Макрогетероциклы
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DOI: 10.6060/mhc180484t

A Sterically Driven Approach to the Efficient Synthesis of Low−Symmetry 1,4−Diazepinoporphyrazines

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We have investigated the general applicability of the synthetic procedure in which a carbonyl compound (in our case, 2,4-pentandione and 3-n-propyl-2,4-pentanedione) is added to a preformed $TiCl_4$–diaminomaleonitrile complex for the preparation of 1,4-diazepine-2,3-dicarbonitriles. It has been shown that triethylamine commonly used as an auxiliary reagent (base) inhibits the formation of the $TiCl_4$–diaminomaleonitrile complex and less basic pyridine was proved to be more suitable. The introduction of the n-propyl group into the C6 position of 5,7-bis(2'-arylethenyl)-6H-1,4-diazepine-2,3-dicarbonitrile has led to an unprecedented increase in the yield of the low-symmetry A_3B-type tribenzodiazepinoporphyrazine from 5 to 40 % under Linstead cross-macrocyclization conditions. The quantum-chemical calculations at the PW6B95-D3/def2-TZVP//BP86-D3/def2-TZVP level of theory demonstrated that steric effects of substituents in 6-alkyl substituted 5,7-bis(2'-arylethenyl)-6H-1,4-diazepine-2,3-dicarbonitriles can play a key role in formation of dimeric intermediates during Linstead macrocyclization, providing high selectivity towards low symmetry porphyrazines with annulated 1,4-diazepine heterocycle(s).

Keywords: Synthesis, 1,4-diazepine, porphyrazine, DFT calculations, steric effect of substituent.

Эффективный синтез низкосимметричных 1,4−диазепино−порфиразинов с использованием стерического контроля

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Исследован новый подход к получению 1,4-диазепин-2,3-дикарбонитрилов, основанный на реакции 1,3-дикетонов (в данном случае, 2,4-пентандиона или 3-н-пропил-2,4-пентандиона) с диаминомалеонитрилом в составе комплекса с $TiCl_4$. Использование триэтиламина в качестве вспомогательного основания приводит к ингибированию образования реакционноспособного комплекса диаминомалеонитрила с $TiCl_4$, что обуславливает необходимость применения более слабого основания – пиридина. Введение н-пропильной группы в 5,7-бис(2'-арилэтенил)-6Н-1,4-диазепин-2,3-дикарбонитрил привело к увеличению выхода низкосимметричного трибензо-

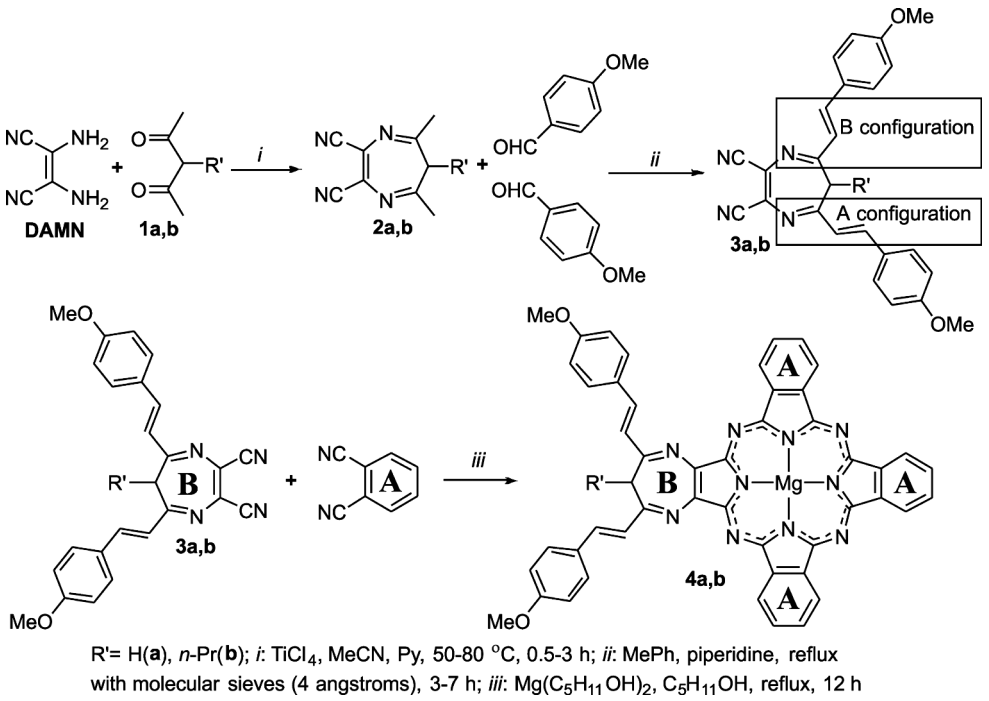
диазепинопорфиразина A_3B-типа в процессе темплатной кросс-циклотетрамеризации с 5 до 40 %. Квантово-химические расчеты на PW6B95-D3/def2-TZVP//BP86-D3/def2-TZVP уровне теории показали, что наличие заместителя в 6 положении 5,7-бис(2'-арилэтенил)-6H-1,4-диазепин-2,3-дикарбонитрилов может играть ключевую роль в создании стерических эффектов при формировании димерных интермедиатов в ходе макроциклизации, обеспечивая высокую селективность образования низкосимметричных порфиразинов, содержащих 1,4-диазепиновые фрагменты.

