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Synthesis of water soluble trisulfonated phthalocyanines via palladium-catalysed cross coupling reactions

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Abstract

A series of novel functionalized trisulfonated phthalocyanines were prepared in good to excellent yield using the monoiodo trisulfonated phthalocyanine as precursor for palladium-catalysed cross coupling reactions (Heck reaction and Buchwald amination).

Keywords: trisulfonated phthalocyanine; coupling reaction; palladium catalyst; photodynamic therapy.

During the past decades phthalocyanines (Pc) and their derivatives have been extensively studied and found numerous applications in widely different areas due to their distinct properties.[1] Our interest in Pc, especially water-soluble sulfonated derivatives for photodynamic therapy (PDT) of cancer, led us to synthesize a variety of substituted phthalocyanines.[2] Depending on the degree of sulfonation, Pc exhibit varying hydrophobic and hydrophilic properties and very different photodynamic effects.[3,4] Adjacently substituted, disulfonated compounds have the appropriate amphiphilic properties for optimal cell membrane penetration, resulting in high photodynamic activity both against tumor cells in culture and experimental animal tumors.[4] Such derivatives are, however, difficult to purify as single isomeric products.[5] Adding different peripheral, lipophilic substituents onto trisulfonated Pc provides compounds with similar amphiphilic properties. A series of such derivatives were prepared via the ring-enlargement reaction of subphthalocyanine (subPc).[6] The success of this procedure depends dramatically on the nature of the substituents on the subPc, the reactivity of the iminoisoindoline, the solvent and other factors,[7] and as such is not suitable for preparing our desired series of trisulfonated Pc. Recently, Leznoff and collaborators[8] reported the use of indole or pyrrole as a protecting group to obtain the symmetric sulfonated and monosulfonated Pc. We used a similar method to make monoiodo trisulfonated Pc as a starting material for further substitu-

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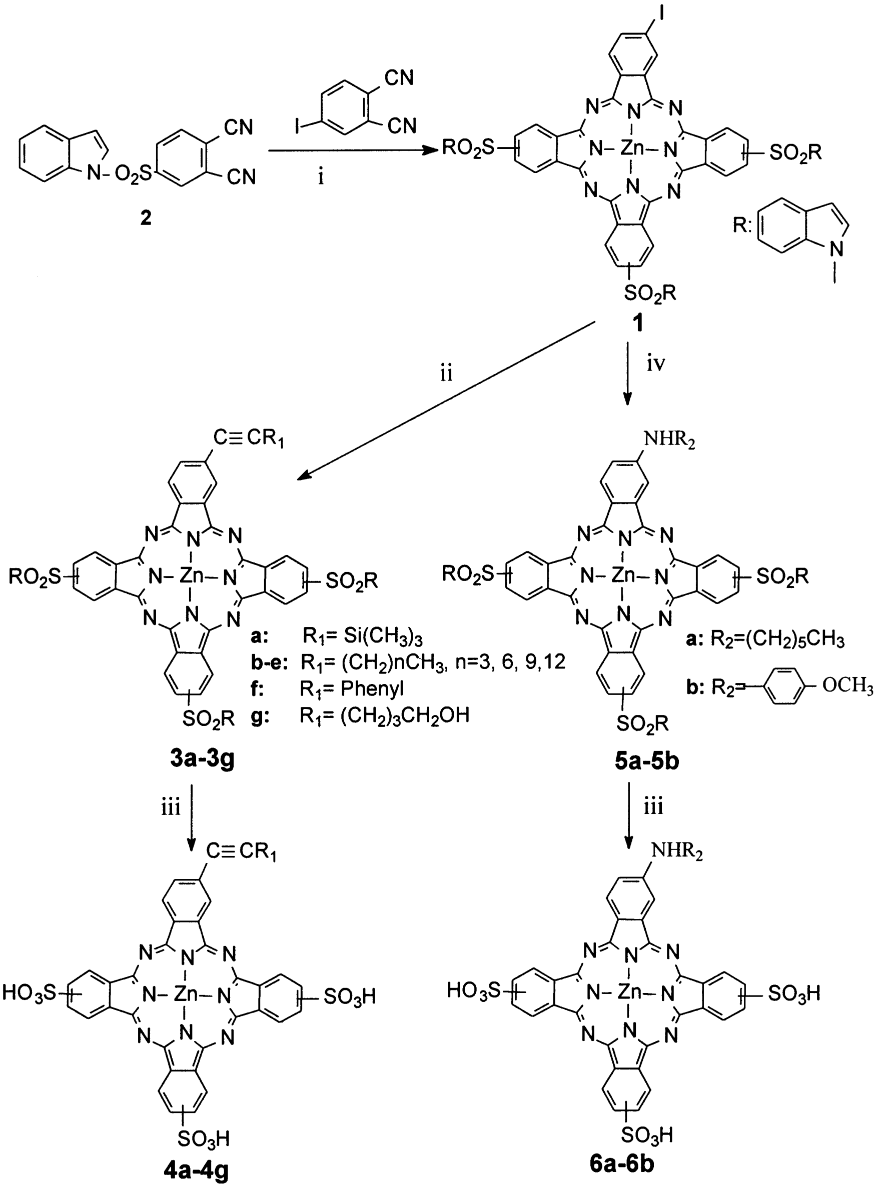
tion. It is well known that the palladium-catalysed coupling of terminal alkynes with aryl halides (aryl iodides or aryl bromides) is an effective method for introducing an alkynyl chain onto the Pc macrocycle.[9] Likewise, the palladium-catalysed Buchwald amination reaction[10] should be useful to attach selected amino-chains onto the Pc. We now report a versatile and convenient method for the synthesis of novel substituted trisulfonated Pc via the monoiodo, protected trisulfonated Pc **1**. Starting from this single precursor we obtained different substituted trisulfonated Pc in good to excellent yield, while the products were easily purified by normal silica gel column chromatography.



