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Studies on Amination of Porphyrins – In Search for Effective and Renewable Nucleophilic Aminating Reagent

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Abstract

Studies on amination of electrophilic porphyrins are described. Several reagents such as hydroxylamine, 4-amino-4*H*-1,2,4-triazole, and seven various sulfenamides were tested in the reactions with nitro-substituted porphyrins. Products of direct amination were observed (formed according to VNS mechanism) which were usually accompanied with other substitution of hydrogen products (formed according to ONSH mechanism), for example compounds substituted with *t*-BuO group when *tert*-butoxide was used as a base in the reaction. The best results were achieved with 2,4,6-trichlorophenylsulfenamide, however, the yields varied from low to moderate.

Keywords: Porphyrins; Amination; Nucleophilic substitution of hydrogen; Sulfenamides.

Introduction

Porphyrins are natural and synthetic compounds of significant importance due to their potential applications in chemistry, biology, medicine, etc. The selective functionalization of porphyrins is intensively studied in recent years.[1]

Aminoporphyrins are considered as valuable intermediates towards a variety of novel compounds. In the recent past, we reported a new method for synthesis of aminoporphyrins with the use of vicarious nucleophilic substitution reaction (VNS).[2] *N*,*N*,*N*-Trimethylhydrazinium iodide $[Me_3N^+–NH_2]I^-$ was used as the aminating agent. However, the commercial availability of precursor for this reagent ($Me_2N–NH_2$) is limited due to its utilization as a rocket fuel. It is also very toxic, flammable, and can not be recycled (what is important herein) because during this process it undergoes degradation to trimethylamine.[2b] In addition, the reaction is not clean. We obtained the desired products, accompanied by several byproducts in various yields.[2b] Thus, the effective nucleophilic aminating agents for porphyrins are still being sought.

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Experimental

General

^{1}H NMR spectra were recorded with a Varian GEMINI-200 spectrometer operating at 200 MHz. Mass spectra were measured with a MARINER (ESI-TOF) PerSeptive Biosystems spectrometer (ESI method). UV-Vis spectra were measured with a Beckman DU-68 spectrometer. TLC analysis was performed on aluminium foil plates pre-coated with silica gel (60 F-254, Merck AG). All the products were separated by column chromatography (silica gel, 230–400 mesh; Merck AG).

Porphyrins **3-5** were obtained according to standard literature procedures.[2b,3] Also the sulfenamides were obtained according to known procedures: **6a**,[4] **6b**,[4] **6c**,[5] **6d**,[6] **6e**,[7] **6f**,[8] **6g**.[7] Hydroxylamine (**1**) and 4-amino-4*H*-1,2,4-triazole (**2**) were purchased from Aldrich.

Procedure A: *Reaction of [5-(4-nitrophenyl)-10,15,20-triphenylporphyrinato]zinc(II) (**3**) with 4-amino-4H-1,2,4-triazole (**2**)*

To a stirred solution of zinc(II) complex (**3**; 19.9 mg, 0.028 mmol) and 4-amino-4*H*-1,2,4-triazole (**2**; 11.8 mg, 0.14 mmol) in DMSO (1 ml), *t*-BuOK (31.4 mg, 0.28 mmol) in DMSO (0.5 ml) was added. The reaction was continued at room temperature. After 3 h of stirring (a deep green colour of the reaction mixture), a new portion of triazole **2** (11.8 mg, 0.14 mmol) was added and the reaction was continued for the next 6 h.

The reaction mixture was poured into water with ice (20 ml), and the product was extracted with $CHCl_3$ (3 × 15 ml). The combined organic layers were washed with H_2O (3 × 50 ml) and dried over anhydrous $MgSO_4$. After evaporating the solvent on a rotary evaporator, the crude residue was chromatographed on silica column (eluent: $CHCl_3$) to give **8**; yield 1.9 mg, 9%.

