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Functionalization of sulfophthalocyanines in aqueous medium by palladium-catalyzed cross-coupling reactions

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Abstract—A series of mono-functionalized trisulfonated phthalocyanines were prepared in aqueous medium under palladium-catalyzed cross-coupling reaction conditions (Sonogashira, Heck and Suzuki) using water-soluble mono-iodo trisufophthalocyanines as precursors.

Phthalocyanines (Pc) have received increasing attention for a wide variety of applications due to their unique physical, chemical, biological and spectral properties.[1] Specific applications require compounds with distinct and well defined structures, often including asymmetric substitutions. A number of different strategies to prepare asymmetrically substituted Pc have been put forth.[2] Conventional methods involve mixed condensation of phthalonitrile precursors and metal salt at elevated temperature, either as solid or in solvent, with or without microwave irradiation.[3] However, all such approaches result in complex reaction mixtures requiring tedious purification of the desired product.[4] More recently ring enlargement of the subPc has also been developed as an alternative method to synthesize modified Pc.[5]

Carbon–carbon bond formation is the essential step for the synthesis of complicated organic molecules. Prominent among these procedures is the Pd-catalyzed C–C bond-forming reaction.[6] Based on this methodology a number of novel Pc-based photosensitizers have been prepared with improved catalytic, photophysical and biological activities.[7] Previously we reported a two-step procedure for the synthesis of mono-functionalized, trisulfonated Pc involving a Pd-catalyzed cross-coupling reaction in organic solvent, with the sulfo groups protected as indole derivatives. The final deprotection step yields the water-soluble sulfonated Pc.[8] There has been increasing recognition that organic synthesis can proceed well in aqueous media and that an overall green chemistry approach can provide several advantages over reactions conducted in organic medium.[9] In the past few years, great emphasis has been placed on developing inexpensive, active and efficient catalysts and ligands that perform well under aqueous conditions.[10] We recently applied green chemistry conditions to the modification of cationic porphyrins using a Pd-catalyst.[11]

Here, we report a versatile and convenient method for the synthesis of novel substituted trisulfonated Pc via a mono-iodo trisulfonated precursor in aqueous medium. Starting from this single precursor we obtained differently substituted trisulfonated Pc in good yield that were readily purified by reversed-phase column chromatography. The mono-iodo $GaPcS_3I$ (**1a**) was prepared by the mixed condensation of the mono sodium salt of 4-sulfophthalic acid and 4-iodophthalonitrile (molar ratio 5:1) in the presence of ammonium chloride, ammonium molybdate, urea and gallium chloride. All components were thoroughly mixed and heated at 200–210 °C for 2 h. The reaction mixture contained mono- through tetrasulfonated products and was purified by C-18 reversed-phase medium pressure column chromatography using a gradient of 5 mM phosphate buffer (pH 5) in MeOH to give **1a** in 10–15% yield. The assigned structures were confirmed by UV–vis and MALDI-TOF MS spectroscopies. Compound **1a** gave a Q band maximum at 684 nm (DMF), which is characteristic of the Pc macrocycle. The MS of **1a**, using α-cyano-4-hydoxy

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cinnamic acid (M.W. 189.04) as a matrix in aqueous acetonitrile, gave a characteristic ion corresponding to the adduct of **1a** ($C_{32}H_{15}GaIN_8O_9S_3$) and the matrix. Similar adducts were observed with other matrixes (unpublished results). Upon treatment of **1a** with an acid, a strong isotopic cluster of peaks centered around *m*/*z* 949.38 (characteristic for the natural Ga isotope abundances) was observed, corresponding to the free acid with the loss of –OH from the central metal ion. Fragments corresponding to the mono- to tetra-sodium salts were also detected.

