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SHORT COMMUNICATION

Phthalocyanines

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SHORT COMMUNICATION

Synthesis of an Octa-tert-butylphthalocyanine: A Low-Aggregating and **Photochemically Stable Photosensitizer**

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Keywords: Dyes / Chromophores / Macrocycles / Photodynamic therapy / Diels-Alder / Domino reactions

The synthesis of a new octa-tert-butylphthalocyanine is described. First, the 4,5-di-tert-butylphthalonitrile building block was synthesized in a six-step approach, in which the last step is a three reaction domino sequence. Then, this

phthalonitrile was cyclotetramerized to furnish a new phthalocyanine dye, which presented no aggregation in solution and good photophysical properties.

Introduction

Phthalocyanines (PCs) are aromatic macrocycles containing 18π electrons that were accidentally discovered at the beginning of the 1900s. However, they were only wellcharacterized by Linstead and Robertson in the 1930s.^[1] As owing to their high thermal stability and low solubility, they were first applied in the dye and textile industries.^[1]

During the last century, several research groups discovered that such systems have a strong absorption in the 600-750 nm range and that they can be applied in many hightechnology areas such as transistors,^[2] liquid crystals,^[3] semiconductors,^[4] gas sensors,^[5] solar cells,^[6] catalysts,^[7] photodynamic therapy (PDT) agents,^[8] and others.^[9,10] However, unsubstituted PCs present limitations for use in some areas because of their tendency to undergo aggregation (π -stacking interactions), which leads to low solubility in most known organic solvents and a reduction in their optical and redox properties.^[1] Known approaches to counter this problem include the functionalization of PCs at the peripheral positions, changing the coordinating metal in the central core, building block functionalization, changing the *meso* atoms or the synthesis of nonsymmetric core structures. However, some of these proposals are quite dispendious.^[1]

We have already shown that nonsymmetric phthalocyanines synthesized from functionalized phthalonitriles present low aggregation and good solubility in both hydrophobic and hydrophilic media.^[11] For example, a nonsymmetric PC

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containing 5-aminolevulinic acid (ALA) and menthyl fragments showed low aggregation, water solubility, and very good properties for PDT.^[11]

The peripheral positions of unsubstituted PCs can be directly functionalized, but this leads to very complex mixtures of isomers and many byproducts, because of the harsh conditions used for these transformations.^[12] However, aiming at solving this problem, cross-coupling reactions have been described with success.^[13]

Generally, functionalization of phthalonitriles with bulky groups^[14,15] has been considered as a versatile solution for the synthesis of non-aggregating PCs. Nevertheless, to the best of our knowledge, phthalonitriles with vicinal bulky groups, such as *tert*-butyl at the 4,5-positions, have not been reported,^[16] and they thus represent an important synthetic challenge.

Herein, we describe the synthesis of 4,5-di-tert-butylphthalonitrile (8) by using a three-step domino sequence that includes a Diels-Alder reaction as the key step in transferring two vicinal *tert*-butyl groups of a thiophene ring to a benzenoid system. In addition, we describe the synthesis of octa-tert-butylphthalocyanines 9 and 10 by using this new phthalonitrile as the building block. Thus, we demonstrate the potential of 8 to synthesize a range of new and useful phthalocyanine derivatives (Scheme 1).

Results and Discussion

For the synthesis of 8, pinacolone (1) was brominated at the α position to furnish **2** in 83% yield.^[17] Compound **2** was subsequently treated with Na₂S·9H₂O by using a modified literature procedure^[18] to afford 3 in 95% yield. Tetrahydrothiophene 4 was obtained by treating 3 with TiCl₄/ Zn⁰ under McMurry reductive coupling conditions.^[18] In our hands, thiophene 5 was obtained by dehydration of 4 in benzene/p-toluenesulfonic acid (PTSA),^[18] but only in

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Scheme 1. Synthesis of PCs 9 and 10.

very low yield (<10%). When we carried out the dehydration by using anhydrous CuSO₄ in anhydrous toluene (high-pressure glass tube), 3,4-di-*tert*-butylthiophene (5) was obtained in 82% yield.^[19]

The Diels–Alder reaction between thiophene **5** and fumaronitrile was tested, and there was no reaction, as expected.^[20] Thus, we performed the oxidation of thiophene **5** by using *m*-chloroperbenzoic acid (*m*CPBA), which gave much more reactive thiophene dioxide **6** in 76% yield.^[18] We then planned a three-step domino transformation involving a Diels–Alder reaction, cheletropic elimination of SO₂, and elimination of HBr to obtain 4,5-di-*tert*-butylphthalonitrile (**8**). The reaction between **6** and bromofumaronitrile 7^[21] (no solvent) gave **8** successfully in 50% yield. All of the compounds were fully characterized by standard spectroscopy techniques, and the structure of new phthalonitrile **8** was confirmed by X-ray crystallography (Figure 1).

