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In two steps from simple *meso*-tetraphenylporphyrin to its derivatives exhaustively β-substituted at the 'Eastern half'

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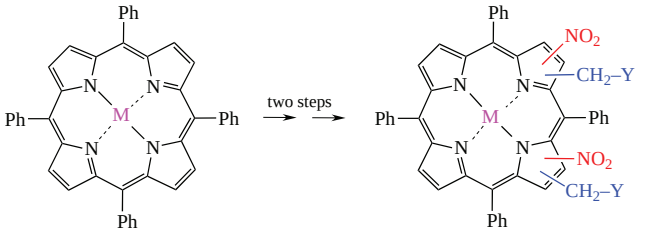
The two-step synthesis of porphyrin derivatives, exhaustively β-substituted at the 'Eastern half', starting from *meso*-tetraarylporphyrin chelates (Cu^{II}, Zn^{II}, Ni^{II}) upon their reaction with nitric acid, is described. The intermediates obtained (mainly dinitro-derivatives) in the reaction with carbanions bearing a leaving group X at the reactive centre give tetrasubstituted at the β-positions products, the ones of vicarious nucleophilic substitution of hydrogen. The products seem to be potential anticancer PDT agents, practically unavailable by other methods.



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Porphyrins are intensively studied in recent years.[1–3] These systems are present in well-known biological materials (*e.g.* chlorophyll, heme, or vitamin B_{12}) and play important roles in nature. Of significant importance is the selective functionalization of readily available porphyrins, *e.g.*, in this way the porphyrin hydrophobic moieties can be transformed into the hydrophilic ones. The compounds thus obtained, being soluble in physiological milieu, may be considered as potential photodynamic therapy agents.[4–6]

Our ongoing research, among others, is focused on the synthesis of highly functionalized porphyrins. Earlier,[7,8] we elaborated a convenient synthesis of β,β-dinitroporphyrins (and porphyrinates) utilizing electrophilic nitration with nitric acid in chloroform (Scheme 1). For zinc, copper, and nickel chelates of *meso*-tetraphenylporphyrin (*m*-TPP), usually 2,7-dinitro and 3,7-dinitro derivatives are formed as the major products; however, we have demonstrated that even all the five possible isomers could be isolated.[7(a)] These compounds seem promising for nucleophilic substitution of hydrogen. This type of substitution, so called vicarious nucleophilic substitution (VNS), is a useful tool for introduction of a variety of functional groups into nitroaromatic rings (for review concerning nitroarenes, see ref. 9).