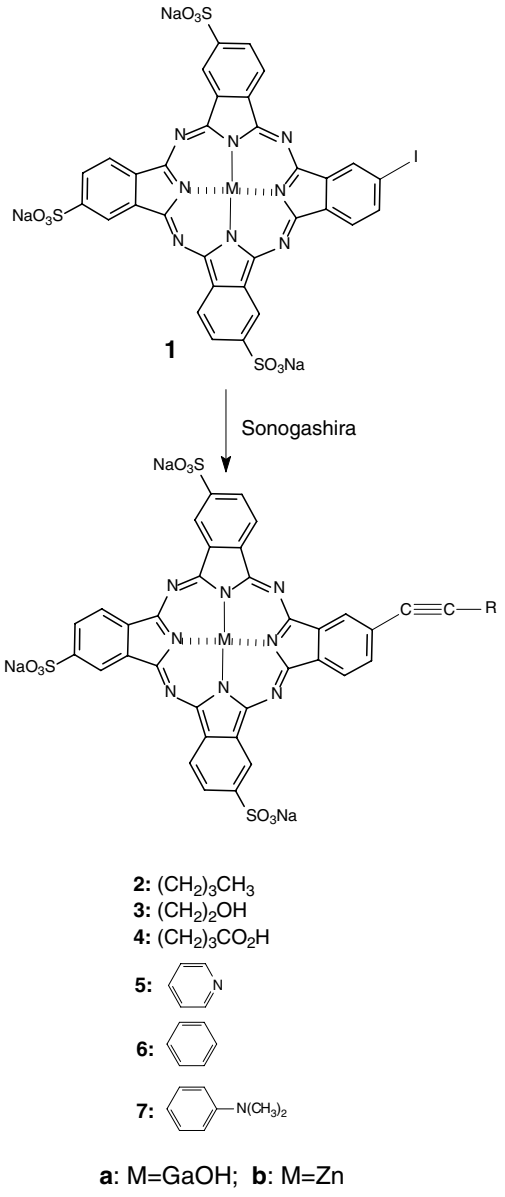
The mono-iodo trisulfonated ZnPc (**1b**) was obtained either by hydrolysis of 2-iodo-9,16,23-tris (1′-indolylsulfonyl) ZnPc using sodium methoxide in THF/methanol or by adapting the same protocol as presented for **1a** (substituting gallium chloride for zinc acetate). However, better yields and cleaner products were obtained using the former approach. The assigned structure was confirmed by UV–vis and MS. The UV–vis spectrum of **1b** gave a characteristic, strong Q band at 765 nm (DMF). MALDI-TOF MS (LD-mode, using THAP as matrix) gave a cluster of peaks (characteristic for the natural Zn isotope abundances), centered at *m*/*z* 988.74 corresponding to the di-sodium salt ($C_{32}H_{13}ZnNa_2IN_8O_9S_3$). The sodium-free form of **1b** did not reveal adduct formation with the matrix. The highly water-soluble **1a** and **1b** were both used as starting materials for a number of Pd-catalyzed modifications.

We first attempted the coupling reaction between **1a** and various terminal alkyne derivatives in aqueous medium (Sonogashira).[12] To the mono-iodo Pc **1a** (25 mg) under an atmosphere of argon was added a catalytic amount of $Pd(OAc)_2$ (5 mg) with trisodium triphenylphosphine 3,3′,3″-trisulfonate (TPPTS) (5 mg) as a ligand, sodium carbonate as base, and 1-hexyne and CH_3CN/H_2O (1:1) (10 mL) as solvent. The mixture was stirred at room temperature and the progress of the reaction was monitored by reversed-phase HPLC on a C-18 column using a phosphate buffer in methanol gradient system. The reaction was completed in 3 h. Different functional groups on the alkynyl side chain such as alcohol and carboxylic acid were well tolerated and products **3a** and **4a** were obtained in good yield (50–60%) (Scheme 1). Likewise the Zn analog **1b** also reacts smoothly with a number of alkynyl compounds in 3–4 h giving products in satisfactory yield.

