Direct introduction of heterocyclic units into porphyrin derivatives

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In the reaction with quinazoline and 5-phenyl-1,2,4-triazin-5(2*H*)-one, 5,10,15,20-tetra(4-methoxyphenyl)porphyrin exhibits nucleophilic properties. In quinazoline excess, C—C coupling occurs at the C=N bond of azines and position 3 of the aryl ring to form 5,10,15,20-tetrakis(3-heteryl-4-methoxyphenyl)porphyrins. Monoheteryl-substituted porphyrin was obtained by the reaction of equimolar amounts of 5,10,15,20-tetra(4-methoxyphenyl)porphyrin and 5-phenyl-1,2,4-triazin-5(2*H*)-one.

Key words: *meso*-tetraarylporphyrins, nonsymmetrical porphyrins, heterylporphyrins, 1,2,4-triazines, quinazoline, nucleophilic addition to azines.

Porphyrin derivatives are of great interest as reagents for photodynamic therapy of oncological diseases.[1] In addition, they find use in catalytic processes[2] and are applied for the development of molecular sensors.[3] Nevertheless, synthetic routes to porphyrin derivatives are strongly limited, and search for new variants of functionalization of this class of compounds is of special interest for modern organic chemistry.

In this work, we proposed a method for one-pot introduction of heterocyclic moieties into *meso*-substituted porphyrins.

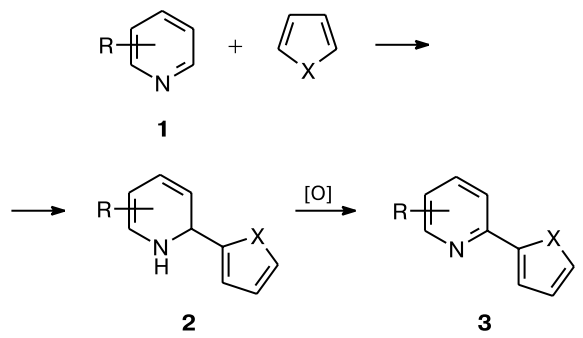
The β-positions of porphyrins are known to be reactive toward electrophiles (for example, nitration reaction[4]). At the same time, azines, *e.g.*, compound **1**, and their cationic forms are highly electrophilic and can add π-excessive heterocycles to the unsubstituted carbon atom. The reaction can be ceased at the step of formation of σ^H-adducts **2** or, under certain conditions, can give products of nucleophilic hydrogen substitution (S_N^H) **3** (Scheme 1).[3]

This synthetic method provides an alluring prospect for direct C—C coupling of porphyrins and π-deficient heterocyclic compounds.

Quinazoline (**4a**) and 3-phenyl-1,2,4-triazin-5(2*H*)-one (**4b**), which earlier showed a high reactivity in the reaction with pyrrole derivatives,[6,7] were chosen as objects for the study.

In porphyrins the pyrrolic α-positions are involved in macrocycle formation. The reactivity of the remained unsubstituted β-positions of the porphyrin system is much

Scheme 1



R is electron-withdrawing group or endocyclic nitrogen atom.

lower than that for the pyrrole system. Therefore, the activation of the azine cycle is the necessary condition for interaction. The most common approach, namely, *in situ* preparation of NH-azinium salts, was used for the activation of compounds **4a,b**. Based on the NMR spectroscopic data, we found that the reaction of **4a,b** with *meso*-tetraphenylporphyrin (TPP) in acetic or trifluoroacetic acid did not occur and no addition products similar to products **2** were formed. The ^{1}H NMR spectra of the reaction mixtures contain no signals from the C(sp^3)H protons in the 4.0—6.5 ppm region characteristic of the σ^H-adducts. Evidently, the reaction is prevented by the protonation of the porphyrin system. The properties of the metalloporphyrin complexes differ, as a rule, from those of the corresponding free bases, and the most of

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 155—158, January, 2004.