Ключевые слова: Синтез, 1,4-диазепин, порфиразин, DFT расчеты, стерический эффект заместителя.

In recent ten years, there has been a considerable progress in the research of porphyrazines with annulated diazepine ring(s). A set of diazepinoporphyrazines known to date includes both metalated and free-base symmetrical (A_4) and unsymmetrical (A_3B) macrocycles with various substitution patterns.[1–22] Up to now, only standard approaches have been used to synthesize both 1,4-diazepine-2,3-dicarbonitriles[15,23–26] and the macrocycles based on them.[5,13,15–17,19,20,22] Development of convenient selective approaches to synthesis of diazepinoporphyrazines and their precursors is critical for expanding the scope of their possible applications. In this work, we report new optimized technique for the synthesis of 1,4-diazepine-2,3-dicarbonitriles and novel approach to unsymmetrical A_3B-type diazepinoporphyrazines, most promising candidates for potential applications.

Recently, it has been demonstrated that the physicochemical properties of diazepinoporphyrazine macrocycles can be easily controlled by the specific choice of peripheral diazepine substituents with a special accent on their steric effect.[2–4,27] However, classical procedure of the condensation between diaminomaleonitrile (DAMN) and sterically hindered 2-substituted-1,3-diketone[26] (in our case, 3-*n*-propyl-2,4-pentanedione **1b**) proved to be ineffective, resulting in low yield of 1,4-diazepine-2,3-dicarbonitrile **2b**. Therefore, we have attempted to increase the yield of **2b**[†] by applying the method[28–30] commonly used for synthesis of imines from sterically hindered ketones. This method is based on the reaction of ketone with titanium tetrachloride-amine complex $TiCl_4$–$(NH_2R)_n$ in the presence of triethylamine (Et_3N) as an auxiliary base. In our case, however, the use of Et_3N led to inhibition of the reaction because DAMN appears to have lower complexation activity towards $TiCl_4$ than Et_3N. In order to trigger the reaction, we modified the method by replacing Et_3N with less basic pyridine (Py). As compared to the classical condensation procedure,[27] this led to a significant shortening of the reaction time from 9 to 3 h, but did not increase the yield of the diazepine-2,3-dicarbonitrile (Scheme 1). Evidently, the basicity of the auxiliary base affects the equilibrium concentration of the reactive $TiCl_4$–DAMN complex and, thus, the reaction kinetics, while the formation of 1,4-diazepine heterocycle can also be determined by the structural features of the $TiCl_4$–DAMN complex.

Preparation of 6-substituted 5,7-*bis*(2'-arylethenyl)-6*H*-1,4-diazepine-2,3-dicarbonitriles is of special interest since the use of 6-propyl substituted dinitrile **3b**[†] in the synthesis of unsymmetrical A_3B-type tribenzodiazepinoporphyrazine **4b** has led to the unprecedented increase in the yield (up to 40 %) as compared with 6-unsubstituted derivative **3a** (5 % yield of A_3B product **4a**) (Scheme 1)[††]. Initially, we assumed that the introduction of alkyl group into the C6 position of the 1,4-diazepine ring would prevent dimeriza-



Scheme 1. Synthesis of 1,4-diazepine-2,3-dicarbonitriles **2**, **3** and A_3B-type diazepinoporphyrazines **4**.