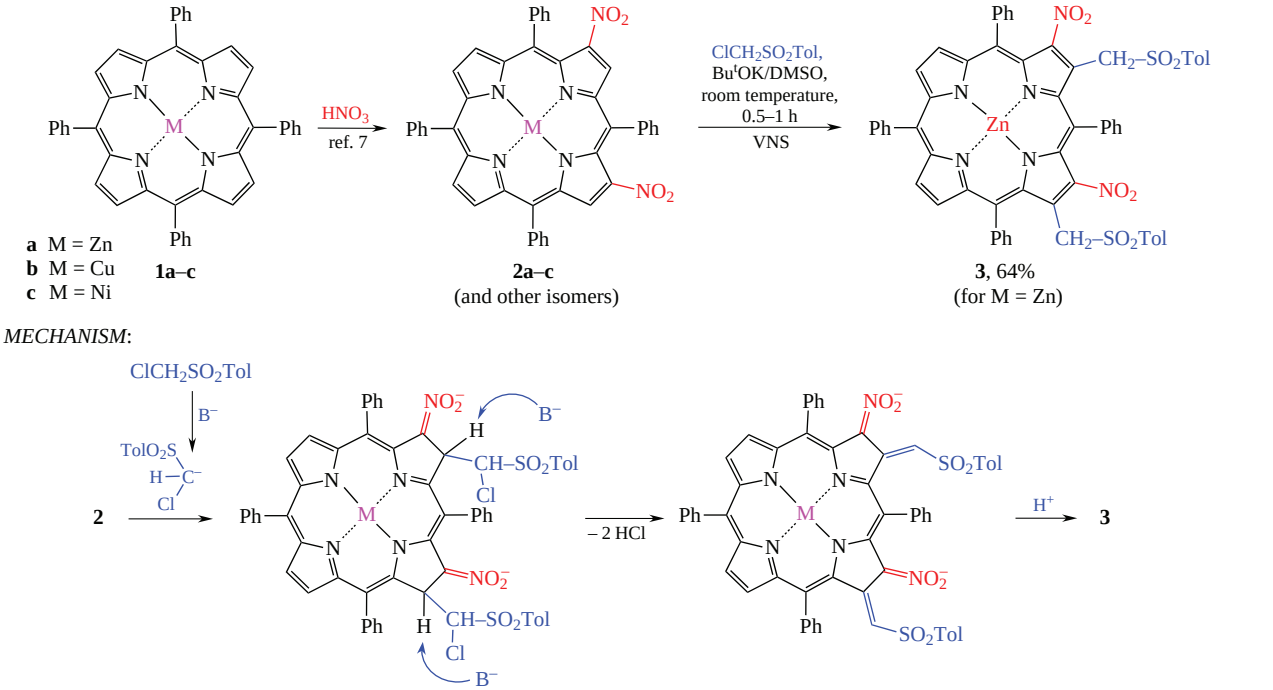
The VNS process consists in addition of carbanions, *O*-anions, or *N*-anions bearing a leaving group X at the reactive centre to nitroarenes at positions occupied by hydrogen to form σ^H-adducts that subsequently undergo base-induced β-elimination of HX to give products of nucleophilic substitution of hydrogen (see mechanism presented for porphyrins in Scheme 1; below the main reaction). The presence of each NO_2 group enables substitution of one H-atom. Some other electrophilic aromatic compounds that do not contain activating NO_2 group (heterocyclic and carbocyclic) undergo this reaction as well, *e.g.* triazines,[10,11] quinoxalines,[12] benzothiazole,[10] pteridines,[13] fused quinones,[14] cyano naphthalene derivatives,[15,16] cyano-1,6-methano[10]-annulenes,[17] *etc*.

Combination of the above two reactions (electrophilic dinitration and VNS) gives an opportunity of easy and fast synthesis of tetrasubstituted porphyrins. We applied it herein. It is worth mentioning that the selected substrates in this case could make it possible to synthesize more attractive, but at the same time, more difficult to be accessed, porphyrins exhaustively β-substituted at the 'Eastern half'.

Many attempts were undertaken in this area and there are some elegant total syntheses of such porphyrin derivatives described in the literature, however with low overall yields varying from 0.04 to *ca.* 7% (see: Battersby,[18] Jacobi,[19] or Woodward[20]). Admittedly, they had more sophisticated structures, but unfortunately they were achievable only in multi-step transformations. In our methodology, this is not the case and the preparation is very convenient.

Thus, the respective dinitro-porphyrins of type **2** (bearing nitro groups in the neighbouring pyrrole rings) enable to use this attractive and facile approach to the desired 'half-exhaustively' β-substituted porphyrins. As it was mentioned above, the preparation and isolation of β,β-dinitro intermediates were elaborated in details in our previous investigations. We have demonstrated that even all of the five possible isomers could be isolated.[7(a)] An important point is the fact that primary substrate for this synthesis, *m*-TPP, is commercially available. If needed, it can be also easily synthesized in multi-gram scale in laboratory[21–23] and converted quantitatively into complexes that were used here for preparation of dinitro-chelates **2**. They would react readily with carbanions.

For example, zinc dinitroporphyrinate **2a** attaches carbanion of chloromethyl *p*-tolyl sulfone followed by base-induced β-elimination to give VNS product bearing new group at the position neighbouring to NO_2. Similarly, the substitution takes place at the position next to the second nitro group affording thus the target product **3** in good yield (64%). The reaction is easy to carry out, proceeds very fast, and is high yielding. The structure



Scheme 1

of the carbanion can be designed any way one can want, enabling access to a variety of substitution patterns on two neighbouring pyrrole rings in the macrocyclic skeleton (see examples **3**–**7** in Scheme 1). Also the mutual orientation of NO_2 groups can be different. Furthermore, various metal cations (Zn^{2+}, Cu^{2+}, Ni^{2+}) can be coordinated by the porphyrin core ring. This gives finally an opportunity for preparation of broad spectrum of the title products.