Compound **8** was then cyclotetramerized in *n*-pentanol/ Na⁰ at 140 °C and subsequently quenched with water to yield non-metalated phthalocyanine **9** in 22% yield after purification.^[22] When crude PC **9** was heated at reflux in a mixture of Zn(OAc)₂ and THF/CHCl₃/MeOH (1:1:0.5), compound **10** was obtained in 21% yield over the last two steps (**8** to **10**).^[22,23]

Fluorescence and singlet-oxygen quantum yields as well as aggregation studies of new PC derivatives **9** and **10** were determined to demonstrate their preliminary photophysical properties. These initial studies showed that the introduction of two neighboring *tert*-butyl groups at the periphery of these macrocycles results in compounds that present excellent photostability (Figure 2), no aggregation in solution (Figure 3), promote singlet-oxygen production (Figure 4), and a good fluorescence quantum yield (see also Figure S12 in the Supporting Information).



Figure 1. Molecular structure of **8** showing the atom labeling and displacement ellipsoids at the 50% probability level (arbitrary spheres for the H atoms). The molecule sits on a mirror plane so that C11 and C11_i are symmetry related.

The photobleaching studies (example in Figure 2 for compound 10) were performed in THF, and both compounds 9 and 10 showed no significant degradation after irradiation with a red light of intensity 50 mW cm^{-2} (see the Supporting Information for further details and Figures S15–S18).

Aggregation studies were accomplished by using UV/Vis analysis at different concentrations. As observed, PCs 9 and 10 (see the example for compound 10 in Figure 3) presented

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Figure 2. Photobleaching study of phthalocyanine10 in THF.

no maximum distortion of the Q bands and no blueshift, which indicates that there is aggregation at the limit of the Lambert–Beer law. Very similar behavior was found for compound 9. Additional experiments accomplished with polar and nonpolar solvents for both compounds 9 and 10, and the results are provided in the Supporting Information (Figures S19–S26).



Figure 3. Aggregation study of compound 10 in ethyl acetate.

Singlet-oxygen quantum yields (Φ_{Δ}) were measured for compounds **9** and **10** and were 0.10 and 0.13, respectively (see the example in Figure 4; for further details, calculations, and measurements see also the Supporting Information, Figures S1–S9; for comparison with standard ZnPC, see Figures S10 and S11).^[24,25] These results are consistent with values for alkylphthalocyanines, as described in the literature.^[26,27] The fluorescence quantum yields ($\Phi_{\rm F}$) of PCs **9** and **10** were also measured, and the values obtained were typical for alkyl-substituted PCs, being $\Phi_{\rm F} = 0.15$ and $\Phi_{\rm F} = 0.42$, respectively (for further details see the Supporting Information, Figures S12–S14).^[27,28] Stokes shift (the difference in the maxima of the absorption and emission bands) of PCs **9** and **10** were 5 and 7 nm, respectively.



Figure 4. 1,3-Diphenylisobenzofuran (DBPF) decay under singletoxygen quantum yield experiments for phthalocyanine **10** in THF.

Conclusions

In conclusion, phthalonitrile **8** was synthesized and fully characterized including by X-ray diffraction. Phthalocyanines **9** and **10** were synthesized by cyclotetramerization of **8** and showed good preliminary photophysical proprieties and non-aggregating behavior.

Above all, the main purpose of this work was to present the synthesis of compound **8** and its transformation into simple and symmetrical phthalocyanines **9** and **10**. As far as we can determine, this is the first synthesis of a vicinal di*tert*-butylphthalonitrile.^[16b] This work certainly opens the possibility to prepare more sophisticated PC derivatives, as well as nonsymmetric compounds.

CCDC-924160 (for **8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data along with copies of the ¹H NMR and ¹³C NMR spectra and high-resolution mass spectra for new compounds.

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