Procedure B: *Reaction of [5-(4-nitrophenyl)-10,15,20-triphenylporphyrinato]zinc(II) (**3**) with sulfenamides **6a**,**b**,**d**,**e** (t-BuOK / DMF / room temp.)*

To a stirred solution of *t*-BuOK (38 mg, 0.34 mmol) in dry DMF (4 ml), a solution of [5-(4-nitrophenyl)-10,15,20-triphenylporphyrinato]zinc(II) (**3**; 65 mg, 0.09 mmol) and a corresponding sulfenamide (**6a**, **6b**, **6d**, or **6e**; 0.09 mmol) in DMF (2 ml) was added dropwise *via* syringe. After 0.5 h (for **6b** – 1 h), additional portions of *t*-BuOK (38 mg, 0.34 mmol; for **6b** – 45 mg, 0.40 mmol) and sulfenamide (0.09 mmol) were added to the reaction mixture, and the reaction was continued for the following hour [in a case of sulfenamide **6b**, the additional portion of *t*-BuOK (38 mg, 0.34 mmol) and **6b** (19 mg, 0.09 mmol) were added after the next 1 h, and the reaction was continued until the substrate **3** disappeared]. The reaction mixture was then poured into a 3% aqueous solution of HCl with ice (30 ml). The products were extracted with $CHCl_3$ (3 × 30 ml), the combined organic layers were washed with H_2O (3 × 50 ml), and dried over anhydrous Na_2SO_4. After evaporating the solvent on a rotary evaporator, the products were separated by column chromatography (eluent: $CHCl_3$/*n*-hexane, 2:1).

The following amounts of {5-[4-amino-3-(*tert*-butoxy)phenyl]-10,15,20-triphenylporphyrinato}zinc(II) (**7**) were obtained: (a) 11 mg, 16% (in the reaction with **6a**); (b) 12 mg, 18% (in the reaction with **6b**), which was accompanied by [5-(3-amino-4-nitrophenyl)-10,15,20-triphenylporphyrinato]zinc(II) (**8**), 6.0 mg, 9%; (c) 7.5 mg, 11% (in the reaction with **6d**); (d) 6.9 mg, 10% (in the reaction with **6e**).

Procedure C: *Reaction of 5-(4-nitrophenyl)-10,15,20-triphenylporphyrinates (**3**, **4**, **5**) with sulfenamide **6b** (t-BuOK / DMF / room temp.)*

To a stirred solution of *t*-BuOK (38 mg, 0.34 mmol) in dry DMF (4 ml), a solution of a corresponding 5-(4-nitrophenyl)-10,15,20-triphenylporphyrinate (**3**, **4**, or **5**; 0.09 mmol) and 2,4,6-trichlorobenzenesulfenamide (**6b**; 19 mg, 0.09 mmol) in DMF (2 ml) was added dropwise *via* syringe. After 1 h, additional portions of *t*-BuOK (45 mg, 0.40 mmol) and sulfenamide **6b** (19 mg, 0.09 mmol) were added to the reaction mixture, and the reaction was continued for the following hour. Then, an additional portion of *t*-BuOK (38 mg, 0.34 mmol) and sulfenamide **6b** (19 mg, 0.09 mmol) were added, and the reaction was continued until the porphyrin substrate disappeared (*ca* 1–5 h; TLC control). The reaction mixture was poured into a 3% aqueous solution of HCl with ice (30 ml), the products were extracted with $CHCl_3$ (3 × 30 ml), and the combined organic layers were washed with H_2O (3 × 50 ml). After drying over anhydrous Na_2SO_4 and evaporating the solvent on a rotary evaporator, the products were separated by column chromatography (eluent: $CHCl_3$/*n*-hexane, 2:1).

The following products were obtained:

(a) [5-(3-amino-4-nitrophenyl)-10,15,20-triphenylporphyrinato]zinc(II) (**8**; 6.0 mg, 9%) and {5-[4-amino-3-(*tert*-butoxy)phenyl]-10,15,20-triphenylporphyrinato}zinc(II) (**7**; 12 mg, 18%);

(b) [5-(3-amino-4-nitrophenyl)-10,15,20-triphenylporphyrinato]copper(II) (**9**; 7.9 mg, 12%) and {5-[4-amino-3-(*tert*-butoxy)phenyl]-10,15,20-triphenylporphyrinato}copper(II) (**11**; 12 mg, 17%);

(c) [5-(3-amino-4-nitrophenyl)-10,15,20-triphenylporphyrinato]nickel(II) (**10**; 3.2 mg, 5%).

