Synthesis of Highly Unsymmetrical Phthalocyanines†

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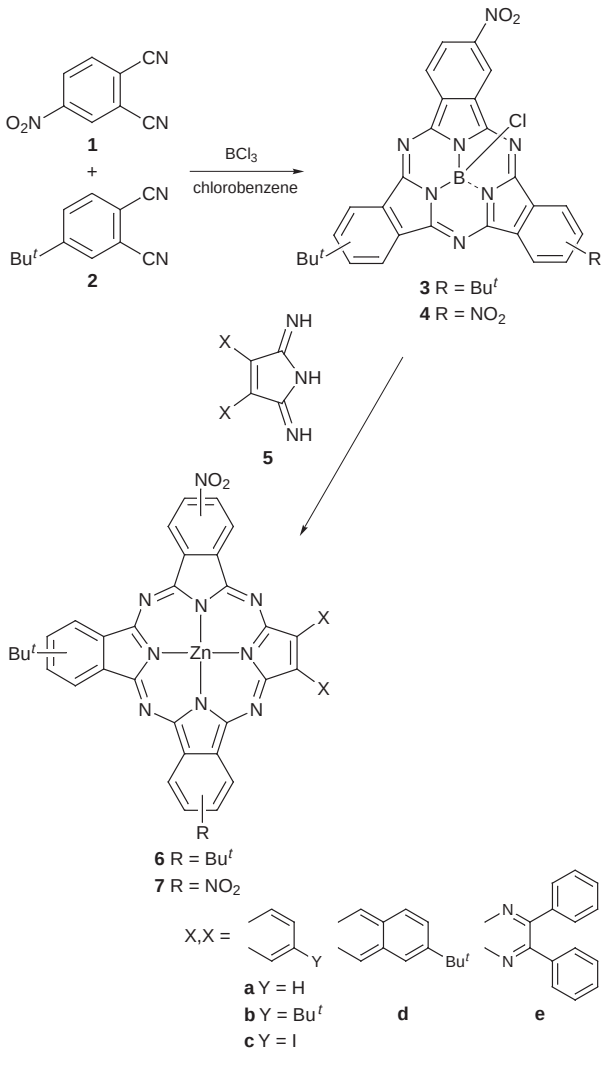
Hasrat Ali, Siv K. Sim and Johan E. van Lier*

MRC Group in the Radiation Sciences, Faculty of Medicine, Université de Sherbrooke, Sherbrooke (Québec), Canada J1H 5N4

The synthesis of unsymmetrical sub-phthalocyanines and their ring enlargement to yield the highly unsymmetrical phthalocyanines is reported.

The phthalocyanines (Pcs) represent an important class of molecules with increasingly diverse applications from industrial (catalyst, photoconductors) to biomedical (photodynamic therapy), which frequently require modifications of the Pc core to allow attachment of functional groups.[1] Phthalocyanines form stable complexes with a variety of metals and are typically prepared *via* the metal-templated tetramerization of phthalonitrile precursors, which are readily available, to yield symmetrical Pcs.[1] The amphiphilic, unsymmetrical Pc derivatives are of interest for photodynamic applications in medicine due to their cell penetrating properties.[2] However, much less is reported on their synthesis. Most of the methods developed for the synthesis of unsymmetrical Pc involves the use of two differently substituted phthalonitrile derivatives, which are condensed in the presence of metal salt, resulting in the formation of complex reaction mixtures.[1] Preorganization of the three phthalonitrile units as a symmetrical sub-phthalocyanines (subPcs) of boron[3] and subsequent ring enlargement, either with substituted phthalonitrile or diiminoisoindoline to yield the Pc macrocycle, is an efficient procedure to obtain unsymmetrical Pcs that are otherwise difficult to prepare.[5,6] Previously we reported an alternative method for the synthesis of unsymmetrical, monofunctionalized Pc using the palladium-catalyzed cross-coupling reaction.[7] Here we report a first example of the synthesis of unsymmetrical subPcs and subsequently their ring enlargement reaction, using various phthalonitrile derivatives, resulting in the formation of highly unsymmetrical Pcs.