1066-5285/04/5301-0160

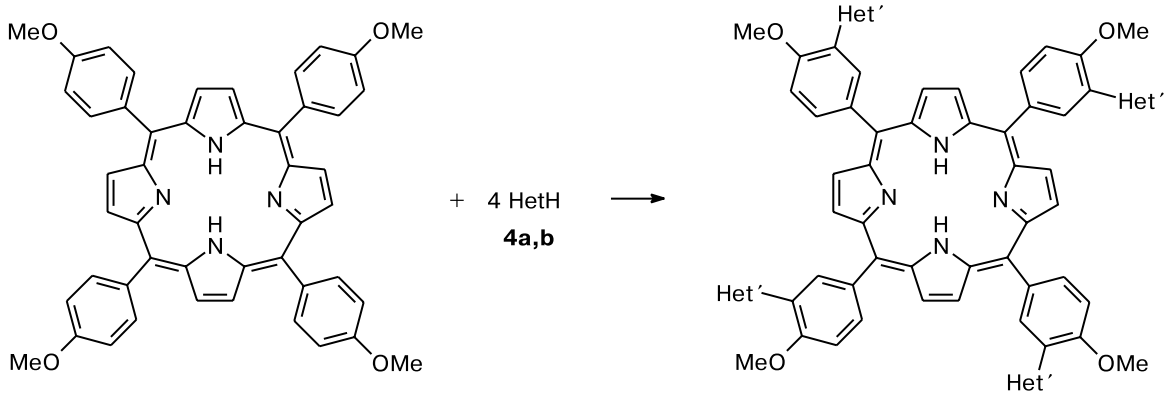
them are stable in solutions of acids. Therefore, the copper and zinc TPP complexes were introduced into the reaction. However, no heterylation products were observed when the reactions of either CuTPP or ZnTPP were carried out in acetic acid. In stronger trifluoroacetic acid, the metal is gradually displaced from the complex. Thus, attempts of direct C—C coupling of azines and pyrrole moieties of TPP were unsuccessful.

Another possibility to introduce heterocyclic substituents into porphyrins is provided by the reactions of aromatic *meso*-substituents. A combination of azines and π-donating compounds of the aromatic series is well studied as a synthetic methodology and described.[5,8] We extended this approach to *meso*-tetramethoxyphenylporphyrin **5** (Scheme 2).

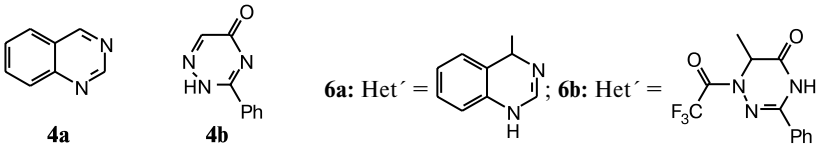
The reaction of compound **5** with a fourfold molar excess of quinazoline **4a** and triazinone **4b** in trifluoroacetic acid afforded tetraheteryl derivatives **6a,b**.

In the latter case, trifluoroacetic anhydride was introduced into the reaction mixture for the additional activa-

