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Two-steps synthesis of hexasubstituted porphyrins at the β-pyrrolic positions

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Abstract: *meso*-Tetraarylporphyrin chelates are easily available from parent porphyrins. Their reactions with nitric acid (yellow fuming HNO_3, d = 1.52), under optimized conditions in $CHCl_3$ at room temperature, can be carried out selectively, thus giving mainly β,β,β-trinitro-substituted moieties (usually two or three isomers of the above complexes). These intermediates (Cu^{2+}-derivatives; obtained in overall yields of up to 38%), upon the reaction with carbanions bearing a leaving group X at the reactive centre afforded the target products, the ones of *vicarious nucleophilic substitution of hydrogen* (VNS). This approach allows the synthesis of porphyrin derivatives exhaustively β-substituted in three pyrrole rings (in yields of up to 69%), starting from a simple *meso*-tetraarylporphyrin complexes. The above two-steps procedure including very attractive VNS reaction gives hydrophilic or amphiphilic moieties that seem to be potential agents in anticancer photodynamic therapy (PDT), practically unavailable by alternative methods.

Keywords: Porphyrin complexes; β-derivatization; carbanions; vicarious nucleophilic substitution; nitro group; photodynamic therapy.

1. Introduction

Porphyrins are intensively studied in the past decades as they can be used as valuable materials in many areas.[1] In this context, it needs to be highlighted that β-nitro-porphyrins (and derivatives), due to their interesting properties, are in the spotlight. For example, electron-withdrawing β-NO_2 groups affect the electronic structure of porphyrin chelates.[2] A blue shift of the Soret band and red shift of the peaks around 630 nm are observed with an increase in the electron-withdrawing effect of these groups. The electronic absorption bands shift to the near infrared region cause that these systems may find use in photodynamic therapy[3-5] or dye-sensitized solar cells.[6-10] They could be also considered as the most suitable models for mimicking the key roles of naturally occurring dyes in vital processes. Thus, synthesis of β-substituted porphyrins is described in many papers. Some of them regarding nucleophilic β-derivatization come from our laboratory.[11-16] This type of approach has also been investigated by other groups.[17-21]

In our ongoing research we are trying to functionalize the β,β,β-trinitroporphyrin derivatives *via* nucleophilic substitution reactions to prepare highly decorated products: penta- and hexa-substituted ones at the β-positions. It was planned to introduce carbon substituents into unoccupied sites,

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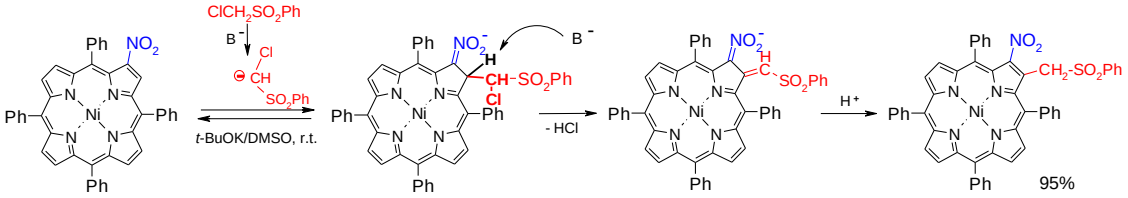
neighbouring the nitro groups. Thus, the previously synthesized trinitro isomers have been reacted with the respective carbanions.

Excellent tool to realize this task is the *vicarious nucleophilic substitution of hydrogen* process (VNS).[22,23] Its mechanism is presented below using an example reaction of (2-nitro-5,10,15,20-tetraphenylporphyrinato)nickel(II) with chloromethyl phenyl sulphone, recently published in the literature (Scheme 1).[14] VNS consists of addition of carbanion (also *O*-anions and *N*-anions) bearing a leaving group X at the reactive centre to nitroarene (and other electrophilic arenes and heteroarenes) at positions occupied by hydrogen to form σ^H-adduct(s) that are subsequently followed by base induced β-elimination of HX to give product(s) of nucleophilic substitution of hydrogen (see below).