The preparation of an unsymmetrical subPc involves the mixed condensation method, using two different phthalonitriles. Condensation of 4-nitrophthalonitrile (**1**) and 4-*tert*-butylphthalonitrile (**2**) in a molar ratio of 6:1 in chlorobenzene in the presence of BCl_3 at 220 °C for 0.5 h gave a mixture of subPcs, consisting of the mononitro subPc (**3**) (45%) the dinitro subPc (45%) and the trinitro subPc (10%) (see Experimental). The relative yield of each subPc depends on the molar ratio of the reactants[8] as well as the reaction temperature.[9] This is in accordance with published results that the trinitro subPc can be prepared at a much lower temperature as compared with the tri-*tert*-butyl subPc, which requires temperature > 200 °C.[5] The presence of polar nitro groups facilitates the separation of the reaction products on silica gel chromatography. Furthermore, the nitro substituent can readily be transformed into other functional groups. Careful chromatography using a mixture of dichloromethane/hexane (9:1) permits the separation of the mono- and di-nitro subPcs. Analytical data (HRMS-FAB) are consistent with the proposed structures of subPcs **3** and **4**. The recorded *m/z* values of the subPcs do not reveal the presence of a chlorine atom, which could arise as a side reaction of chlorine generated from BCl_3 with the macrocyles. Such secondary products have been detected in related reactions; however, the presence of the NO_2 group on the benzene ring deactivates the ring system towards halogen attack. The UV–VIS spectra of the unsymmetrical subPcs **3** and **4** are similar, but different from the corresponding symmetrical subPcs, *i.e.* the trinitro and tri-*tert*-butyl subPcs. The Q-band of the former is split, reflecting the lack of symmetry of the macrocycle and also the electron-withdrawing effect of the NO_2 group. The ^{1}H NMR spectra of **3** and **4** gave singlets in the region of δ 1.3–1.6, corresponding to the *tert*-butyl group, and distinct signals at δ 7.8–9.8, corresponding to the aromatic protons of the subPc, confirming the presence of the regioisomer. Reaction conditions for the ring enlargement



* To receive any correspondence (*e-mail*: jvanhier@courrier.usherb.ca).

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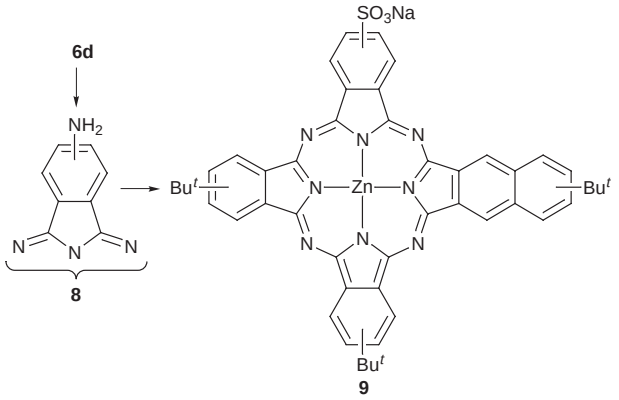

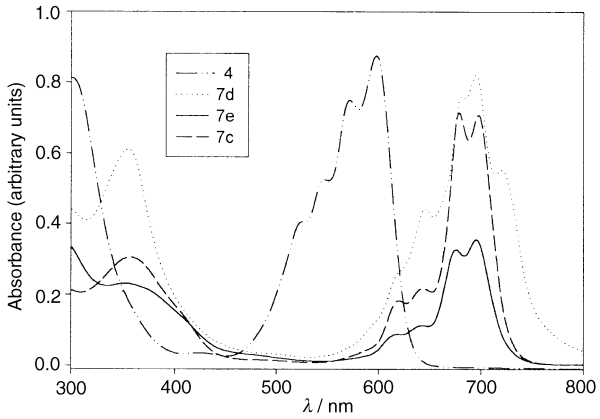

Figure 1

are similar to those previously reported, *i.e.* the subPc is heated with substituted diiminoisoindoline derivatives (**5**) in DMSO at 60–90 °C for 1 h. The products are metalated in DMF with an excess of zinc(II) acetate dihydrate at 90–100 °C for 1 h to yield metallo Pcs in 30–40% yield. The Pcs are obtained as mixtures of isomers since the starting compounds consist of regioisomeric mixtures. The final products were characterized by HRMS-FAB and by their characteristic UV–VIS spectra (Fig. 1). The mononitro group of **6d** was reduced to an amino group to give **8**, using $Na_2S{\cdot}9H_2O$. The amino group was subsequently converted into a sulfonato group using Meerwein reaction conditions,[10] to yield the monosulfonated Pc **9**. Although some of the Pc with only two different substituents can be prepared and purified using statistical synthesis, most of the more complex derivatives attainable *via* the unsymmetrical subPc would give unextractable mixtures using such conventional synthesis.