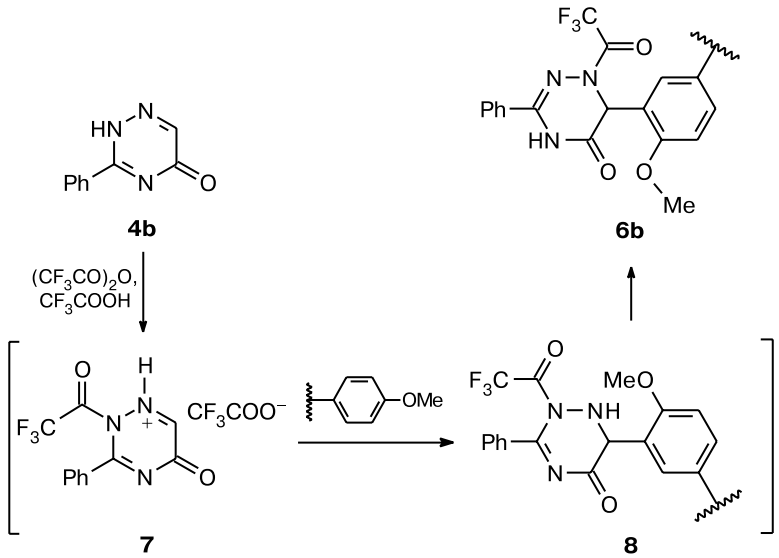
Scheme 2



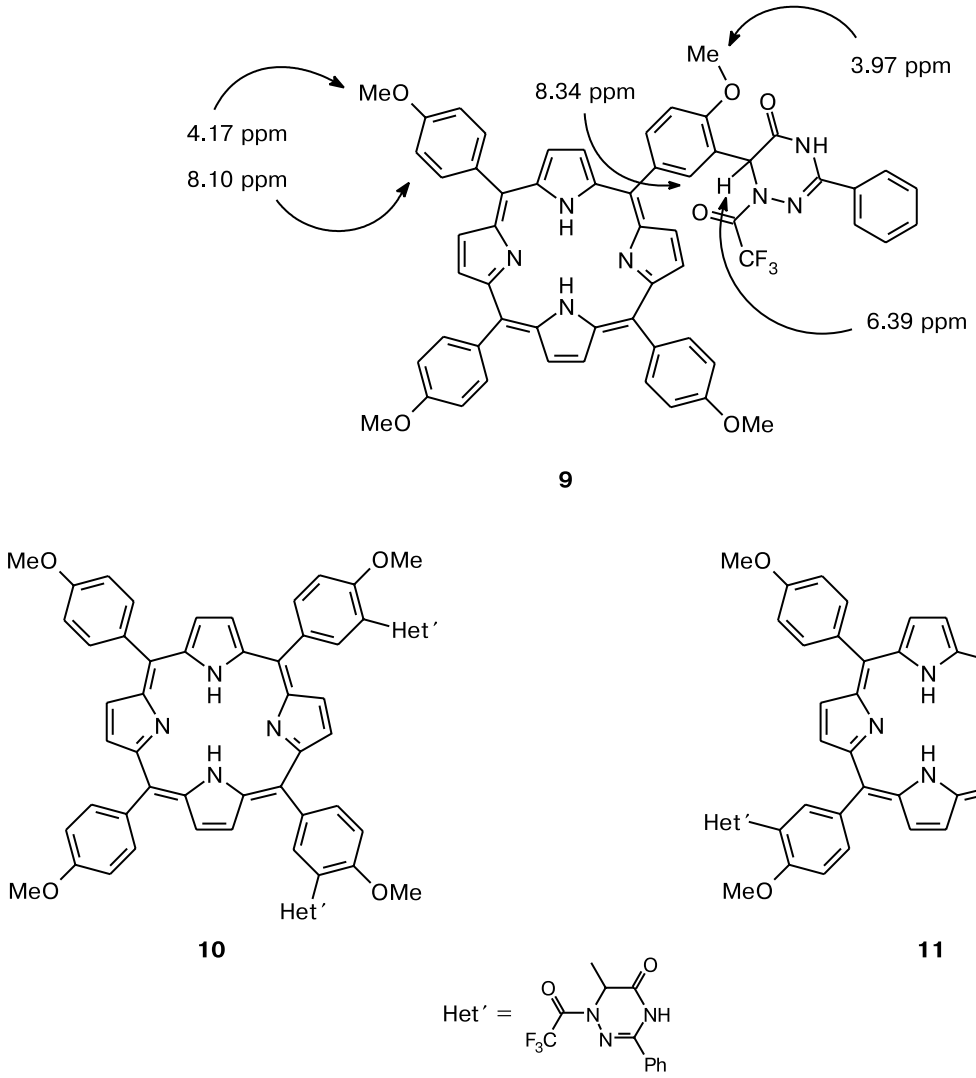
Reagents, conditions, and yields: 1) **4a**, CF_3COOH; K_2CO_3, H_2O, yield of **6a** 71%; 2) **4b**, CF_3COOH, $(CF_3CO)_2O$; K_2CO_3, H_2O, yield of **6b** 65%.