Scheme 1. General scheme of the vicarious nucleophilic substitution of hydrogen in porphyrin system.

VNS is a very powerful reaction for derivatization of electrophilic aromatic and heteroaromatic systems. It is a process of general character and its application for porphyrin functionalization is known for more than two decades.[23] This approach was used earlier in our laboratory for preparation of di-, tri-, and tetrasubstituted porphyrins at the β-positions, affording the respective products with good or very good yield.[11-16] Substrates for this type of nucleophilic functionalization were β-nitro- and β,β-dinitro-porphyrins described in several publications.[24-33] In the last year we also published a paper dealing with the synthesis of β,β,β-trinitro-isomers[34] that can be used (by applying VNS reaction) for transformation to obtain hexasubstituted porphyrinyl macrocycles. Such preliminary attempts are described in this communication.

2. Experimental

2.1. Chemical Materials and Apparatus

^{1}H NMR spectra were recorded with a Varian MR-400 spectrometer, operating at 400 MHz. Coupling constants *J* are expressed in hertz [Hz]. Mass spectra were measured with a GCT Premier (Waters, FD-TOF) spectrometer (FD method) and MARINER (PerSeptive Biosystems, ESI-TOF) spectrometer (ESI method); *m/z* intensity values for peaks are given as a % of relative intensity. UV-vis spectra were measured with a Metertech SP-8001 spectrophotometer. TLC analysis was performed on aluminium foil plates pre-coated with silica gel (60 F-254, Merck AG). All the products were isolated by column chromatography (silica gel, 230-400 mesh; Merck AG). Some compounds were rechromatographed on preparative TLC plates (silica gel, 60 F-254, 2 mm and 0.5 mm; Merck AG). Molecular formulas of new compounds were confirmed by HR-MS (ESI method), and by comparing the isotope molecular patterns (theoretical and experimental).

All the reactions were carried out in light-shielded flasks equipped with a septum. Preparation of starting β,β,β-trinitro-5,10,15,20-tetraphenylporphyrinate **1** was described in the earlier literature.[34] Carbanion precursors were also obtained according to known procedures: α-chloromethyl *para*-tolyl sulphone (**2a**),[35] α-bromomethyl *para*-tolyl sulphone (**2b**),[36] and α-chloromethyl phenyl sulphone (**2c**).[36]

2.2. Chemistry

*2.2.1. Reaction of 3,7,12-trinitro-5,10,15,20-tetraphenylporphyrin–copper(II) (**1**) with chloromethyl para-tolyl sulphone (**2a**) and bromomethyl para-tolyl sulphone (**2b**)*

In a round-bottomed, light-shielded flask 3,7,12-trinitro-5,10,15,20-tetraphenylporphyrin–copper(II) (**1**; 65 mg, 0.080 mmol) was dissolved in anhydrous DMSO (30 mL). The mixture was stirred for *ca* 30 min due to solubility problem of porphyrinate. To this mixture carbanion precursor (**2a** – 225

mg, 1.10 mmol; or **2b** – 317 mg, 1.27 mmol) was added in one portion and the solution obtained was dropped *via* syringe (under argon) to a stirred *t*-BuOK (230 mg, 2.05 mmol) in anhydrous DMSO (10 mL) over a period of *ca* 5 min. After the next 5 min of stirring the second portion of CH-acid (**2a**, 97 mg, 0.47 mmol; or **2b**, 140 mg, 0.56 mmol) was added followed by addition of the next portion of *t*-BuOK (101 mg, 0.90 mmol).