*Procedure D: Reaction of [5-(4-nitrophenyl)-10,15,20-triphenylporphyrinato]zinc(II) (**3**) with sulfenamide **6b** (t-BuOK / THF / 0–5°C)*

To a stirred solution of *t*-BuOK (31 mg, 0.28 mmol) in anhydrous THF (1 ml) at temperature 0–5°C, a solution of [5-(4-nitrophenyl)-10,15,20-triphenylporphyrinato]-zinc(II) (**3**; 43 mg, 0.06 mmol) and 2,4,6-trichlorobenzenesulfenamide (**6b**; 27 mg, 0.12 mmol) in THF (1.5 ml) was added dropwise *via* syringe.

After 10 h of stirring at this temperature, additional portions of *t*-BuOK (31 mg, 0.28 mmol) and sulfenamide **6b** (13 mg, 0.06 mmol) were added to the reaction mixture, and the reaction was continued for the next 10 h. The reaction mixture was then poured into a 3% aqueous solution of HCl with ice (20 ml). The products were extracted with $CHCl_3$ (3 × 10 ml), the combined organic layers were washed with H_2O

(3 × 25 ml), and dried over anhydrous Na_2SO_4. After evaporating the solvent on a rotary evaporator, the product, [5-(3-amino-4-nitrophenyl)-10,15,20-triphenylporphyrinato]zinc(II) (**8**), was isolated by column chromatography (eluent: $CHCl_3$/*n*-hexane, 2:1), 11 mg, yield 24%. The main product was accompanied by {5-[4-amino-3-(*tert*-butoxy)phenyl]-10,15,20-triphenylporphyrinato}zinc(II) (**7**), 2.3 mg, yield 5%.

In the reaction carried out under similar conditions (*t*-BuOK/DMF, 0–5°C, reaction time – 10 h) from [5-(4-nitrophenyl)-10,15,20-triphenylporphyrinato]copper(II) (**4**) [scale – 100 mg, 0.14 mmol], [5-(3-amino-4-nitrophenyl)-10,15,20-triphenylporphyrinato]copper(II) (**9**; 10.0 mg, 10%) and {5-[4-amino-3-(*tert*-butoxy)phenyl]-10,15,20-triphenylporphyrinato}copper(II) (**11**; 5.4 mg, 5%) were obtained.

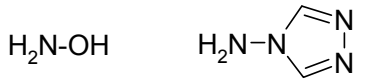
All the above products obtained have been already described in our previous papers.[2a,2b] Their ^{1}H NMR, MS, and UV-Vis spectra were in agreement with those reported earlier in these articles: {5-[4-amino-3-(*tert*-butoxy)phenyl]-10,15,20-triphenylporphyrinato}zinc(II) (**7**),[2b] [5-(3-amino-4-nitrophenyl)-10,15,20-triphenylporphyrinato]zinc(II) (**8**),[2a,2b] [5-(3-amino-4-nitrophenyl)-10,15,20-triphenylporphyrinato]copper(II) (**9**),[2b] [5-(3-amino-4-nitrophenyl)-10,15,20-triphenylporphyrinato]nickel(II) (**10**),[2b] {5-[4-amino-3-(*tert*-butoxy)phenyl]-10,15,20-triphenylporphyrinato}copper(II) (**11**).[2b]

Results and Discussion

In continuation of our studies in the field of efficient porphyrin amination and application of the products obtained in further synthesis, we investigated the introduction of NH_2 group using various aminating reagents. The starting porphyrin used was converted into its zinc, copper, and nickel complexes to avoid NH deprotonation under the strongly basic conditions during amination reactions. Preliminary attempts with the use of hydroxylamine for this purpose, failed. In the first goals, when porphyrin zinc(II) complex bearing NO_2-substituted phenyl group (**3**) was reacted with hydroxylamine, which was successfully used by Meisenheimer,[9] no products were observed (*t*-BuOK/DMF, room temp.; reaction time – up to 6 h). Despite several experiments and various modifications of conditions we could not obtain the desired aminoporphyrin.