Scheme 1. (i) ZnAc·$2H_2O$, 200–220°C, 30 min, 19%; (ii) alkyne, $PdCl_2(Ph_3P)_2$, CuI, THF, Et_3N, rt, 15–24 h, 85–95%; (iii) LiOMe, MeOH, THF, reflux, 24 h, 80–85%; (iv) $Pd_2(dba)_3$/(*S*)-BINAP, Cs_2CO_3, THF, reflux, 14–20 h, ~63%

The monoiodo trisulfonated Pc **1** was readily prepared by the mixed condensation of 1-(3,4-dicyanophenylsulfonyl)-indole **2** with 4-iodophthalonitrile (molar ratio 3:1) in reasonable yield (19%). The protected monoiodo Pc **1** is soluble in most polar organic solvents and could easily be purified by silica gel column chromatography. The UV–vis spectrum of **1** shows a split Q band (687 and 673 nm) due to the presence of the three bulky protecting groups, which affect the Pc symmetrical properties.[11]

The protected monoiodo Pc **1** was reacted with different terminal alkynes under palladium/Cu(I) catalysed conditions to yield a series of Pc with different functionalized substituents, i.e. **3a**–**g** (Scheme 1), in good to excellent yields. All the Pc could be easily purified by silica gel column chromatography, and showed similar absorption spectra with two Q bands (692 and 675 nm). After hydrolysis of the protecting groups by treatment with lithium methoxide in methanol and THF, trisulfonated Pc **4a**–**g** were obtained in >85% yield, all showing a single Q absorption band at 678 nm in methanol.

Buchwald's palladium catalysed amination reaction was used to introduce amino chains on the Pc. Since the protecting group of indolysulfonate is unstable in strong base we chose the weak base Cs_2CO_3 for the amination reaction. Compound **1** was treated with hexylamine or *p*-anisidine to afford compound **5a** or **5b** in >60% yield (Scheme 1). Both compounds exhibit a Q band at 692 nm with a shoulder at 710 nm. Subsequent hydrolysis gave Pc **6a** and **6b**. Both compounds show a 10 nm red-shifted Q band absorption at 690 nm due to the presence of the electron-rich amino chain.

All new Pcs were characterized by UV–vis and FAB or electron-spray mass spectroscopy.[12] The trisulfonated Pcs were purified by reverse phase, medium pressure liquid chromatography and analysed by reversed phase HPLC.[5] All derivatives showed three closely eluting peaks with longer retention times as compared with those of the non-substituted trisulfonated Pcs. This observation confirms that the attachment of a lipophilic chain augments the hydrophobic properties of the trisulfonated Pc. Preliminary studies on the photodynamic efficacy against tumor cells in culture indicate that the added lipophilic substituent substantially increases the photoinactivating potential of the Pc. Further biological testing is currently in progress in our laboratory.

