformable enables fine-tuning of physical properties, thereby enhancing the technological applications of the phthalocyanines.

Acknowledgements

This work was supported by Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) of Argentina, SECYT UNC and FONCyT.

Supporting information

General methods and materials. ^{1}H NMR and ^{13}C NMR spectra, and MS of compounds **4**, **6**, **Pc1**, **Pc2** are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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