The reaction was continued at room temperature for the next 20 min. Then, the mixture was poured into 3% NH_4Cl containing ice (400 mL). The precipitate was filtered, washed with water (200 mL), and then dissolved in $CHCl_3$ (45 mL). After drying with anhydrous $MgSO_4$ and evaporation of the solvent, the products were isolated: (a) for **2a**: column chromatography (eluent: $CHCl_3$/MeOH, 100:1), to give a mixture of **4-6** and [3,7,12-trinitro-2,8,13-tris{(toluene-4-sulphonyl)methyl}-5,10,15,20-tetraphenylporphyrinato]copper(II) (**3**; 34.0 mg, 32%); the above mixture **4-6** was separated on preparative TLC ($CHCl_3$/MeOH, 100:1) to give three pentasubstituted isomers respectively: product R_f=0.40 (18.4 mg, 20%), product R_f=0.35 (6.4 mg, 7%), and product R_f=0.28 (20.2 mg, 22%); (b) for 2b: the products were isolated on preparative TLC (eluent: $CHCl_3$/MeOH, 100:1) to give respectively: **3** (7.4 mg, 7%) and a mixture of β,β,β-trinitro-β,β-bis[(toluene-4-sulphonyl)methyl]-5,10,15,20-tetraphenylporphyrins–copper(II) **4-6** (47.7 mg, 52%).

*[3,7,12-Trinitro-2,8,13-tris{(toluene-4-sulphonyl)methyl}-5,10,15,20-tetraphenylporphyrinato]copper(II) (**3**)*: R_f=0.24 [$CHCl_3$/MeOH (50:1)]. mp>300ºC. UV-vis ($CHCl_3$): λ_{max}, nm (log ε), 667 (3.88), 610 (3.83), 482.5 (4.80, Soret), 346 (4.25). MS (ESI): *m/z* (% rel. int.) 2659 (3), 2658 (5), 2657 (7), 2656 (11), 2655 (13), 2654 (13), 2653 (13), 2652 (8), 2651 (5) (isotope $[2M+Na]^+$); 1342 (16), 1341 (34), 1340 (61), 1339 (100), 1338 (81), 1337 (96) (isotope $[M+Na]^+$). HR-MS (ESI): *m/z* 1337.1812 (calcd. for $C_{68}H_{49}N_7O_{12}S_3CuNa$ $[(M+Na)^+]$ 1337.1795).

Product R_f=0.40: R_f=0.40 [$CHCl_3$/MeOH (50:1)]. mp>300ºC. UV-vis ($CHCl_3$): λ_{max}, nm (log ε), 652.5 (3.97), 598 (3.97), 471.5 (4.96, Soret), 345 (4.33). MS (ESI): *m/z* (% rel. int.) 2323 (5), 2322 (8), 2321 (13), 2320 (18), 2319 (26), 2318 (28), 2317 (30), 2316 (19), 2315 (14) (isotope $[2M+Na]^+$); 1174 (12), 1173 (26), 1172 (56), 1171 (90), 1170 (79), 1169 (100) (isotope $[M+Na]^+$). HR-MS (ESI): *m/z* 1169.1534 (calcd. for $C_{60}H_{41}N_7O_{10}S_2CuNa$ $[(M+Na)^+]$ 1169.1550). The molecular formula was also confirmed by comparing the theoretical and experimental isotope pattern for the $[M+Na]^+$ ion ($C_{60}H_{41}N_7O_{10}S_2CuNa$; MS (ESI)) – it was found to be identical within the experimental error limits.

Product R_f=0.35: R_f=0.35 [$CHCl_3$/MeOH (50:1)]. mp>300ºC. UV-vis ($CHCl_3$): λ_{max}, nm (log ε), 651 (3.95), 600.5 (4.00), 477 (4.91, Soret), 345 (4.34). MS (ESI): *m/z* (% rel. int.): 2323 (6), 2322 (9), 2321 (14), 2320 (22), 2319 (31), 2318 (33), 2317 (33), 2316 (22), 2315 (16) (isotope $[2M+Na]^+$); 1174 (14), 1173 (28), 1172 (58), 1171 (91), 1170 (80), 1169 (100) (isotope $[M+Na]^+$). HR-MS (ESI): *m/z* 1169.1534 (calcd. for $C_{60}H_{41}N_7O_{10}S_2CuNa$ $[(M+Na)^+]$ 1169.1550). The molecular formula was also confirmed by comparing the theoretical and experimental isotope pattern for the $[M+Na]^+$ ion ($C_{60}H_{41}N_7O_{10}S_2CuNa$; MS (ESI)) – it was found to be identical within the experimental error limits.

