

## [3+2]–Cycloaddition Reaction between Tetraphenylporphyrinylazide and Ferrocenyl Dipolarophiles

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*The regioselectivity of [3+2]-cycloaddition reaction of tetraphenylporphyrinylazide with ferrocenyl dipolarophiles in the absence of copper(I) salts was studied.*

**Keywords:** [3+2]-Cycloaddition, tetraphenylporphyrin, ferrocene.

## Реакция [3+2]–циклоприсоединения тетрафенилпорфириназида с ферроценсодержащими дипольярофилами

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*Исследована реакция [3+2]-циклоприсоединения тетрафенилпорфириназида с ферроценсодержащими дипольярофилами в отсутствие солей меди. Показано, что реакция протекает региоселективно.*

**Ключевые слова:** [3+2]-Циклоприсоединение, тетрафенилпорфирин, ферроцен.

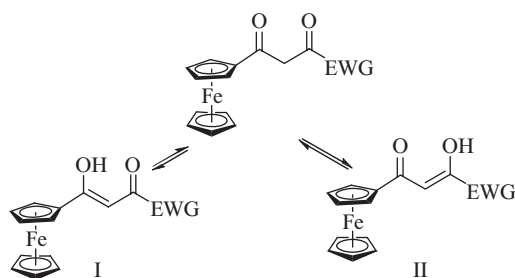
For many years, porphyrins have been successfully used in PDT.<sup>[1]</sup> Ferrocenylheterocyclic compounds have been found to exhibit a wide range of biological activities (e.g. antitumor<sup>[2,3]</sup> and antimicrobial<sup>[4]</sup>). Ferrocene containing porphyrins have already been synthesized by various synthetic methods.<sup>[5-12]</sup> The difference of bounding ways in the ferrocenylporphyrin assemblies suggests the variety of applications. Their donor-acceptor properties have been

employed to study photoinduced electron transfer processes and to simulate photosynthesis active sites.<sup>[13-18]</sup> Thus, such structures have been used as molecular sensors<sup>[19,20]</sup> and for an increase of memory density that allowed multibit information storage.<sup>[21-23]</sup>

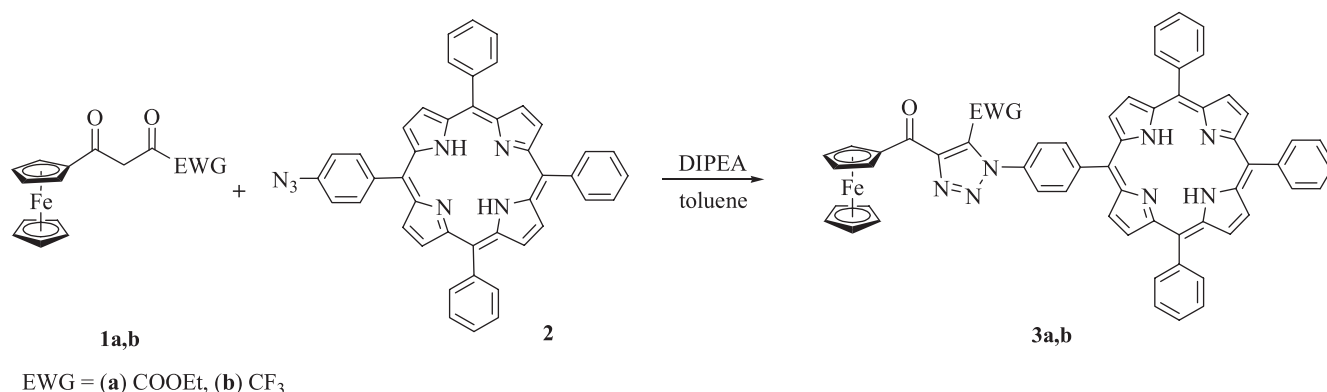
Previously, we have studied the reductive amination reaction of ferrocenylpyrazolecarboxaldehydes with 5-(*p*-aminophenyl)-10,15,20-triphenylporphyrin.<sup>[22,24,25]</sup>

Therefore, we used these reactions to produce ferrocene-porphyrins in which the ferrocene is linked to porphyrin through the pyrazole. Moreover, the possibility of applying of synthesized compounds for sonodynamic therapy was studied.

In present work, we construct porphyrin–heterocycle–ferrocene triad by means of [3+2]-cycloaddition reaction with azidotetraphenylporphyrin. The possibility of using diketones as dipolarophiles stems from the fact that they exist mostly in the enol form due to the keto-enol tautomerism. The regioselectivity of dipolar addition to such substrates depends mainly on the relative stability of the resulting enol forms.



**Figure 1.** Keto-enol tautomerism in ferrocene-containing  $\beta$ -diketones.



**Scheme 1.** [3+2]-Cycloaddition between tetraphenylporphyrinazide and ferrocenyldiketones.

The preferential formation of ketoenol **II** is possible only in the presence of a strong electron-withdrawing group; in the other case, the formation of both enol forms is equally probable. Thus, in our work we used ferrocenyl pyruvic ether (EWG=COOEt) as ferrocene-containing dipolarophiles and ferrocenyl trifluoroacetone (EWG=CF<sub>3</sub>). Compounds **1a,b** were obtained *via* Claisen condensation between acetylferrocene and diethyl oxalate or ethyltrifluoroacetate respectively.<sup>[26]</sup> Indeed, it was shown by means of NMR spectroscopy that there was only one enol form **II** in solution at room temperature.