Acknowledgements

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12. Selected data for Pcs. **3a**: UV–vis ($CHCl_3$) λ_{max}/nm (log ε) 690 (5.26), 676 (5.26), 615 (4.65), 359 (4.90), MS (FAB) m/z calculated for $C_{61}H_{39}N_{11}O_6S_3Zn$ 1211.70, found 1211.0. **3b**: UV–vis ($CHCl_3$) λ_{max}/nm (log ε) 691 (5.28), 676 (5.26), 613 (4.59), 361 (4.89), MS (FAB) m/z calculated for $C_{62}H_{39}N_{11}O_6S_3Zn$ 1195.62, found 1195.1. **3c**: UV–vis ($CHCl_3$) λ_{max}/nm (log ε) 691 (5.28), 677 (5.26), 614 (4.60), 362 (4.88), MS (FAB) m/z calculated for $C_{65}H_{45}N_{11}O_6S_3Zn$ 1237.70, found 1237.0. **3d**: UV–vis ($CHCl_3$) λ_{max}/nm (log ε) 692 (5.27), 675 (5.25), 613 (4.59), 362 (4.90), MS (FAB) m/z calculated for $C_{68}H_{51}N_{11}O_6S_3Zn$ 1279.78, found 1278.9. **3e**: UV–vis ($CHCl_3$) λ_{max}/nm (log ε) 692 (5.23), 676 (5.22), 614 (4.58), 362 (4.87), MS (FAB) m/z calculated for $C_{72}H_{59}N_{11}O_6S_3Zn$ 1335.89, found 1234.9. **3f**: UV–vis ($CHCl_3$) λ_{max}/nm (log ε) 692 (5.26), 676 (5.24), 614 (4.57), 359 (4.85), MS (FAB) m/z calculated for $C_{64}H_{35}N_{11}O_6S_3Zn$ 1215.64, found 1214.2. **3g**: UV–vis ($CHCl_3$) λ_{max}/nm (log ε) 691 (5.21), 675 (5.19), 613 (4.49), 362 (4.49), MS (FAB) m/z calculated for $C_{62}H_{39}N_{11}O_7S_3Zn$ 1211.62, found 1211.4. **4a**: UV–vis (MeOH) λ_{max}/nm (log ε) 671 (5.27), 607 (4.58), 344 (4.81), MS (Electron-spray) m/z calculated for $C_{34}H_{16}N_8O_9S_3Zn$ 842.11, found 840.8 (M−1). **4b**: UV–vis (MeOH) λ_{max}/nm (log ε) 671 (5.20), 607 (4.48), 344 (4.79), MS (Electron-spray) m/z calculated for $C_{38}H_{24}N_8O_9S_3Zn$ 898.22, found 896.9 (M−1). **4c**: UV–vis (MeOH) λ_{max}/nm (log ε) 671 (5.31), 607 (4.52), 345 (4.82), MS (Electron-spray) m/z calculated for $C_{41}H_{30}N_8O_9S_3Zn$ 940.30, found 939.0 (M−1). **4d**: UV–vis (MeOH) λ_{max}/nm (log ε) 671 (5.30), 607 (4.51), 345 (4.81), MS (Electron-spray) m/z calculated for $C_{44}H_{36}N_8O_9S_3Zn$ 982.38, found 981.0 (M−1). **4e**: UV–vis (MeOH) λ_{max}/nm (log ε) 678 (5.14), 607 (4.36), 356 (4.68), MS (Electron-spray) m/z calculated for $C_{48}H_{44}N_8O_9S_3Zn$ 1038.49, found 1037.8 (M−1). **4f**: UV–vis (DMF) λ_{max}/nm (log ε) 677 (5.15), 611 (4.41), 350 (4.70), MS (Electron-spray) m/z calculated for $C_{40}H_{20}N_8O_9S_3Zn$ 918.21, found 916.5 (M−1). **4g**: UV–vis (DMF) λ_{max}/nm (log ε) 678 (5.21), 612 (4.46), 353 (4.77), MS (Electron-spray) m/z calculated for $C_{38}H_{24}N_8O_{10}S_3Zn$ 914.22, found 913.1 (M−1). **5a**: UV–vis ($CHCl_3$) λ_{max}/nm (log ε) 710 (sh) (4.80), 688 (5.03), 630 (4.53), 355 (4.84), MS (FAB) m/z calculated for $C_{62}H_{44}N_{12}O_6S_3Zn$ 1214.67, found 1214.2. **5b**: UV–vis ($CHCl_3$) λ_{max}/nm (log ε) 710 (sh) (4.92), 689 (5.01), 628 (4.49), 353 (4.84), MS (FAB) m/z calculated for $C_{63}H_{38}N_{12}O_7S_3Zn$ 1236.63, found 1236.0. **6a**: UV–vis (DMF) λ_{max}/nm (log ε) 689 (5.10), 626 (4.53), 346 (4.96), MS (Electron-spray) m/z calculated for $C_{38}H_{28}N_9O_9S_3Zn$ 916.26, found 915.25 (M−1). **6b**: UV–vis (DMF) λ_{max}/nm (log ε) 694 (5.13), 627 (4.61), 346 (4.77), MS Electron-spray m/z calculated for $C_{39}H_{22}N_9O_{10}S_3Zn$ 938.22, found 937.4 (M−1).