Similar results were observed with the use of 4-amino-4*H*-1,2,4-triazole (**2**), which was previously used as a good aminating reagent by Katritzky.[10] Zinc, copper, and nickel porphyrin complexes (**3**, **4**, **5**) did not give the desired products (conditions: KOH/DMSO, 60–70ºC or *t*-BuOK/DMF, room temp.). Finally, the modified method (*t*-BuOK/DMSO, room temp.), which was effective for azulenes amination,[11] allowed us to obtain aminoporphyrins, however the observed yields were low (below 10%; *e.g.*, in the reaction of **3** with triazole **2**: 9%). The lack of promising results in this case might be a consequence of the observed preference of bulky 4-amino-4*H*-1,2,4-triazole anion

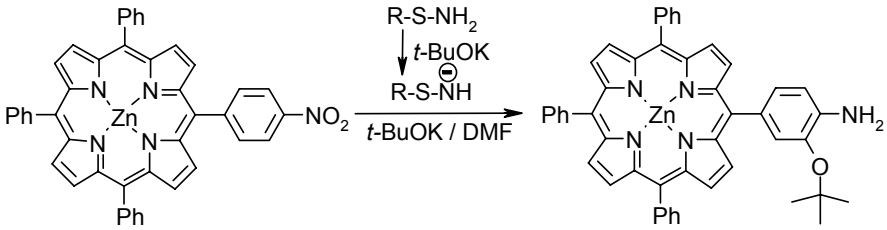
(**2'**) to form in aromatic systems *para*-aminosubstituted products. It is impossible herein because this position in all the investigated instances is occupied by porphyrinyl moiety, thus impeding the reaction.



1 **2**

Figure 1

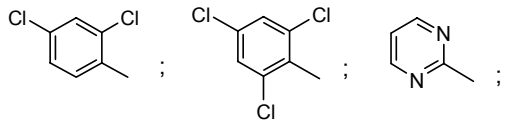
Finally, in searching for more effective and renewable aminating reagent, we studied the usefulness of sulfenamides. Several compounds were tested (**6a-g**, Scheme 1), previously successfully applied for amination of nitrobenzene derivatives and nitronaphthalenes.[7,12]



3

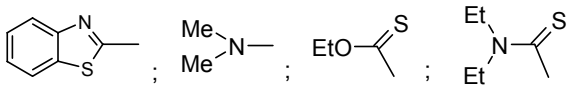
7, 16% (for **6a**)
18% (for **6b**) + 9% of **8***)
11% (for **6d**)
10% (for **6e**)

