JOC Article

Synthesis of N-Confused Phlorins via an Addition/Cyclization Pathway

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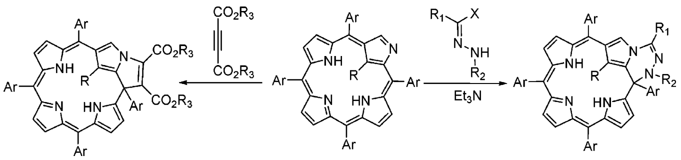

The syntheses of N-confused phlorins are provided by reactions of N-confused porphyrins with nitrilimines and with dialkyl acetylenedicarboxylate. Both reactions involve zwitterionic intermediates and proceed through an addition/cyclization pathway.

Introduction

Phlorins, a kind of porphyrinic macrocycle that differs from porphyrins by the presence of an sp^3-hybridized carbon atom at one of the four meso-positions, are synthesized either by reduction of porphyrins at one of the meso positions or by the addition of nucleophiles to the porphyrin macrocycle.[1]

An N-confused porphyrin (NCP) is a porphyrin isomer with an "inverted" pyrrolic ring.[2] The nonconventional coordination modes of the NCP complexes[3] and the unusual reactivity of the inverted pyrrole ring of NCP[4] have attracted the chemists' interest.[5]

Recently, we reported the synthesis of N-confused phlorins via the Staudinger-type imine−ketene protocol of the reaction of NCPs.[6] The unusual reactivity of the peripheral carbon−nitrogen double bond of a free base NCP drove us to a further study on the synthesis of N-confused phlorins via the reaction at this site.

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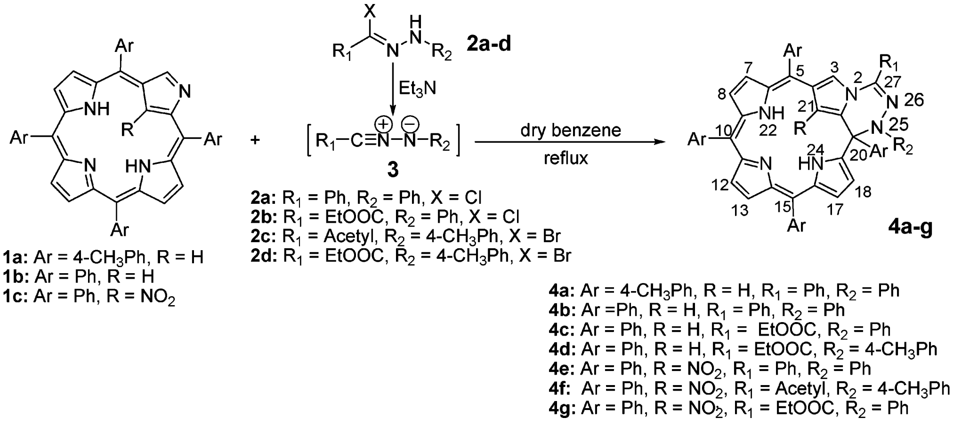
SCHEME 1. Synthesis of N-Confused Phlorins 4a−g



Nitrilimines, an important class of 1,3-dipoles,[7] can react with the C, N double bond of pyridine, quinoline, and isoquinoline, giving rise to a variety of 1,2,4-triazoles.[8] In the present work, we report the results of our attempt to apply the nitrilimine 1,3-dipolar cycloaddition protocol in the reaction involving NCPs **1** and several nitrilimines **3** generated in situ by the reaction of hydrazonyl halides **2** and triethylamine (Scheme 1). Such an approach resulted in a regioselective cyclization, yielding various N-confused phlorins **4** (Scheme 1).

The reaction of NCPs with dialkyl acetylenedicarboxylate, which gives the similar N-confused phlorins, is also reported.

Results and Discussion

A solution of NCP **1a**, hydrazonyl chloride **2a**, and triethylamine in dry benzene was refluxed under a nitrogen atmosphere for 26 h. Chromatographic separation of the reaction mixture afforded N-confused phlorin **4a** on the basis of its mass, UV−vis, and NMR (^{1}H, ^{13}C, COSY, HMQC, HMBC, NOESY) spectra.

The matrix-assisted laser desorption ionization−time-of-flight mass spectrometry (MALDI-TOFMS) of **4a** gave the molecular ion peak at m/z 864, which indicates the addition of one molecule of diphenyl nitrilimine **3a** to **1a**. The UV−vis spectrum of **4a** (Figure 1), characterized by two major bands at ~399 and 698 nm, resembles those observed for N-confused phlorins.[6]

The ^{1}H NMR spectrum of **4a** (223 K, $CDCl_3$) is shown in Figure 2 along with the signal assignments. The alteration of the resonance positions with respect to those observed for the starting porphyrinoid **1a**[2] is in line with the absence of the aromatic ring current in **4a**. The spectrum is characterized by six β-pyrrole proton signals in the region of 6.48−7.10 ppm, the inner CH signal (21-H) of the inverted pyrrole at 4.46 ppm, and by two signals of inner NH's appearing at 8.66 and 8.14 ppm, the assignment of which was confirmed by the deuterium exchange experiment with D_2O.