Herein, we have demonstrated this approach with four examples.† In the reaction presented above we achieved a yield of 64%. The yields of other products were also good and even higher. The use of *p*-chlorophenoxyacetonitrile (*p*-$ClC_6H_4OCH_2CN$) with dinitroporphyrinate **2a** led to the corresponding product **4** with the same yield of 64%, while the reaction of copper complex of 3,7-dinitro-5,10,15,20-tetraphenylporphyrin with chloromethyl *p*-tolyl sulfone allowed us to obtain product **5** in higher yield of 76%. In the latter case small amounts (11%) of trisubstituted by-product **8** were also observed. This increased the total yield of the reaction products up to 87%.

Finally, nickel chelate **2c** reacting with carbanion of chloromethyl phenyl sulfone ($ClCH_2SO_2Ph$) gave product **6** (64%). This methodology has been immediately used in our group in other projects.[24] For example, some initial studies allowed us to obtain porphyrins tetrasubstituted with nitrogen-containing

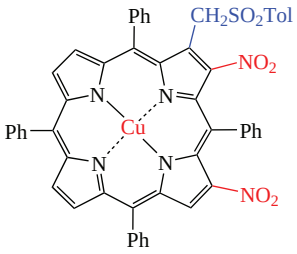
† All reactions were carried out under argon in light-shielded flasks equipped with a septum. Preparation of starting dinitro-5,10,15,20-tetraphenylporphyrinates was described previously.[7,8] Carbanion precursors were obtained according to known procedures (all the references have been collected and cited in our previous paper[28]). All the products were isolated by column chromatography (silica gel, 230–400 mesh; Merck AG).

[3,7-Dinitro-2,8-bis(p-tolylsulfonylmethyl)-5,10,15,20-tetraphenylporphyrinato]copper(II) (**5**) *(general procedure).* To a stirred solution of ButOK (58 mg, 0.52 mmol) in anhydrous DMSO (6 ml) a mixture of copper(II) 3,7-dinitro-5,10,15,20-tetraphenylporphyrinate (44 mg, 0.057 mmol) and chloromethyl *p*-tolyl sulfone (50 mg, 0.24 mmol) in anhydrous DMSO (6 ml) was syringed for 5 min at room temperature. The reaction was continued for 1 h, and then the mixture was poured into HCl containing ice (3% aq., 150 ml). The precipitate was filtered off, washed with water (300 ml), and dried. The crude product was dissolved in small amount of $CHCl_3$ and purified using column chromatography (eluent: $CHCl_3$/MeOH; 100 : 1) to give 47.7 mg of the title product **5** (76%) and [3,7-dinitro-2-(*p*-tolylsulfonylmethyl)-5,10,15,20-tetraphenylporphyrinato]copper(II) (**8**; 11%).

Other reactions, modifications.

Reaction of (2,7-dinitro-5,10,15,20-tetraphenylporphyrinato)zinc(II) (**2a**) *with chloromethyl p-tolyl sulfone.* Compound **2a** (49.8 mg, 0.065 mmol) and chloromethyl *p*-tolyl sulfone (54 mg, 0.26 mmol) in DMSO (8 ml) were added to a stirred solution of ButOK (74 mg, 0.66 mmol) in anhydrous DMSO (8 ml); after *ca.* 30 min additional portion of ButOK (74 mg, 0.66 mmol) in DMSO (1 ml) was slowly syringed followed by addition of more chloromethyl *p*-tolyl sulfone (40 mg, 0.20 mmol); eluent for chromatography: $CHCl_3$, then $CHCl_3$/MeOH (100 : 1). Yield of product **3** was 46.0 mg (64%).