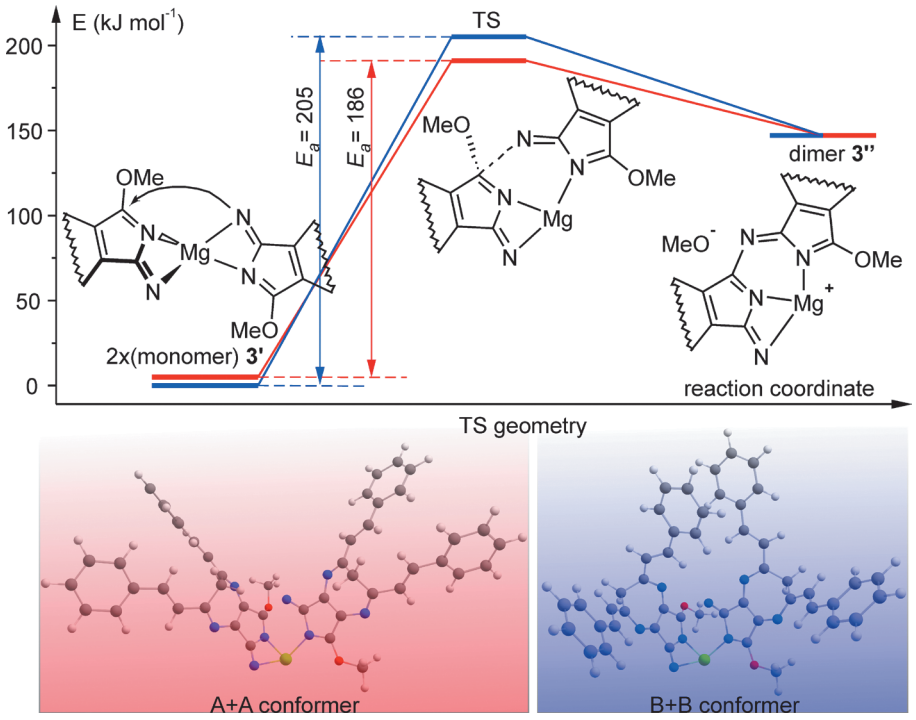


Figure 1. Theoretical analysis of the formation of dimeric intermediates around Mg^{2+} template for the different rotational isomers.

tion of the corresponding diazepinoporphyrazine[2,4,5] since the formation of the intermolecular hydrogen bonds with participation of axial protons at the C6 position will be sterically blocked. It turned out that 6-propyl substituted dinitrile **3b** exists as a 1:1 mixture of two isomers with equatorial and axial positions of the propyl group.[27] Moreover, owing to the steric effect of the propyl group, the equatorial isomer exists exclusively as a conformer (rotational isomer) with the B type configuration of the arylalkenyl substituents. We suppose that such predominant configuration of the arylethenyl group is responsible for the highly selective formation of A_3B-type product during cross-condensation of the dinitrile **3b** with phthalodinitrile under Linstead macrocyclization conditions.

In accordance with the generally accepted theory for macrocyclization mechanism[31–34] and our reaction monitoring data obtained by using UV-Vis and TLC, the key step responsible for the reaction selectivity should be the formation of dimeric intermediates. Quantum-chemical calculations at the PW6B95-D3/def2-TZVP//BP86-D3/def2-TZVP level of theory for the step of formation of dimeric intermediates **3''** from monomeric forms **3'** around Mg^{2+} template ion showed that there is a significant difference (19 kJ·mol^{-1}) between the activation barriers of this process for different rotational isomers of 5,7-*bis*(2'-arylethenyl)-6*H*-1,4-diazepine-2,3-dicarbonitrile (Figure 1).

Initially, the mean planes of the 1,4-diazepine fragments in **3'** are approximately perpendicular to each other, and, during the further condensation, they strive to form a common plane, which results in steric hindrance in the case of conformer with the type B configuration of the arylalkenyl fragments (Figure 1, transition-state geometry). Thus, the isomers of 6-substituted 5,7-*bis*(2'-arylethenyl)-6*H*-1,4-diazepine-2,3-dicarbonitriles with the type B configuration of the arylalkenyl substituents are poorly able to form dimeric intermediates **3''**, while they are highly capable of forming dimeric intermediates of mixed composition. We believe that this effect can also provide high selectivity towards the formation of unsymmetrical ABAB-type diazepinoporphyrazines. This work is in progress now.

Acknowledgements. The work was financially supported by the RSF (Grant 17-73-10413).

References and Notes

† *General procedure for the preparation of 5,7-dimethyl-6H-1,4-diazepine-2,3-dicarbonitriles* (***2a,b***). Complex $TiCl_4$–DAMN was prepared by adding a suspension of $TiCl_4$ (12 mmol) in dry MeCN (20 mL) to a suspension of DAMN (12 mmol) in dry MeCN (20 mL) under inert atmosphere at 5 °C. Then, dry pyridine (48 mmol) was added to the resulting red-orange solution of the complex. After 5 min, ice-bath was removed and **1a** or **1b** (12 mmol) was introduced in one portion. Next, the reaction mixture was refluxed under stirring for 0.5 h (**1a**) or 3 h (**1b**). The course of the reaction was monitored by TLC. The reaction mixture was cooled and filtered, and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$, filtered, and purified by column chromatography (SiO_2, $CHCl_3$/MeOH). This yielded **2a** (2.0 g, 96 %) and **2b** (1.3 g, 50 %) in the form of white crystals. **2a**: Mp 199–201 °C,[23] **2b**: Mp 123–124 °C.[27] 5,7-*Bis*[2′-(4-methoxyphenyl)ethenyl]-6*H*-1,4-diazepine-2,3-dicarbonitrile (**3a**) and 5,7-*bis*[2′-(4-methoxyphenyl)ethenyl]-6-propyl-6*H*-1,4-diazepine-2,3-dicarbonitrile (**3b**) were prepared according to the published procedures in the form of red-orange solids.[27] **3a**: Mp 267 °C, **3b**: Mp 174–175 °C.