Product R_f=0.28: R_f=0.28 [$CHCl_3$/MeOH (50:1)]. mp>300ºC. UV-vis ($CHCl_3$): λ_{max}, nm (log ε), 657 (3.63), 593 (3.48), 463 (4.57, Soret), 349.5 (3.96), 316 (4.06). MS (ESI): *m/z* (% rel. int.) 2323 (4), 2322 (6), 2321 (9), 2320 (13), 2319 (15), 2318 (19), 2317 (19), 2316 (13), 2315 (10) (isotope $[2M+Na]^+$); 1173 (28), 1172 (57), 1171 (92), 1170 (79), 1169 (100) (isotope $[M+Na]^+$). HR-MS (ESI): *m/z* 1169.1534 (calcd. for $C_{60}H_{41}N_7O_{10}S_2CuNa$ $[(M+Na)^+]$ 1169.1550). The molecular formula was also confirmed by comparing the theoretical and experimental isotope pattern for the $[M+Na]^+$ ion ($C_{60}H_{41}N_7O_{10}S_2CuNa$; MS (ESI)) – it was found to be identical within the experimental error limits.

*2.2.2. Reaction of 3,7,12-trinitro-5,10,15,20-tetraphenylporphyrin-copper(II) (**1**) with chloromethyl phenyl sulphone (**2c**)*

In a round-bottomed, light-shielded flask 3,7,12-trinitro-5,10,15,20-tetraphenylporphyrin–copper(II) (**1**; 60 mg, 0.074 mmol) in anhydrous DMSO (30 mL) was dissolved. The mixture was stirred for *ca* 30 min due to solubility problem of porphyrinate. To this mixture carbanion precursor **2c** (210

mg, 1.10 mmol) was added in one portion and the solution obtained was dropped *via* syringe (under argon) to a stirred *t*-BuOK (225 mg, 2.00 mmol) in anhydrous DMSO (10 mL) over a period of *ca* 5 min. After 5 min of stirring the second portion of CH-acid (**2c**, 88 mg, 0.46 mmol) was added followed by dropwise addition of the next portion of *t*-BuOK (120 mg, 1.07 mmol). The reaction was continued at room temperature for *ca* 20 min. Then, the mixture was poured into 3% NH_4Cl containing ice (400 mL). The precipitate was filtered off, washed with water (200 mL), and then dissolved in $CHCl_3$ (45 mL). After drying with anhydrous $MgSO_4$ and evaporation of the solvent, the product was isolated by column chromatography (eluent: $CHCl_3$, then $CHCl_3$/MeOH, 100:1). It was rechromatographed on preparative TLC (eluent: $CHCl_3$/MeOH, 100:1) to give [3,7,12-trinitro-2,8,13-tris{(phenylsulphonyl)-methyl}-5,10,15,20-tetraphenylporphyrinato]copper(II) (**7**; 64.6 mg, 69%).
Another experiment:
Modifications: *t*-BuOK (540 mg, 4.81 mmol) in anhydrous DMSO (20 mL) was added to the solution of porphyrinate **1** and CH-acid **2c** – in reverse order to the previous reaction. The following products were obtained: (a) [3,7,12-trinitro-2,8,13-tris{(phenylsulphonyl)methyl}-5,10,15,20-tetraphenyl-porphyrinato]copper(II) (**7**) – 52.8 mg, 56%; (b) [3,7,12-trinitro-β,β-bis{(phenylsulphonyl)methyl}-5,10,15,20-tetraphenylporphyrinato]copper(II) (**8**)*) – 5.2 mg, 6%; (c) [3,7,12-trinitro-β-{(phenylsulphonyl)methyl}-5,10,15,20-tetraphenylporphyrinato]copper(II) (**9**)**) – 22.4 mg, 31%.
*) one of the three possible pentasubstituted isomers (the structure was not assigned)
**) one of the three possible tetrasubstituted isomers (the structure was not assigned)

