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Communications

Selective Derivatization of TPP on One Phenyl Ring by Nitration and Subsequent Nucleophilic Substitution of Hydrogen

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Many porphyrin derivatives are widely used as photosensitizers in Photodynamic Theraphy (PDT). This simple technique is currently evaluated in multiple clinical trials with promising results.[1] PDT is relatively new cancer treatment which is based on the administration of tumor-localizing photosensitizers and their subsequent activation by visible light to destroy cancer cells. However, their mode of action is still not clear. It has been known that human serum albumin (HSA) binding affinity of various photosensitizers plays an important role in their biodistribution within the tumor stroma.[2] This distribution of porphyrins among serum proteins is dependent upon their chemical structure.[3] So, new methods for the synthesis of hydrophilic, lipophilic and amphiphilic, especially unsymmetrical porphyrins are continuously sought.

Herein, we present a new tool for selective derivatization of porphyrin systems using Vicarious Nucleophilic Substitution of Hydrogen (VNS).[4] As a model compound *meso*-tetraphenylporphyrin (TPP) was selected which after mononitration in *para*- position of one phenyl ring and subsequent transformation to its Cu or Zn complexes[5] can readily enter the direct substitution of hydrogen. The VNS reaction proceeds smoothly and gives high yield when free OH or NH groups are "blocked" (*e.g.* with Me, CH_2Ph, THP, etc.). In the porphyrin system it was enough to transform two NH-centers in the core ring into metal complexes. Hence, the metalation offers very labile protection of NH groups and can be easily removed after reaction if needed.[6]

Nitro-porphyrin complexes (**3**, **4**) react with carbanions, bearing leaving groups at the carbanionic center, in *t*-BuOK/DMSO system at room temperature giving good yields of the desired products. The substitution takes place selectively in the *ortho*- position to NO_2, however bulky carbanion of lower nucleophilicity **5c** did not react. By this way we synthesized a series of new TPP derivatives substituted with α-functionalized alkyl groups, *e.g.* arylsulphonyl-methyl- (**6a**, **7a**, **b**), cyanomethyl- (**6d**, **7d**), etc.. Some of these compounds give opportunity for further transformations and might be easily converted into other derivatives, *e.g.* **6d** or **7d** to carboxylic acids and their esters.

Until now, the direct peripheral functionalization of porphyrins has been mainly restricted to electrophilic or free radical modification of the macrocycle ring.[7] In this paper we applied very useful nucleophilic methodology. By chance it was also shown that the central metal cation in the porphyrin complexes can play role as a very convenient protective group for this reaction.

Typical Procedure. *t*-BuOK/DMSO:[8] - To a stirred solution of *t*-BuOK (112 mg, 1.0 mmol) in anhydrous DMSO (3.5 mL, under argon) a solution of porphyrin derivative[9] (**3** or **4**; 0.15 mmol) and carbanion precursor (0.30 mmol) in DMSO (1.5 mL) was added dropwise *via* syringe at room temp. during *ca* 10 min. After additional 20 min of stirring the mixture was poured into 10% HCl with ice (50 mL). The precipitate was filtered, washed with water, and then dissolved in $CHCl_3$. After drying with Na_2SO_4 and evaporation

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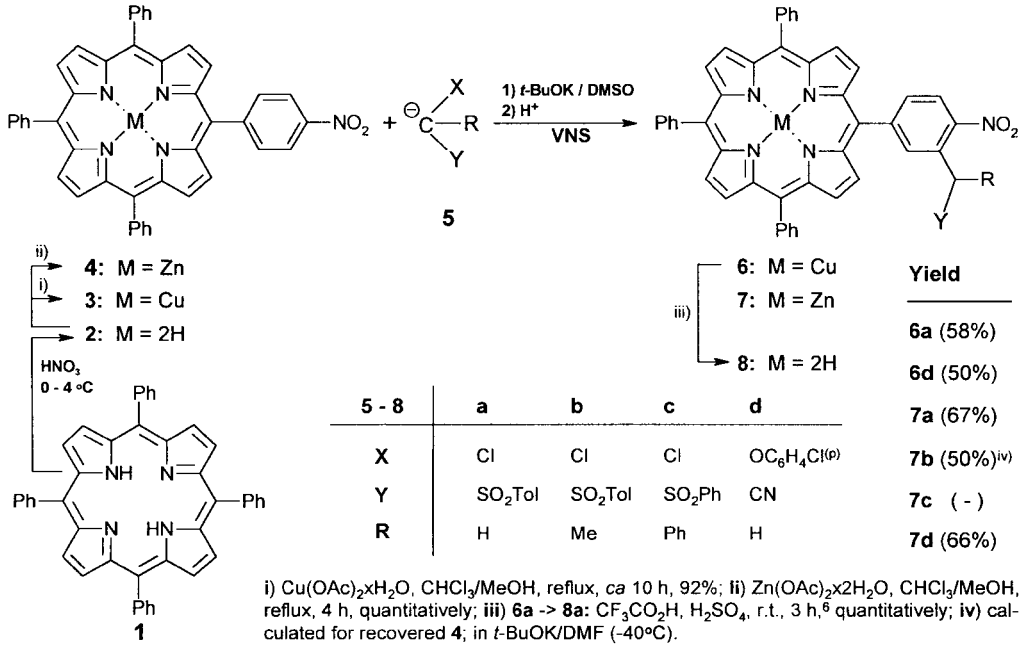

Scheme 1

of the solvent the product was isolated by column chromatography (eluent $CHCl_3$ or $CHCl_3$/ MeOH – 100 : 1). Data for **7d**: - m.p. >300 °C. - ^{1}H NMR ($CDCl_3$, 200 MHz): 9.03 (d, J = 4.7 Hz, 2H, H$^{\beta}$-pyrrole), 8.99 (s, 4H, H$^{\beta}$-pyrrole), 8.83 (d, J = 4.7 Hz, 2H, H$^{\beta}$-pyrrole), 8.60 (d, J = 8.8 Hz, 1H, H-Ar(NO_2)), 8.58 (s, 1H, H-Ar(NO_2)), 8.43 (dd , J = 8.8,1.4 Hz, 1H, H-Ar(NO_2)), 8.29-8.21 (m, 6H, H-Ph), 7.83-7.74 (m, 9H, H-Ph), 4.50 (s, 2H, CH_2CN). - UV-VIS (CH_2Cl_2), λ_{max} (lgε): 591 (3.77), 549 (4.23), 512 (3.72), 420 (5.41, Soret), 351 (4.03), 302 (4.14). MS (EI), *m/z* (% rel. int.): 764 (42), 762 (70), 760 (100) [isotopic $M^{+\cdot}$], 719 (47), 636 (12), 380 (7), 299 (12), 149 (10), 91 (10). HR-MS calcd. for $C_{46}H_{28}N_{36}O_2Zn_1$ - 760.1565, found - 760.1566.

References and Notes

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8. For bulky tertiary carbanion **5b** because of its instability at higher temperature the *t*-BuOK/DMF system (-40 °C) was used (see: Mudryk, B.; Makosza, M. *Tetrahedron* **1988**, *44*, 209).
9. Zinc 5-(4-Nitrophenyl)-10,15,20-triphenylporphyrin was prepared quantitatively from 5-(4-Nitrophenyl)-10,15,20-triphenylporphyrin[10] as usual by using saturated methanol solution of zinc acetate dihydrate in methylene chloride with refluxing for an hour. The absorption bands in UV/Vis spectroscopy show a typical metalloporphyrins (λ = 587.8, 548.2, 419.0).
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