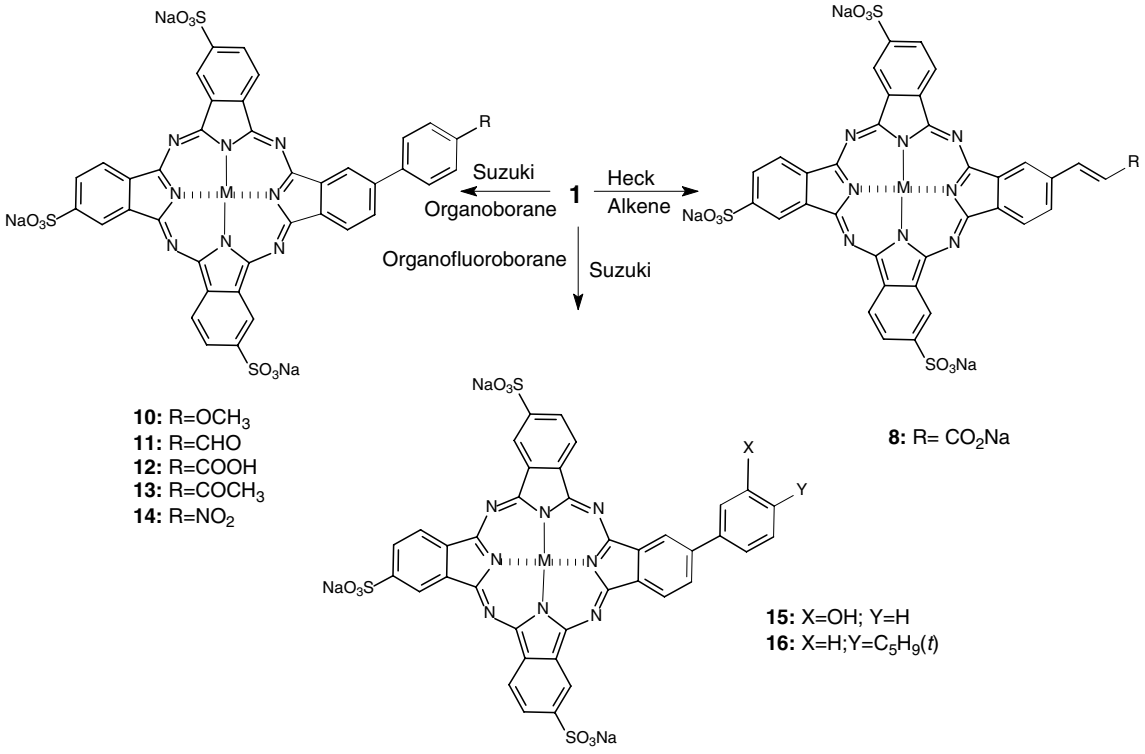
The mono-iodo Pc **1a** (25 mg) was also reacted with sodium acrylate (Heck reaction)[13] under the above condition using $Pd(OAc)_2$ (5 mg), sodium carbonate and tri-(4,6-dimethyl-3-sulfonatophenyl)phosphine trisodium salt (TXPTS) (5 mg) as ligand in H_2O:CH_3CN (1:1) to yield **8a** in 2–3 h in 70–80% yield. Overall the TXPTS ligands gave better yields as compared to TPPS. The analogous $ZnPcS_3I$ (**1b**) likewise reacted smoothly under these conditions (Scheme 2).

Finally we also evaluated the Pd-catalyzed cross-coupling of aryl halides **1a** and **1b** (25 mg) with boronic acids in aqueous medium (Suzuki).[14] Reaction of **1a** with 4-methoxyphenyl boronic acid using $Pd(OAc)_2$/TXPTS (5 mg each) and sodium carbonate in H_2O:CH_3CN gave **10a** in 70–80% yield. Similarly a number of aryl boronic acids containing various functional groups were also successfully coupled in good yield. Organofluoroboranes are more stable and more reactive as compared to boronic acids, and also give superior yields in Pd-catalyzed coupling reactions.[15] On such account we also performed the Suzuki reaction with **1a** using different organofluoroboranes, under the same reaction conditions as described for organoboranes, to yield **15a** and **16a** (Scheme 2). The vinyl substituted analog of **1a**, that is, compound **9** (compound **8** with R = H) was obtained using potassium vinyltrifluoro borate under Suzuki conditions.

All new products were identified by their characteristic UV–vis spectra and MALDI-TOF MS.[16] In the case



Scheme 1.



Scheme 2.

of the GaPc derivatives, the molecular ion is represented by the free acid or the adduct with the matrix. However, in case of the ZnPc derivatives, no adduct formation with the matrix was observed. This paper represents a first account of the successful modification of phthalocyanines using palladium catalysis in aqueous medium.