Reaction of (2,7-dinitro-5,10,15,20-tetraphenylporphyrinato)zinc(II) (**2a**) *with p-chlorophenoxyacetonitrile.* Compound **2a** (50.4 mg, 0.066 mmol) and *p*-chlorophenoxyacetonitrile (45 mg, 0.27 mmol) in anhydrous DMSO (6 ml) were added to a stirred solution of ButOK (75 mg, 0.67 mmol) in DMSO (8 ml); after 1 and 2 h the additional portions of ButOK (60 mg, 0.53 mmol) in DMSO (1 ml) were syringed



8, 11%

groups (*e.g.* **7**[24]) that are sought in many areas of porphyrin chemistry. We confirmed the structures of products obtained using standard spectroscopic methods: ^{1}H NMR (except for the paramagnetic chelates of copper), UV/VIS, MS, and HR-MS.‡

The new groups introduced into porphyrin scaffold, *e.g.* CN, allow a broad spectrum of further transformations (hydrolysis to amides and carboxylic acids, reduction to aminomethyl derivatives, subsequent reactions of amines, a variety of reactions with organometallic reagents, *etc.*).[25] Finally, it is worth mentioning that NO_2 group also gives plenty of synthetic possibilities.

In summary, the use of two-step approach described in this communication leads to useful target molecules, namely exhaustively β-substituted porphyrins at the *Eastern half*. This easy and fast preparation is very convenient. A broad spectrum of carbanions that can be used in VNS step[9] allows synthesizing numerous differently designed porphyrin-like moieties. They are valuable materials themselves and versatile intermediates for subsequent transformations into compounds of a high degree of complexity – ready to use in many areas of chemistry and related fields.[26,27] A number of them are potential sensitizers for anticancer photodynamic therapy.[4–6]

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.021.

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followed by addition of two portions of *p*-chlorophenoxyacetonitrile (36 mg, 0.21 mmol) in DMSO (1 ml), and the reaction was continued for the next 30 min; eluent for chromatography: $CHCl_3$, then $CHCl_3$/MeOH (100 : 1). Yield of product **4** was 35.7 mg (64%).

Reaction of (2,7-dinitro-5,10,15,20-tetraphenylporphyrinato)nickel(II) (**2c**) *with chloromethyl phenyl sulfone*. Compound **2c** (34.4 mg, 0.045 mmol) and $ClCH_2SO_2Ph$ (45.6 mg, 0.24 mmol) dissolved in DMSO (12 ml) were added to Bu^{t}OK similarly to the above procedures (the substrates dissolved fully after ~1 h). After 15 min, an additional portion of Bu^{t}OK (26 mg, 0.23 mmol) in DMSO (1 ml) was syringed. Final chromatography ($CHCl_3$/*n*-hexane – 3 : 1, then $CHCl_3$/MeOH – 100 : 1) afforded 2.4 mg of recovered substrate **2c** and 28.5 mg (64%) of the title product **6**.

‡ *Characterization of the products. [2,7-Dinitro-3,8-bis(p-tolylsulfonylmethyl)-5,10,15,20-tetraphenylporphyrinato]zinc(II)* (**3**), mp > 300 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.63–8.47 (m, 4H, H$^\beta$-pyrrole), 8.28–8.10 (m, 8H, H–Ph), 7.81–7.65 (m, 12H, 8H of H–Ph and 4H of H–Tol), 7.10–6.93 (m, 8H, 4H of H–Ph and 4H of H–Tol), 4.64 (br. s, 4H, 2×CH_2), 2.30 (s, 6H, 2×CH_3). UV/VIS ($CHCl_3$), λ_{max} (logε): 657.0 (3.92), 583.0 (3.75), 453.5 (5.00, Soret band), 346 nm (4.39). MS (FD), *m/z* (%): 1108 (19), 1107 (28), 1106 (76), 1105 (65), 1104 (89), 1103 (80), 1102 (100) [isotope M$^{+\cdot}$]. HR-MS (FD), *m/z*: 1102.1843 (M$^+$) (calc. for $C_{60}H_{42}N_6O_8S_2Zn$, *m/z*: 1102.1797). The molecular formula was also confirmed by comparing the theoretical and experimental isotope patterns for the M$^+$ ion ($C_{60}H_{42}N_6O_8S_2Zn$); it was found to be identical within the experimental error limits.