Further assignment of the proton and carbon signals in the NMR spectra of **4a** was conducted by means of combination of 2D homo- and heteronuclear experiments. In the low-temperature ^{1}H−^{1}H COSY spectrum (223 K, $CDCl_3$; see the Supporting Information) the NH protons at 8.66 ppm (H24) or 9.14 ppm (H22) correlate to β-protons at 6.48 (H18) and 6.61 ppm (H17) or at 7.10 (H7) and 6.82 ppm (H8), respectively. The ^{1}H−^{1}H COSY map shows also correlations between H3 and H21, as well as between β-protons belonging to each of the pyrrole rings.

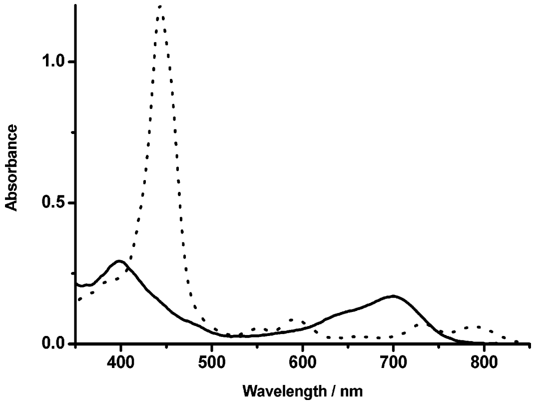


FIGURE 1. UV−vis spectra of **4a** (solid line) and **1a** (dotted line) in $CHCl_3$ (8.5×10^{-6} M).

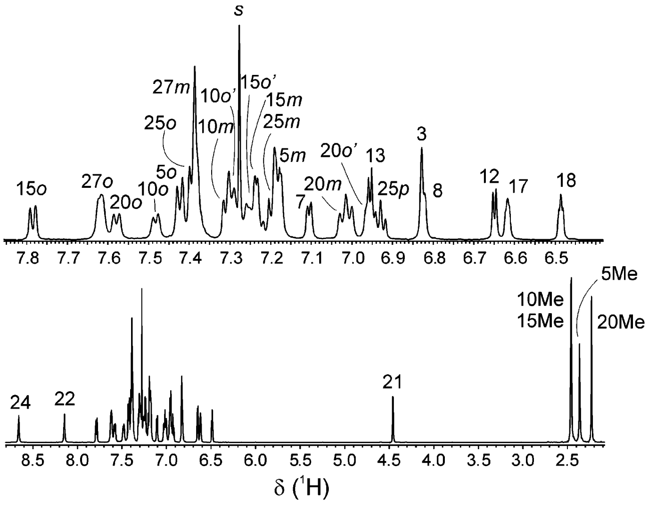


FIGURE 2. ^{1}H NMR spectrum (600 MHz, 223 K, $CDCl_3$) of **4a**. Resonance assignments (obtained from COSY and NOESY experiments) follow the numbering scheme given in Scheme 1.

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TABLE 1. Reaction of NCP's with Various Hydrazonyl Halides

entry	NCP	**2**	product	time[a] (h)	yield[b] (%)
1	**1a**	**2a**	**4a**	26	70
2	**1b**	**2a**	**4b**	26	67
3	**1b**	**2b**	**4c**	15	71
4	**1b**	**2d**	**4d**	5	74
5	**1c**	**2a**	**4e**	28	66
6	**1c**	**2c**	**4f**	5	64
7	**1c**	**2b**	**4g**	15	69

[a] Reaction time for consuming all of the starting materials. [b] Isolated yields.

At low-temperature the rotation of *meso*-aryl groups is slowed down, which resulted in differentiation of the chemical shift of the ortho-protons which, however, correlate with each other within the particular tolyl group in the $^1H-^1H$ NOESY map (223K, $CDCl_3$, see Supporting Information), due to the chemical exchange. The differentiation of the aryl protons and an array of β-H$-$*o*-H interprotonic contacts allow detailed analysis of scalar and dipolar interaction starting from H3 and going to H24 or vice versa. The through-space interactions between ortho-protons of phenyl substituents at N25 or C27 and protons belonging to the macrocyclic ring (H18 or H3, respectively) are consistent with the formation of an exocyclic triazine.

