



Synthesis of trimethylammoniumphenylthio-substituted phthalocyanines with different pattern of substitution

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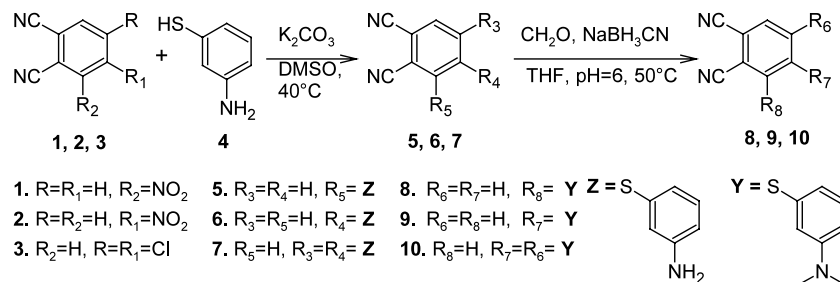
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Abstract—The base-catalyzed cyclotetramerization of 3-, 4- and 4,5-dimethylaminophenylthio phthalonitriles with zinc(II)acetate afforded 1(4),8(11),15(18),22(25)- and 2(3),9(10),16(17),23(24)-tetrasubstituted and 2,3,9,10,16,17,23,24-octasubstituted Zn(II)phthalocyanines, respectively. The statistical mixed condensation of the same phthalonitriles with 1,2-dicyanobenzene gave the corresponding mono- and disubstituted derivatives. Methylation of such products afforded a series of cationic Zn(II)phthalocyanines with different pattern of substitution, with potential use as photodynamic agents in microbial infections. © 2002 Elsevier Science Ltd. All rights reserved.

Phthalocyanines are molecules which are receiving considerable attention in relation to their possible use as dyes,¹ catalysts,² chemical sensors,³ for optical data storage,⁴ and as sensitizers in photodynamic treatment of several diseases.^{5,6} These dyes show high molar extinction coefficients in the 680–700 nm region of the visible spectrum and are capable of generating singlet oxygen, which is the reactive species generally believed to be the main responsible of the cytotoxic effect in the photodynamic process.⁷ Photosensitization could represent a useful approach to kill microbial cells, since it was demonstrated that several porphyrins and related compounds exhibit phototoxicity against many types of microbial agents; in particular, cationic photosensitizers

showed a higher photodynamic efficiency against bacteria, mycoplasma and yeast cells.^{8,9} In spite of the interest in phthalocyanines as potential antimicrobial agents,¹⁰ to our knowledge few papers have appeared so far concerning the synthesis of phthalocyanine derivatives specifically aimed at this purpose. As a part of our current interest in this field^{11,12} we have undertaken the synthesis of a series of zinc(II)phthalocyanines bearing the same substituent in different degrees and positions of substitution to use as antimicrobial photosensitizers against yeast and bacterial cells. Such structural variations on the macrocycle were aimed to evaluate the effect of the pattern of substitution on the photobiocidal activity of the molecules.



Scheme 1.

Keywords: zinc(II)phthalocyanines; phthalonitriles; cationic photosensitizers; PDT.

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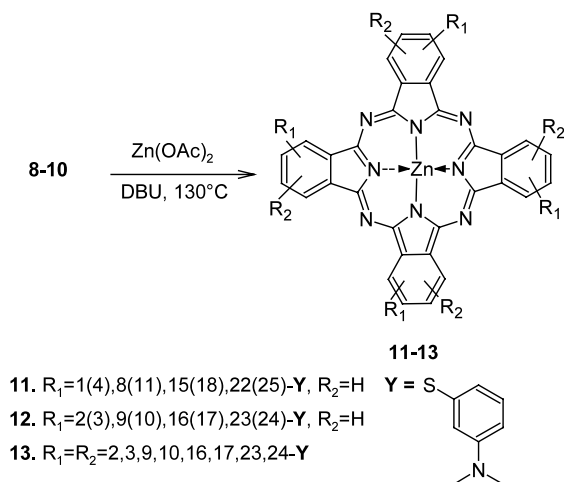
The phthalocyanines and phthalonitriles were synthesized according to the literature procedures with minor modifications.^{13,14} 3- and 4-Monosubstituted phthalonitriles **5**, **6**, were prepared by base catalyzed aromatic nucleophilic substitution¹⁵ of 3-aminothiophenol **4** on 3- and 4-nitrophthalonitriles, respectively, in anhydrous DMSO. The 4,5-disubstituted derivative **7** was obtained with the same procedure starting from 4,5-dichlorophthalonitrile. The primary amines **5–7** thus obtained were methylated in the presence of formaldehyde and NaCNBH₃ (Scheme 1).¹⁶ The preparation of the tertiary amines **8–10** previous to the cyclotetramerization was preferable because attempts of cyclization of **5–7** showed that the presence of primary amino groups on the phthalocyanines interfered with their purification processes.