*[3,7,12-Trinitro-2,8,13-tris{(phenylsulphonyl)methyl}-5,10,15,20-tetraphenylporphyrinato]copper(II) (**7**)*: mp>300ºC. UV-vis ($CHCl_3$): λ_{max}, nm (log ε), 672.5 (3.98), 611 (3.91), 485.5 (4.83, Soret), 349.5 (4.31). MS (FD): *m/z* (% rel. int.) 1279 (8), 1278 (12), 1277 (9), 1276 (26), 1275 (62), 1274 (100), 1273 (68), 1272 (96) (isotope M^+). HR-MS (ESI): *m/z* 1272.1415 (calcd. for $C_{65}H_{43}N_7O_{12}S_3Cu$ [M^+] 1272.1428). The molecular formula was also confirmed by comparing the theoretical and experimental isotope pattern for the M^+ ion ($C_{65}H_{43}N_7O_{12}S_3Cu$; MS (ESI)) – it was found to be identical within the experimental error limits.

*[3,7,12-Trinitro-β,β-bis{(phenylsulphonyl)methyl}-5,10,15,20-tetraphenylporphyrinato]copper(II) (**8**)*: mp>300ºC. UV-vis ($CHCl_3$): λ_{max}, nm, 646, 589, 466 (Soret). MS (ESI(-)): *m/z* (% rel. int.) 1158 (15), 1157 (29), 1156 (36), 1155 (64), 1154 (42), 1153 (60) (isotope $[M+Cl]^-$); 1121 (21), 1120 (54), 1119 (85), 1118 (78), 1117 (100) (isotope $[M–H]^-$). HR-MS (ESI): *m/z* 1117.1256 (calcd. for $C_{58}H_{36}N_7O_{10}S_2Cu$ [$(M–H)^-$] 1117.1261).

*[3,7,12-Trinitro-β-{(phenylsulphonyl)methyl}-5,10,15,20-tetraphenylporphyrinato]copper(II) (**9**)*: mp>300ºC. UV-vis ($CHCl_3$): λ_{max}, nm (log ε), 641 (3.45), 589 (3.36), 457 (4.43, Soret), 329 (3.75). MS (ESI(-)): *m/z* (% rel. int.) 1004 (13), 1003 (32), 1002 (53), 1001 (90), 1000 (59), 999 (100) (isotope $[M+Cl]^-$); 968 (8), 967 (20), 966 (32), 965 (48), 964 (49), 963 (52) (isotope $[M–H]^-$). MS (ESI(+)): *m/z* (% rel. int.) 991 (13), 990 (32), 989 (67), 988 (62), 987 (100) (isotope $[M+Na]^+$). HR-MS (ESI): *m/z* 999.0917 (calcd. for $C_{51}H_{31}N_7O_8SClCu$ [$(M+Cl)^-$] 999.0939).