Scheme 3



Scheme 4



tion of the triazine cycle. The mechanism of this reaction is probably similar to that described previously[9] and includes (Scheme 3) the acylation of 1,2,4-triazine **4b** at the N(2) atom and the addition of porphyrin followed by the acylotropic rearrangement of *N*(2)-trifluoroacetyl derivative **8** to thermodynamically more favorable[10] *N*(1)-acetylated isomer **6b**.

The interaction of porphyrin **5** with an equivalent amount of triazinone **4b** yields a mixture of products. Only monoheteryl-substituted porphyrin **9** was isolated in the pure state (33% yield) and characterized. In addition, a mixture of disubstituted porphyrins **10** and **11** (total yield 10%) and unreacted porphyrin **5** (18%) were isolated by chromatography (Scheme 4).

The structures of the obtained products were established on the basis of NMR spectroscopic data. The formation of addition products to the C=N bond of the heterocycle is unambiguously indicated by signals from the H atoms bound with the reaction center of the heterocycle, *i.e.*, singlets at 6.33 ppm (**6a**) and 6.35 ppm (**6b**). The absence of spin-spin coupling of the C(sp^3)H protons of the triazine cycle with the protons of the NH group in compound **6b** indicates the position of the trifluoroacetyl substituent at the N(1) atom. The NMR spectrum of compound **9** exhibits resonance signals of both the substituted and unsubstituted *meso*-methoxyphenyl groups (see Scheme 4). In addition, the nonsymmetrical character of the structure is proved by nonequivalent protons in the β-positions of the porphyrin cycle. These protons resonate in the ^{1}H NMR spectrum as a multiplet in a region of 8.80—8.91 ppm.

Experimental

The reaction course and purity of the synthesized products were monitored by TLC on Sorbfil PTSKh-UV plates using

a hexane—methylene dichloride (2 : 1) mixture as eluent. ^{1}H NMR spectra were recorded on a Bruker DRX 400 spectrometer in DMSO-d_6 or $CDCl_3$ using Me_4Si as internal standard. Elemental analysis was carried out on a Carlo Erba EA 1108 automated analyzer. Preparative flash chromatography was performed on Lancaster silica gel 0.040—0.063 mm (230—400 mesh) using a methylene dichloride—methanol (10 : 1) mixture as eluent.

5,10,15,20-Tetrakis[3-(1,4-dihydroquinazolin-4-yl)-4-methoxyphenyl]porphyrin (6a). Quinazoline **4a** (35.5 mg, 0.27 mmol) was added to a solution of porphyrin **5** (50 mg, 0.068 mmol) in trifluoroacetic acid (3 mL), and the reaction mixture was kept at 20 °C for 1.5 months. The solvent was distilled off *in vacuo*, and the residue was dissolved in methylene dichloride (5 mL) and washed with an aqueous solution of sodium hydrocarbonate until the green color disappeared. The solvent was distilled off *in vacuo*, and porphyrin **6a** was isolated by flash chromatography and dried *in vacuo*. The yield was 60 mg (71%), m.p. > 300 °C. Found (%): C, 76.18; H, 4.82; N, 13.25. $C_{80}H_{62}N_{12}O_4$. Calculated (%): C, 76.54; H, 4.98; N, 13.39. ^{1}H NMR (DMSO-d_6), δ: 4.02 (br.s, 3 H, OMe); 6.33 (br.s, 1 H, C(6)H of quinazoline); 7.39—7.64 (m, 4 H, C(Ar)H); 7.85—7.94, 8.15—8.26 (both m, 2 H each, C(Ar)H); 8.78—8.90 (m, 2 H, CH of porphyrin); 11.8 (br.s, 1 H, NH of quinazoline).