The reaction of tetraphenylporphyrinylazide<sup>[27]</sup> with ferrocenyl-containing dicarbonyl compounds leads to the formation of the desired 1,2,3-triazoles. It should be noted that the nature of the base plays a significant role. The use of various bases (potassium carbonate, sodium methoxide, triethylamine in toluene, pure triethylamine,

diisopropylethylamine (DIPEA) in toluene) led to the conclusion that the best yields of porphyrins **3a** and **3b** can be obtained using DIPEA in toluene.<sup>†</sup> In this case, regioselectivity does not depend on the nature of the base.

Noteworthy, that the reaction proceeds at the absence of toxic copper salts. This is very important because we are planning to study the application of these compounds for sonodynamic therapy of cancer and inflammations. Moreover, in the absence of copper the target porphyrins **3a** and **3b** remain metal-free, which simplifies their purification. The structures of the compounds synthesized were established on a basis of 2D heteronuclear NMR correlations.

Hereby, ferrocenylheterocyclic porphyrins were synthesized by means of [3+2]-cycloaddition reaction between tetraphenylporphyrinylazide and ferrocenyl dipolarophiles. The effectiveness of the method was established using DIPEA as a base in toluene. Structures of the resulted substances were confirmed by UV, NMR-spectroscopy and ESI mass-spectrometry methods. At the next stage of work it is planned to study the electrochemical properties and biological activity of these compounds.

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## References and Notes

<sup>†</sup> *General procedure.* 5-(*p*-Azidophenyl)-10,15,20-triphenylporphyrin (**2**) (0.01 mmol) and appropriate ferrocenyldiketone (**1a,b**) (0.01 mmol) were dissolved in toluene (5 mL). *N,N*-Diisopropylethylamine (0.01 mmol) was added and reaction mixture was refluxed for 3 h, cooled to room temperature and washed with water (3×15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>. Solvent was removed *in vacuo* and the residue was chromatographed on silica (eluent: petroleum ether–ethyl acetate = 4:1).

1-(5-(*p*-(4-Ferrocenyl-5-carboxyethyl-1,2,3-triazolyl)-phenyl)-10,15,20-triphenylporphyrin) (**3a**). Yield 60 %. Violet powder. MS (ESI) *m/z* (%): 967 (100) [M+H]<sup>+</sup>. UV-Vis (CH<sub>2</sub>Cl<sub>2</sub>) λ<sub>max</sub> nm (ε): 418 (202,000), 514 (10,000), 550 (5,000), 589 (3,600), 648 (3,000). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 30 °C) δ<sub>H</sub> ppm: –2.76 (s, 2H, 2NH), 1.47 (t, 3H, *J*=8 Hz, CH<sub>3</sub>), 4.36 (s, 5H, Cp), 4.58–4.63 (m, 2H, CH<sub>2</sub>), 4.76 (s, 2H, Cp), 5.50 (s, 2H, Cp), 7.74–7.83 (m, 9H, Ph), 8.05–8.07 (d, 2H, *J*=8 Hz, Ph),

- 8.23–8.25 (d, 6H,  $J=8$  Hz, Ph), 8.43–8.45 (d, 2H,  $J=8$  Hz, Ph), 8.85–8.93 (m, 8Ha $\beta$ , Py).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 30 °C)  $\delta_{\text{C}}$  ppm: 14.02; 63.45; 70.52; 71.48; 73.54; 117.46; 120.52; 122.45; 126.74; 127.84; 134.57; 135.33; 142.01; 144.57; 159.98.
- 1-(5-(p-(4-Ferrocenyl-5-trifluoromethyl-1,2,3-triazolyl)phenyl)-10,15,20-triphenylporphyrin) (3b)*. Yield 43 %. Violet powder. MS (ESI)  $m/z$ : 962.28  $[\text{M}+\text{H}]^+$ . UV-Vis ( $\text{CH}_2\text{Cl}_2$ )  $\lambda_{\text{max}}$  nm ( $\epsilon$ ): 418 (153,000), 514 (7,640), 551 (3,900), 589 (2,860), 645 (2,240).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 30 °C)  $\delta_{\text{H}}$  ppm: –2.76 (s, 2H, 2NH), 1.47 (t, 3H,  $J=8$  Hz,  $\text{CH}_3$ ), 4.36 (s, 5H, Cp), 4.58–4.63 (m, 2H,  $\text{CH}_2$ ), 4.76 (s, 2H, Cp), 5.50 (s, 2H, Cp), 7.74–7.83 (m, 9H, Ph), 8.05–8.07 (d, 2H,  $J=8$  Hz, Ph), 8.23–8.25 (d, 6H,  $J=8$  Hz, Ph), 8.43–8.45 (d, 2H,  $J=8$  Hz, Ph), 8.85–8.93 (m, 8Ha $\beta$ , Py).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 30 °C)  $\delta_{\text{C}}$  ppm: 63.45; 70.50; 71.45; 73.55; 117.46; 120.52; 124.50; 126.69; 127.84; 134.55; 136.26; 142.01; 147.74; 184.10.
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