2.2.3. Demetallation of copper(II)–complexes of hexasubstituted products

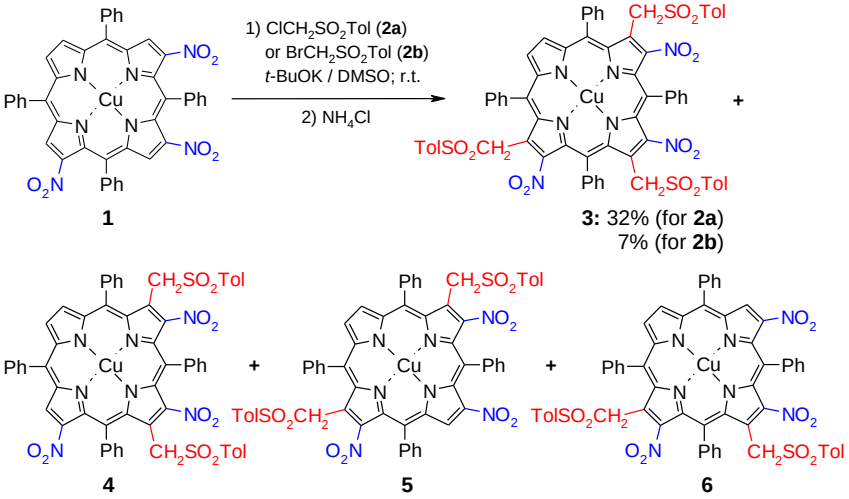
In a round-bottomed flask (20 mL), to the corresponding copper(II)–porphyrinate (**3**: 33 mg or **7**: 32 mg; 0.025 mmol) concentrated H_2SO_4 (95%; 0.6 mL) was added followed by dropwise addition of TFA (3 mL). The mixture was stirred under argon at room temperature during *ca* 20 min. Then, it was poured into water (30 mL) and extracted with $CHCl_3$ (3×30 mL). The combined organic layers were washed with water (3×100 mL) and dried over anhydrous $MgSO_4$/Na_2CO_3. The solvent was evaporated to dryness. The residue was subjected to column chromatography using a mixture of $CHCl_3$/CH_3OH (100:1) as eluent, and then it was rechromatographed on preparative TLC (eluent: $CHCl_3$/MeOH, 100:1) to give free-base porphyrin **10** (19.4 mg, 62%) or **11** (21.8 mg, 72%).
*3,7,12-Trinitro-2,8,13-tris[(toluene-4-sulphonyl)methyl]-5,10,15,20-tetraphenylporphyrin (**10**)*: mp>300ºC. UV-vis ($CHCl_3$): λ_{max}, nm (log ε), 650 (3.52), 584 (3.45), 480 (4.70, Soret), 362 (4.08). ^1H NMR ($CDCl_3$, 400 MHz): δ, ppm, 8.69 and 8.68 (AB, J = 5.3 Hz, 2H, H^β-pyrrole), 8.34–8.02 (m, 8H,

H-Ph), 7.98–7.62 (m, 12H, H-Ph), 6.91 (apparent d, J = 8.4 Hz, 2H, H-Tol), 6.83 (apparent d, J = 8.0 Hz, 2H, H-Tol), 6.79–6.68 (m, 8H, H-Tol), 5.12–4.90 (m, 6H, 3×CH_2), 2.21 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), NH – undetected. MS (ESI(+)): *m/z* (% rel. int.) 1281 (2), 1280 (6), 1279 (15), 1278 (37), 1277 (69), 1276 (84) (isotope $[M+Na]^+$); 1259 (2), 1258 (6), 1257 (17), 1256 (43), 1255 (77), 1254 (100) (isotope $[M+H]^+$). MS (ESI(-)): *m/z* (% rel. int.) 1257 (1), 1256 (5), 1255 (15), 1254 (39), 1253 (76), 1252 (100) (isotope $[M–H]^–$). The molecular formula was confirmed by comparing the theoretical and experimental isotope pattern for the $[M+H]^+$ ion ($C_{68}H_{52}N_7O_{12}S_3$; MS (ESI)) – it was found to be identical within the experimental error limits.

3,7,12-Trinitro-2,8,13-tris[(phenylsulphonyl)methyl]-5,10,15,20-tetraphenylporphyrin ***(11)***: mp>300ºC. UV-vis ($CHCl_3$): λ_{max}, nm (log ε), 658 (3.68), 592 (3.49), 483 (4.81, Soret), 358 (4.19). ^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm, 8.75 and 8.73 (AB, J = 5.2 Hz, 2H, H^β-pyrrole), 8.38–8.12 (m, 8H, H-Ph), 7.96–7.54 (m, 12H, H-Ph), 7.24–6.52 (m, 15H, H-Ph), 5.18–4.90 (m, 6H, 3×CH_2), NH – undetected. MS (ESI(+)): *m/z* (% rel. int.) 1238 (1), 1237 (5), 1236 (10), 1235 (18), 1234 (23) (isotope $[M+Na]^+$); 1217 (2), 1216 (6), 1215 (16), 1214 (39), 1213 (73), 1212 (100) (isotope $[M+H]^+$). MS (ESI (-)): *m/z* (% rel. int.) 1215 (1), 1214 (5), 1213 (13), 1212 (34), 1211 (72), 1210 (100) (isotope $[M–H]^–$). The molecular formula was confirmed by comparing the theoretical and experimental isotope pattern for the $[M+H]^+$ ion ($C_{65}H_{46}N_7O_{12}S_3$; MS (ESI)) – it was found to be identical within the experimental error limits.