5,10,15,20-Tetrakis[4-methoxy-3-(5-oxo-3-phenyl-1-trifluoroacetyl-1,4,5,6-tetrahydro[1,2,4]triazin-6-yl)phenyl]porphyrin (6b). Triazinone **4b** (47 mg, 0.27 mmol) was added to a solution of porphyrin **5** (50 mg, 0.068 mmol) in a mixture of trifluoroacetic anhydride (1 mL) and trifluoroacetic acid (2 mL). The reaction mixture was kept at ~20 °C for 2 months. The solvent was distilled off *in vacuo*, and the residue was dissolved in methylene dichloride and washed with an aqueous solution of sodium hydrocarbonate until the green color disappeared. The solvent was distilled off, and the product was purified by flash chromatography and dried *in vacuo*. The yield of compound **6b** was 38 mg (65%), m.p. > 300 °C. Found (%): C, 60.81; H, 3.41; N, 12.29. $C_{92}H_{62}F_{12}N_6O_{12}$. Calculated (%): C, 61.00; H, 3.45; N, 12.37. ^{1}H NMR (DMSO-d_6), δ: 4.02 (s, 3 H, OMe); 6.35 (br.s, 1 H, C(6)H of triazine); 7.45—7.60 (m, 4 H, C(Ar)H); 7.87—7.96, 8.15—8.27 (both m, 2 H each, C(Ar)H); 8.78—8.90 (m, 2 H, CH of porphyrin); 11.8 (br.s, 1 H, NH of triazine).

5-[4-Methoxy-3-(5-oxo-3-phenyl-1-trifluoroacetyl-1,4,5,6-tetrahydro-1,2,4-triazin-6-yl)phenyl]-10,15,20-tris(4-methoxyphenyl)porphyrin (9) was obtained similarly to compound **6b** from compound **5** (50 mg, 0.068 mmol) and triazinone **4b** (12 mg, 0.069 mmol). The products were isolated by flash chromatography. The fraction with R_f = 0.9 (dichloromethane—methanol, 10 : 1) contained the starting porphyrin **5** (9 mg, 18%), and that with R_f = 0.3 was attributed to porphyrin **9** (23 mg, 33%). M.p. > 300 °C. Found (%): C, 70.19; H, 4.22; N, 9.62. $C_{59}H_{44}F_3N_7O_6$. Calculated (%): C, 70.58; H, 4.42; N, 9.77. ^{1}H NMR ($CDCl_3$), δ: −2.82 (br.s, 0.25 H, NH of porphyrin); −2.78 (br.s, 0.75 H, NH of porphyrin); 3.97 (s, 0.75 H, OMe); 4.17 (s, 2.25 H, OMe); 6.39 (s, 0.25 H, C(6)H of triazine); 7.20—7.31 (m, 2.25 H, C_6H_4OMe + C_6H_3OMe); 7.42—7.44 (m, 0.75 H, Ac); 7.77—7.79 (m, 0.5 H, Ar); 8.07—8.12 (m, 2.25 H, C_6H_4OMe + C_6H_3OMe); 8.34 (d, 0.25 H, C_6H_3OMe, J = 1.6 Hz); 8.80—8.90 (m, 2 H, CH of porphyrin). The last fraction eluted from the column was a mixture of disubstituted products **10** and **11** with an overall yield of 10 mg (10%). ^{1}H NMR ($CDCl_3$), δ: −2.83 (br.s, 4 H, NH of porphyrin); 3.99—4.05 (m, 3 H, OMe); 4.11 (s, 3 H, OMe); 6.37—6.41 (m, 1 H, C(6)H of triazine); 7.30—7.51 (m, 3 H, Ar); 7.25—7.30 (m, 2 H, Ar); 7.67—7.82 (m, 2 H); 8.08—8.12 (m, 3 H, C(Ar)H); 8.12—8.34 (m, 2 H, C(Ar)H); 8.74—8.95 (m, 4 H, CH of porphyrin).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 02-03-32332-a), President of the Russian Federation (Program for Support of Leading Scientific Schools, Grant RF NSh 1766.2003.3), and the International Scientific Technical Center (Project 708).

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Received October 15, 2003;
in revised form January 14, 2004