The ring enlargement reaction was also attempted with 4-chlorosulfonyl-1,2-phthalodicarbonitrile. Although the color of the reaction mixture changed instantaneously, FAB-MS analysis did not support the presence of the expected Pc product, nor was the self-condensation product (tetrasulfo Pc) detected.

Experimental

Compound **1** (2.64 mM) and 2 (15.84 mM) were suspended in 2 mL of 1-chloronaphthalene, stirred at room temperature in an atmosphere of nitrogen and an equimolar quantity of BCl_3 was added. The reaction mixture was placed in a preheated oil bath (220 °C) for 0.5 h. The 1-chloronaphthalene was removed by filtration over silica gel and washing with hexane. The products were recovered with dichloromethane. Column chromatography using 10% hexane in dichloromethane resolved the mixture and gave the subPcs as pure compounds. **3**: FAB-MS (NBA): *m/z* 587 [M^+]; HRMS-FAB *m/z* calcd. for $C_{32}H_{26}O_2N_7{}^{35}Cl^{11}B$ ($M^+ - 1$) 586.1910; found 586.19293; UV–VIS (CH_2Cl_2) λ_{max}/cm^{-1}, 600 (1), 567 (0.72), 542 (0.55), 520 (0.45), 342 (0.34). **4**: FAB-MS (NBA): *m/z* 576 [M^+]; HRMS-FAB *m/z* calcd. for $C_{28}H_{18}O_4N_8{}^{35}Cl^{11}B$: 576.12480; found 576.12323; UV–vis (CH_2Cl_2): λ_{max}/cm^{-1}, 593 (1), 564 (0.73), 518 (0.39) 427 (0.05).

Selected Spectral Data for **6d** *and* **7a–e**.—**7a**: FAB-MS (NBA): *m/z* 723 [M^+]; HRMS-FAB *m/z* calcd. for $C_{36}H_{22}O_4N_{10}{}^{64}Zn$: 722.10920; found 722.11169; UV–VIS (DMF): λ_{max}/cm^{-1} 692 (0.98), 678 (1), 641 (0.29), 618 (0.2), 357 (0.42). **7b**: FAB-MS (NBA): *m/z* 778 [M^+]; UV–VIS (CH_2Cl_2): λ_{max}/cm^{-1} 677 (1), 611 (0.16), 345 (0.23). **7c**: FAB-MS (NBA): *m/z* 848.9 [M^+]; UV–VIS (DMF): λ_{max}/cm^{-1}, 698 (0.98), 680 (1), 644 (0.32), 620 (0.25), 358 (0.43), 280 (0.35).**7d**: FAB-MS (NBA): *m/z* 830 [M^++2]; HRMS-FAB *m/z* calcd. for $C_{44}H_{34}O_4N_{10}{}^{64}Zn$: 830.20709; found 830.20557; UV–VIS (DMF): λ_{max}/cm^{-1} 724 (s), 699 (1), 684 (s), 645 (0.47), 620 (s), 357 (0.54). **7e**: FAB-MS (NBA): *m/z* 877 [M^++1]; HRMS-FAB *m/z* calcd. for $C_{46}H_{29}O_4N_{12}{}^{64}Zn$: 877.17261; found 877.17020; UV–VIS (DMF): λ_{max}/cm^{-1} 697 (1), 679 (0.92), 642 (s), 621 (s), 356 (0.64). **6d**: FAB-MS (NBA): *m/z* 840 [M^+]; UV–VIS (DMF): λ_{max}/cm^{-1} 696 (1), 628 (0.2), 348 (0.45).

In summary, we have described for the first time the synthesis of unsymmetrical subPcs and their subsequent ring opening to yield highly unsymmetrical Pcs which are difficult to prepare *via* alternative methods.

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8 A 2:1 molar ratio of reactants mainly yielded the trinitro subPc, a 4:1 ratio gave 20% mono-, 50% di- and 30% trinitro subPc and a ratio of 8:1 gave tri-*tert*-Bu subPc along with 20–30% mono- and dinitro subPc.
9 The product ratios completely changed when the temperature of the reaction mixture was slowly raised from room temperature to 90 °C by placing in an oil bath and slowly heating. Precursors **1** and **2** react differently, depending on the temperature.
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