[2,7-Dinitro-3,8-bis(cyanomethyl)-5,10,15,20-tetraphenylporphyrinato]zinc(II) (**4**), mp > 300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.87–8.67 (m, 4H, H$^\beta$-pyrrole), 8.21–7.42 (m, 20H, H–Ph), 3.54 (s, 4H, 2×CH_2). UV/VIS ($CHCl_3$), λ_{max} (logε): 621.0 (3.78), 572.5 (3.80), 441.0 (5.06, Soret band), 326 nm (4.31). MS (FD), *m/z* (%): 1688 ([2×M]$^{+\cdot}$), 850 (5), 849 (14), 848 (35), 847 (22), 846 (45), 845 (36), 844 (50) [isotope M$^{+\cdot}$], 788 (100, M – CH_2CN – O), 732 (91, M – 2×[CH_2CN – O]). HR-MS (FD), *m/z*: 844.1489 (M$^+$) (calc. for $C_{48}H_{28}N_8O_4Zn$, *m/z*: 844.1525). The molecular formula was also confirmed by comparing the theoretical and experimental isotope patterns for the M$^+$ ion ($C_{48}H_{28}N_8O_4Zn$); it was found to be identical within the experimental error limits.

[3,7-Dinitro-2,8-bis(p-tolylsulfonylmethyl)-5,10,15,20-tetraphenylporphyrinato]copper(II) (**5**), mp > 300 °C. UV/VIS ($CHCl_3$), λ_{max} (logε): 645.1 (3.89), 591.1 (3.92), 471.4 (4.89, Soret band), 408.3 (4.42), 314.4 nm (4.28). MS (FD), *m/z* (%): 1106 (6), 1105 (20), 1104 (42), 1103 (76), 1102 (67), 1101 (100) [isotope M$^{+\cdot}$]. HR-MS (FD), *m/z*: 1101.1766 (M$^+$) (calc. for $C_{60}H_{42}N_6O_8S_2Cu$, *m/z*: 1101.1802). The molecular formula was also confirmed by comparing the theoretical and experimental isotope patterns for the M$^+$ ion ($C_{60}H_{42}N_6O_8S_2Cu$); it was found to be identical within the experimental error limits.

[2,7-Dinitro-3,8-bis(phenylsulfonylmethyl)-5,10,15,20-tetraphenylporphyrinato]nickel(II) (**6**), mp > 300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.59 (d, *J* = 5.1 Hz, 1H, H$^\beta$-pyrrole), 8.53 (d, *J* = 5.1 Hz, 1H, H$^\beta$-pyrrole), 8.45 (d, *J* = 5.1 Hz, 1H, H$^\beta$-pyrrole), 8.36 (d, *J* = 5.1 Hz, 1H, H$^\beta$-pyrrole), 8.11–7.61 (m, 20H, H–Ph^{meso}), 7.27–7.15 (m, 2H, H–Ph), 7.02–6.84 (m, 8H, H–Ph), 4.55 (br. s, 2H, CH_2), 4.38 (br. s, 2H, CH_2). UV/VIS ($CHCl_3$), λ_{max} (logε): 618.1 (3.95), 577.1 (4.09), 472.6 (5.00, Soret band), 403.2 (4.42), 347.6 nm (4.33). MS (FD), *m/z* (%): 1073 (10), 1072 (21), 1071 (40), 1070 (71), 1069 (72), 1068 (100) [isotope M$^{+\cdot}$]. HR-MS (FD), *m/z*: 1068.1500 (M$^+$) (calc. for $C_{58}H_{38}N_6O_8S_2Ni$, *m/z*: 1068.1546). The molecular formula was also confirmed by comparing the theoretical and experimental isotope patterns for the M$^+$ ion ($C_{58}H_{38}N_6O_8S_2Ni$); it was found to be identical within the experimental error limits.

[3,7-Dinitro-2-(p-tolylsulfonylmethyl)-5,10,15,20-tetraphenylporphyrinato]copper(II) (**8**), mp > 300 °C. UV/VIS ($CHCl_3$), λ_{max} (logε): 623.6 (3.82), 574.9 (3.83), 456.6 (4.86, Soret band), 399.7 (4.46), 325.6 nm (4.57). MS (FD), *m/z* (%): 938 (3), 937 (12), 936 (35), 935 (67), 934 (61), 933 (100) [isotope M$^{+\cdot}$]. LR-MS (FD), *m/z*: 933.10 (M$^+$) (calc. for $C_{52}H_{34}N_6O_6SCu$, *m/z*: 933.16). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the M$^+$ ion ($C_{52}H_{34}N_6O_6SCu$); it was found to be identical within the experimental error limits.

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