†† *General procedure for the preparation of* $2^5,4^7$*-bis[(E)-2-(4-methoxyphenyl)]tribenzo[g,l,q]-6H-1,4-diazepino[2,3-b] porphyrazinato magnesium(II)* (***4a***) *and* 3^6*-n-propyl-*$2^5,4^7$*-bis[(E)-*

*2-(4-methoxyphenyl)]tribenzo[g,l,q]-6H-1,4-diazepino[2,3-b] porphyrazinato magnesium(II) (**4b**).* Mg metal (1.2 mmol) was boiled in isoamyl alcohol (30 mL) in the presence of a catalytic amount of I_2 until complete dissolution was observed (*ca*. 3 h). The solution of the resulting Mg alkoxide was cooled to room temperature, 1,4-diazepine-2,3-dicarbonitrile **3a** or **3b** (0.22 mmol) was added, and the mixture was stirred for 0.5 h. Then, the first portion of phthalonitrile (1.1 mmol) was added and the reaction mixture was heated for 2 h to reach the boiling temperature. After 1 h of boiling, the second portion of phthalonitrile (1.1 mmol) was added and the reflux was continued for further 9 h. Then, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The resulting dry residue was successively washed with 50 % aqueous acetic acid (4×50 mL), 5 % aqueous solution of sodium bicarbonate (2×50 mL), distilled water (4×50 mL) and finally with MeOH (50 mL) and dried *in vacuo* at 50 °C. The resulting solid was subjected to gel permeation chromatography (Bio-Beads S-X1, pyridine). This yielded **4a** and **4b** in the form of dark-blue solids. **4a**: yield 9 mg (5 %). *m/z* (MALDI-TOF) (%) 817.34 (100) [M^+]. UV-Vis (pyridine) λ_{max} (lgε) nm: 369 (4.86), 468 (4.03), 602 (4.22), 664 (4.84), 706 (5.03). ^{1}H NMR ([D6]DMSO, 298 K) δ_H ppm: 9.46 (4H, m, α-Bz), 9.38 (2H, m, α'-Bz) 8.24–8.30 (8 H, m, β-Bz; =CH-Ar), 7.96 (4H, d ^3J = 8.7 Hz, *o*-ArH), 7.66 (2H, d ^3J = 16.5 Hz, Dz-CH=), 7.12 (4H, d ^3J = 8.8 Hz, *m*-ArH), 3.87 (6H, s, -OCH_3). ^{13}C NMR ([D6]DMSO, 298 K) δ_C ppm: 160.75, 154.96, 154.76, 153.03, 151.45, 148.35, 140.48, 139.43, 138.80, 138.56, 138.31, 130.08, 129.93, 129.63, 128.65, 125.80, 122.90, 122.77, 122.74, 114.67, 55.37, 41.33. **4b**: yield 77 mg (40 %). *m/z* (MALDI-TOF) (%) 859.40 (100) [M^+]. UV-Vis (pyridine) λ_{max} (lgε) nm: 372 (5.05), 474 (4.25), 603 (4.45), 649 (4.91), 666 (5.00), 712 (5.16). ^{1}H NMR ([D6]DMSO, 298 K) δ_H ppm: 9.41–9.47 (6H, m, α-Bz), 8.24–8.28 (8 H, m, β-Bz; =CH-Ar), 7.98 (4H, d ^3J = 8.6 Hz, *o*-ArH), 7.69 (2H, d ^3J = 16.5 Hz, Dz-CH=), 7.12 (4H, d ^3J = 8.6 Hz, *m*-ArH), 5.96 (1H, t ^3J = 7.5 Hz, 6H), 3.87 (6H, s, -OCH_3), 1.43 (2H, sext ^3J = 7.5 Hz, $^{\beta}CH_2$), 1.20 (2H,q ^3J = 7.9 Hz, $^{\alpha}CH_2$), 0.60 (3H, t ^3J = 7.3 Hz, CH_3). ^{13}C NMR ([D6] DMSO, 298 K) δ_C ppm: 160.70, 155.13, 154.90, 153.04, 150.96, 150.88, 139.09, 138.79, 138.56, 138.31, 138.09, 130.09, 129.92, 129.75, 129.63, 128.73, 127.58, 122.89, 122.77, 114.64, 55.37, 45.42, 24.15, 20.70, 13.75.

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Received 22.04.2018
Accepted 06.05.2018