*) see Scheme 2 and Experimental



RSNH$_2$; **R =** **a** **b** **c**

6



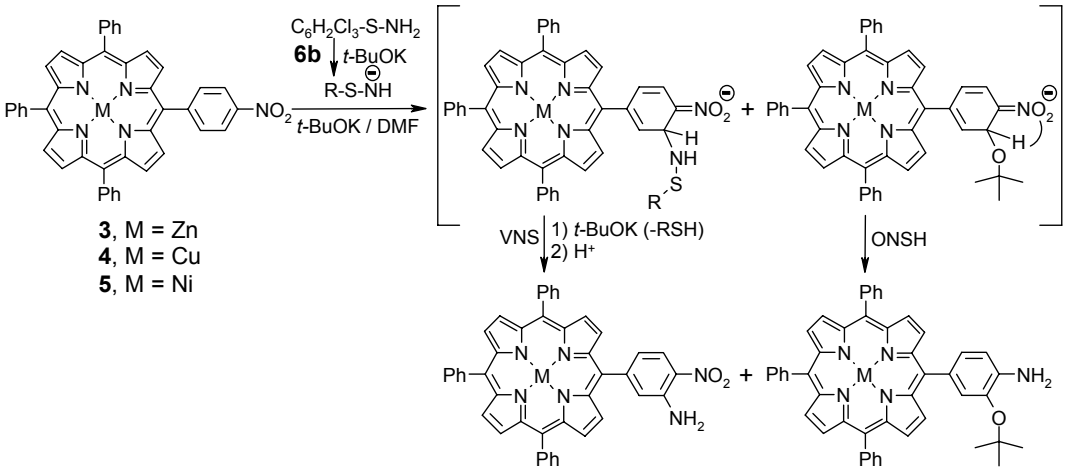
d **e** **f** **g**

Scheme 1

From the preliminary experiments we found that four of them (**6a**,**b**,**d**,**e**) reacted with porphyrins but only one, **6b**, was appropriate for amination of these moieties. For example, in the reaction of **3** with sulfenamide **6b** (*t*-BuOK/DMF, room temp., 3 h) the desired product **8** was obtained with 9% yield only (scale 20 mg, 15% of **3** was recovered). And we observed the formation of the product **7**, which was a result of oxidative nucleophilic substitution of hydrogen (ONSH) involving *t*-BuO$^-$ anion.[2b] In this case parallely the reduction of NO_2 group to NH_2 group occurred (18%; Scheme 1). It was the only product in the reaction of sulfenamides **6a**, **6d**, and **6e** (yield 10–16%).

When copper complex (**4**) reacted with sulfenamide **6b** the desired amino-substituted product **9** was formed in the yield of 12% together with ONSH compound

(**11**, 17%) (Scheme 2). The respective nickel product (**10**) was formed in the yield of 5%. Modification of the reaction conditions (*t*-BuOK/DMF, *t*-BuOK/THF; temp. 0–5ºC) allowed us to enhance the yield of the product **8** up to 24%. Probably this is a kinetic product. In electrophilic aromatic systems, addition of a nucleophile to carbon atom bearing hydrogen is very fast process.[2c] At lower temperature the reaction with *N*-anion R-SNH$^-$ (addition followed by elimination) is more selective: (a) *N*-anion is better nucleophile than *O*-anion (*t*-BuO$^-$), (b) after addition of *t*-BuO$^-$ to porphyrin, which is reversible, oxidative processes are suppressed at lower temperature. Thus, the amination predominated, affording product **8** in better yield.



*) the higher yield of **8** (24%) was obtained during the further optimization of the process (*t*-BuOK/THF, 0-5ºC; see Experimental); the main product was accompanied with **7** (5%)

Scheme 2

5-[4-Amino-3-(*tert*-butoxy)phenyl]-10,15,20-triphenylporphyrinates of Zn and Cu (**7**, **11**) are formed in the competitive reaction (ONSH). There is a simple explanation of their formation. The large excess of *t*-BuOK is a source of *O*-anion, which is reactive enough as a nucleophile in the presence of additives[13a] or in dipolar aprotic solvents (because of their solvation effects).[13b] This type of solvents were used herein (DMSO, DMF). They enhanced the nucleophilicity of the *O*-anion, thus allowing the competitive reaction. ONSH process (substitution of hydrogen with *t*-BuO$^-$ anion) is probably an intramolecular redox process, as the NO_2 group in these reactions was always reduced to NH_2 group.

The use of sodium methoxide as a base and the reaction in heterogeneous system (KOH/DMF, temperature range: 0÷75ºC, and KOH/DMSO, temperature range: r.t. to 75ºC; for sulfenamide **6b**) allowed us to avoid *t*-BuO$^-$ nucleophile, however in the post-reaction mixtures we observed a considerable amounts of starting material only or degradation products.

Usually, the discussed *N*-anions are reagents of moderate nucleophilicity and moderate stability. Thus, instead to enter VNS reaction, they can undergo degradation, for example to disulfides.[14] In conclusion, our attempts to find a more effective

aminating agents for porphyrins failed; however, for some particular reactions some of these reagents could be used – as a easy available or very convenient ones. For example, sulfenamide **6b** gave the total yield of the substitution of hydrogen products up to 30% (**7** + **8**, **9** + **11**, etc.). These sulfenamides, if needed, can be renewable reagents.[15] This is very attractive and important one for reactions carried out in a larger scale. The isolated byproducts (**7**, **11**) are also very interesting porphyrin moieties. Their preparation from the corresponding aldehyde(s) and pyrrole could be an extremely difficult task.

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