3. Results and Discussion

(3,7,12-Trinitro-5,10,15,20-tetraphenylporphyrinato)copper(II) (**1**) was selected to illustrate the synthesis of highly decorated porphyrins at the β-positions. This substrate is now easily available.[34] In the first experiment, chloromethyl *para*-tolyl sulphone (**2a**) was reacted in DMSO with Cu(II)-complex **1** in the presence of *t*-BuOK. Carbanion generated from the above CH-acid, bearing good leaving group at the reactive centre, is a species of moderate nucleophilicity. However, it can effectively attack any position in the porphyrinate ring neighbouring the NO_2 group. Elimination of HCl with *tert*-butoxide anion that plays a role of the base led to the anionic form of the product (see VNS mechanism presented in Scheme 1). The double repetition of this reaction scheme followed by protonation resulted in the formation of hexasubstituted moieties at the rim of the porphyrin core ring (Scheme 2). It is worth noting that we are dealing with only a two-step procedure (electrophilic nitration/nucleophilic substitution of hydrogen).



Scheme 2. Reactions of nitroporphyrinate **1** with carbanions of halomethyl *para*-tolyl sulphones.

In this case, within 30 min from the beginning of the reaction, all the porphyrin substrate disappeared (TLC control). We isolated from the post-reaction mixture (by column chromatography)

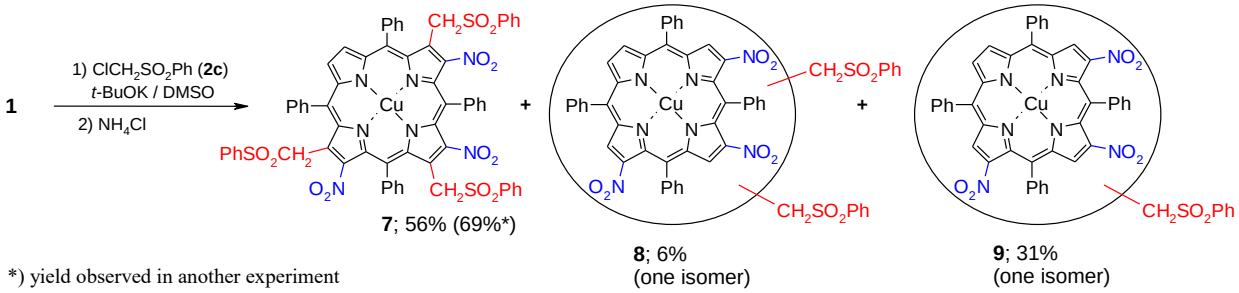
two fractions. The first one consists of three possible pentasubstituted isomers **4-6** (three spots on TLC, with a total yield of 49%), while the next fraction was the desired pure hexasubstituted product **3** (32%; R_f = 0.24, $CHCl_3$/MeOH, 50:1) (Scheme 2). Thus, the combined yield of all four products reached 81%.

The R_f values of the isomers **4-6** are close to each other, however preparative TLC chromatography allowed us to separate them and partially characterize (R_f = 0.40, 18%; R_f = 0.35, 13%; and R_f = 0.28, 18%; respectively). The spectral data are in agreement with the postulated structures, *e.g.*, in all MS spectra the intensive ion *m/z* = 1169 ($[M+Na]^+$) was observed. We did not investigate further the problem concerning assignment of the structure to the particular isomers. It is rather a side issue here. First of all, this is not a trivial task. On the other hand, they are not the aims of this study.