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References and notes

1. *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: Amsterdam, 2003.
2. Ali, H.; van Lier, J. E. *Chem. Rev.* **1999**, *99*, 2379–2450.
3. Jung, K. S.; Ro, J. Y.; Lee, J. Y.; Park, S. S. *J. Mater. Sci. Lett.* **2001**, *20*, 2203–2205.
4. Ali, H.; Langlois, R.; Wagner, J. R.; Brasseur, N.; Paquette, B.; van Lier, J. E. *Photochem. Photobiol.* **1988**, *47*, 713–719.
5. Claessens, C. G.; Gonzalez-Rodriguez, D.; Torres, T. *Chem. Rev.* **2002**, *102*, 835–853; Sharman, W. M.; van Lier, J. E. *Bioconjugate Chem.* **2005**, *16*, 1166–1175; Sharman, W. M.; van Lier, J. E. *J. Porphyrins Phthalocyanines* **2005**, *9*, 651–659.
6. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Tsuji, J., Ed.; Wiley: Chichester, 1995; *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; p 1051.
7. Sharman, W. M.; van Lier, J. E. *J. Porphyrins Phthalocyanines* **2005**, *4*, 441–453; Ali, H.; van Lier, J. E. *Tetrahedron Lett.* **1997**, *38*, 1157–1160; Cauchon, N.; Tian, H.; Langois, R.; La Madeleine, C.; Martin, S.; Ali, H.; Hunting, D.; van Lier, J. E. *Bioconjugate Chem.* **2005**, *16*, 80–89; Li, J.; Linsdey, J. S. *J. Org. Chem.* **1999**, *64*, 9101–9108; Maya, E. M.; Garcia, C.; Garcia-Frutos, E. M.; Vazquez, P.; Torres, T. *J. Org. Chem.* **2000**, *65*, 2733–2739.
8. Tian, H.; Ali, H.; van Lier, J. E. *Tetrahedron Lett.* **2000**, *41*, 8435–8438; Li, Z.; van Lier, J. E.; Leznoff, C. C. *Can. J. Chem.* **1999**, *77*, 138–145.
9. *Organic Synthesis in Water*; Grieco, P. A., Ed.; Thomson Science: Glasgow, Scotland, 1998.
10. Li, C. J. *Chem. Rev.* **2005**, *105*, 3095–3165.
11. Tremblay-Morin, J.-P.; Ali, H.; van Lier, J. E. *Terahedron Lett.* **2005**, *46*, 6999–7002; Tremblay-Morin, J.-P.; Ali, H.; van Lier, J. E. *Terahedron Lett.* **2006**, *47*, 3043–3046.
12. Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324–4330; Depuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savigniac, M.; Genêt, J.-P. *Tetrahedron Lett.* **2001**, *42*, 6523–6526.
13. Okamoto, K.; Akiyama, R.; Kobayashi, S. *Organic Lett.* **2004**, *6*, 1987–1990; Moore, L. R.; Shaughnessy, K. H. *Organic Lett.* **2004**, *6*, 225–228.
14. Hessler, A.; Stelzer, O. *J. Org. Chem.* **1997**, *62*, 2362–2369; Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449–7476; Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11; Stürmer, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 3307–3308.

15. Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49–56.

16. All compounds were purified by HPLC. MS data were obtained by MALDI-TOF using α-cyano-4-hydoxy cinnamic acid in aqueous acetonitrile as a matrix. Compound **2a**: UV–vis (DMF) 683 nm; MS *m*/*z* 1177 (adduct 100%), 987 (10%). Compound **3a**: UV–vis (DMF) 683 nm; MS *m*/*z* 1116 (adduct-2Na). Compound **4a**: UV–vis (DMF) 687 nm; MS *m*/*z* 1116 (adduct-2Na). Compound **5a**: UV–vis (DMF) 683 nm; MS *m*/*z* 923 (free acid-OH). Compound **6b**: UV–vis (DMF) 679 nm; MS *m*/*z* 920 (free acid). Compound **6b**: UV–vis (DMF) 681 nm; MS *m*/*z* 918 (free acid). Compound **7b**: UV–vis (DMF) 685; MS *m*/*z* 962 (free acid). Compound **8a**: UV–vis (DMF) 691 nm; MS *m*/*z* 891 (free acid). Compound **9a**: UV–vis (DMF) 685 nm; MS *m*/*z* 935. Compound **10a**: UV–vis (DMF) 693 nm; MS *m*/*z* 1117 (free acid adduct-OH). Compound **10b**: UV–vis (DMF) 680 nm; MS *m*/*z* 924 (free acid). Compound **11a**: UV–vis (DMF) 688 nm; MS *m*/*z* 1115 (adduct-OH). Compound **12a**: UV–vis (DMF) 690 nm; MS *m*/*z* 1131 (adduct-OH). Compound **13a**: UV–vis (DMF) 686 nm; MS *m*/*z* 1130 (adduct-OH). Compound **14a**: UV–vis (DMF) 684 nm; MS *m*/*z* 1130 (free acid adduct-OH). Compound **14a**: UV–vis (DMF) 690 nm; MS *m*/*z* 1132 (adduct-OH). Compound **15a**: UV–vis (DMF) 685 nm; MS *m*/*z* 1115 (adduct-OH). Compound **16a**: UV–vis (DMF) 685.5 nm; MS *m*/*z* 1143 (free acid adduct-OH).