The phthalonitriles **8–10** were used in cyclotetramerization reactions to yield tetrasubstituted derivatives **11** and **12**, both of which as regioisomeric mixtures, and the octasubstituted derivative **13** (Scheme 2). The reactions were carried in DBU in the presence of zinc acetate at 130°C.

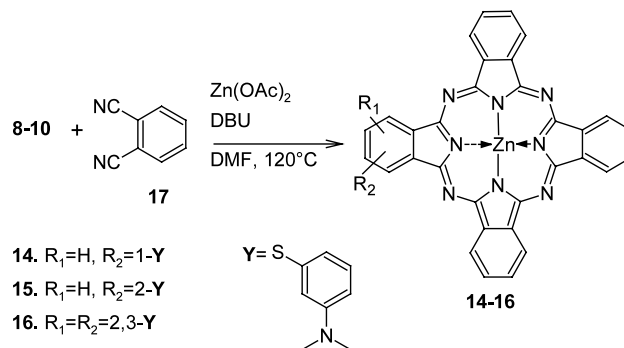
Mono- and disubstituted phthalocyanines **14**, **15** and **16** were synthesized in anhydrous DMF with zinc acetate and DBU at 120°C, using a mixture of 1,2-dicyanobenzene **17** and the mono- or disubstituted phthalonitrile (**8–10**) in a 3:1 molar ratio (Scheme 3). From the crude mixture the phthalocyanine with the lowest degree of substitution was isolated by MPLC from silica gel, eluting with mixtures of THF and hexane.

The yields of the desired phthalocyanines obtained using this synthetic procedure are consistent with literature data (10–15%).¹⁷

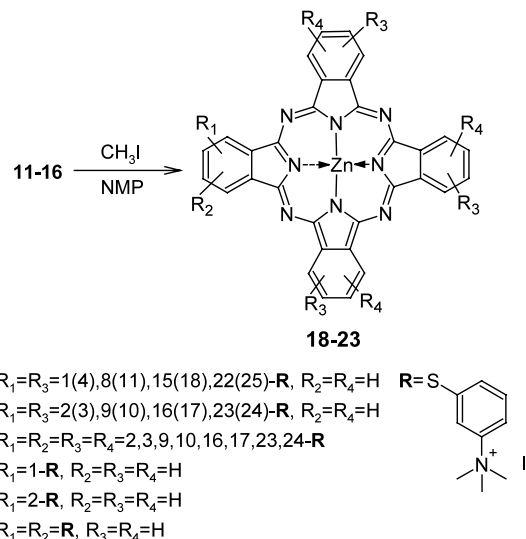
To perform our photoinactivation tests on microbial cells we aimed to obtain positively charged photosensitizers; thus, treating the phthalocyanines **11–16** with methyl iodide in *N*-methyl-2-pyrrolidinone (NMP) afforded the corresponding cationic compounds (**18–23**) in high yields (Scheme 4).



Scheme 2.



Scheme 3.



Scheme 4.

The cationic Zn(II)-phthalocyanines thus obtained are currently used in photoinactivation experiments on different kinds of microbial cells. Preliminary results¹⁸ indicate that the pattern of substitution is important for the biological activity of the photosensitizers: in our conditions (initial cell population: 1×10⁶ UFC/mL, incubation time: 1 h, PBS+5% DMSO, irradiation time: 10 min, 600–700 nm, 50 mW/cm²) against *Candida albicans* (ATCC10131), the phthalocyanines with lowest degree of substitution prove to be more effective in photoinactivating microorganisms, in particular monosubstituted **21** and **22** are able to decrease the cell population by a factor of 5 log at 0.05–0.1 μM.

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