Minor optimization of the reaction conditions, namely prolongation of the reaction time (to 2 hours) did not give better results. Instead of increasing conversion to exhaustively substituted moiety **3**, a spontaneous degradation of the products occurred. The total yield dropped from 81% to 69%; in particular, the yield of main product has decreased, from 32% to 20%.

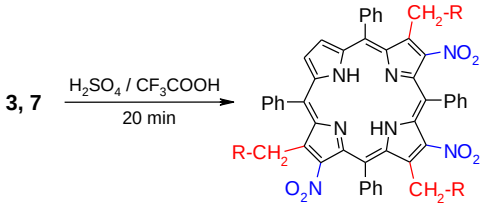
Reaction of the above porphyrinate **1** with carbanion of bromomethyl *para*-tolyl sulphone ($^-CH(Br)SO_2Tol$; **2b**) which is a species of comparable nucleophilicity to $^-CH(Cl)SO_2Tol$ gave a mixture of the same target compounds, however the main product was formed with 7% yield only (accompanied with 52% of pentasubstituted derivatives **4-6**; see Scheme 2). A reasonable explanation of this result is that after addition of carbanion containing better leaving group (X = Br) to porphyrin moiety the σ^H-adduct(s) of the latter will undergo β-elimination faster to give anionic form of VNS product(s). Unfortunately, this triple anion is also more unstable what was observed in the first experiment (for X = Cl; reaction time: 2 h).

The best yield of the exhaustively hexasubstituted product was observed in the reaction of copper(II)-porphyrinate **1** with carbanion of chloromethyl phenyl sulphone (**2c**). Additionally, penta- and tetrasubstituted derivatives **8** and **9** were formed (Scheme 3). The combined yield was very high (93%; 56% of product **7**). Optimization of this reaction (in particular, the reverse order of addition of the reagents and variable amount of base) allowed us to obtain the desired compound **7** as the only product and achieve the yield of 69%.



Scheme 3. Reactions of nitroporphyrinate **1** with carbanion of chloromethyl phenyl sulphone.

For more detailed and accurate characterization of paramagnetic compounds **3** and **7** they were decomplexed in H_2SO_4/CF_3CO_2H mixture to give free-base porphyrins **10** and **11**, which were analyzed including ^{1}H NMR (Scheme 4). In ^{1}H NMR spectrum of **10** one can find AB system originating from the remaining two β-pyrrole protons (8.68 and 8.69 ppm, coupled with *J* = 5.3 Hz), signals from CH_2 groups (4.90-5.12 ppm), and three intensive singlets at 2.16, 2.20, and 2.21 of CH_3-Tol groups. They confirm the structure.



10: R = SO_2Tol, 62%
11: R = SO_2Ph, 72%

Scheme 4. Demetallation of copper(II)-complexes of hexasubstituted products.

We also characterized free-base of multisubstituted porphyrinyl derivative **11**, and observed in ^{1}H NMR spectra a diagnostic AB system originating from the protons of unsubstituted pyrrole ring (8.73 and 8.75 ppm; J = 5.2 Hz). Signals from CH_2 groups appeared in the region 4.90-5.18 ppm.

4. Conclusions

In summary, the studies described in this communication focused on the synthesis of multisubstituted at the β-positions porphyrins. We demonstrated two-step procedure (electrophilic nitration / VNS) for preparation of highly derivatized moieties from parent *meso*-tetraphenylporphyrin Cu(II)-chelates. This type of functionalization gave rise to amphiphilic compounds with six polar groups on the rim of the core ring (*e.g.* NO_2, SO_2R; three pyrrole rings are exhaustively substituted). The products obtained would find interesting applications and can be considered as valuable intermediates for further transformations. Among others, such derivatives are sought in anticancer photodynamic therapy (PDT).

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