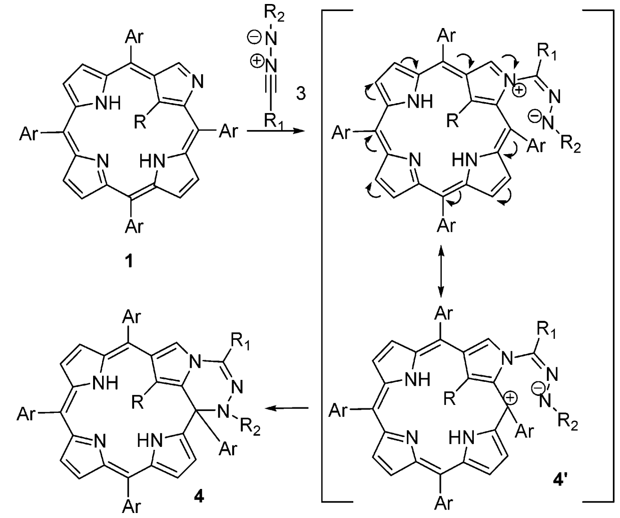
The $^1H-^{13}C$ heteronuclear 2D techniques allow assignment of the carbon resonances which are most important for the elucidation of the structure of **4a**. The inner carbon of the *confused* pyrrole that resonates at 98.8 ppm was assigned on the basis of its correlation with H21 at 4.46 ppm in the HMQC experiment (298 K, $CDCl_3$, see Supporting Information). The chemical shift of this carbon is similar to those of C21 in other N-confused porphyrinoids.[2] The ^{13}C resonance position and the environment of the sp^3-meso C20 can be identified on the basis of its correlations with H21 in the $^1H-^{13}C$ HMBC map of **4a** (298 K, $CDCl_3$, see the Supporting Information). The chemical shift of 66.0 ppm for C20 indicates a direct bond with a heteroatom, in line with the structure involving nitrogen in position 25.

The reaction was found to be general for a number of hydrazonyl halides **2**, affording the N-confused phlorins in moderate yield. The results are summarized in Table 1. The spectral characteristics of the products **4b**$-$**4g** are similar to those of **4a** (see the Supporting Information).

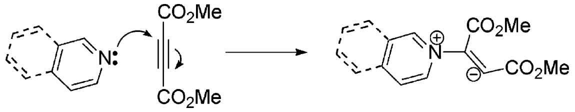
Mechanistically, the reaction originated from the attack of the nitrogen atom of the inverted pyrrole on the dipole carbon, then involving the formation of an initial zwitterionic intermediate **4′**, which undergoes a subsequent ring closure to the corresponding cycloadduct **4** (Scheme 2). The mechanism resembles that of the 1,3-dipolar cycloaddition reactions for pyridine and isoquinoline, which also involve the zwitterionic intermediates.[9]

It was reported that the nitrogen heterocycle, such as pyridine or isoquinoline, can react with dimethyl acetylenedicarboxylate (DMAD) proceeding through the zwitterionic intermediates (Scheme 3).[10]

SCHEME 2. Mechanism of the Reactions of NCP with Nitrilimine



SCHEME 3. The Zwitterions Generated from Pyridine (Isoquinoline) and DMAD



Since the peripheral carbon$-$nitrogen double bond of NCP has similar character as those in pyridine or isoquinoline, formation of a zwitterionic intermediate in the reaction with DMAD can be anticipated. Such an intermediate is expected to undergo a subsequent ring closure to form the N-confused phlorins through the mechanism analogous to that proposed above. The primary results for such NCP reactivity are reported here (Scheme 4).

A solution of NCP **1d** and DMAD **5a** in dry benzene was refluxed under a nitrogen atmosphere for 3 h. Chromatographic separation of the reaction mixture afforded N-confused phlorin **6a** on the basis of its mass, UV$-$vis, and NMR (^1H, ^{13}C, COSY, HMQC, HMBC, NOESY) spectra.

The MALDI-TOF spectra of **6a** gave the molecular ion peak at *m/z* 1116, which indicates the addition of one molecule of DMAD to the NCP **1d**.

The absorption spectrum of **6a** resembles that of N-confused phlorin **4a** in the features of the visible and the near-infrared absorption bands, except for the red shifts of the absorption maxima. These results suggest that the π-electron system of the porphyrin ring of **6a** is broken, as is that of **4a** (see the Supporting Information).

The ^1H NMR spectrum of **6a** (Figure 3) also resembles that of N-confused phlorin **4a** in the feature of the upfield shift of β-pyrrole signals. The detailed analysis of the 2D spectra of **6a** allows full assignment of the proton signals (see Supporting Information). The resonances of "inner" protons, i.e., H21, H22, and H24, are considerably more downfield shifted in comparison with those observed for **4a**. These differences may arise from

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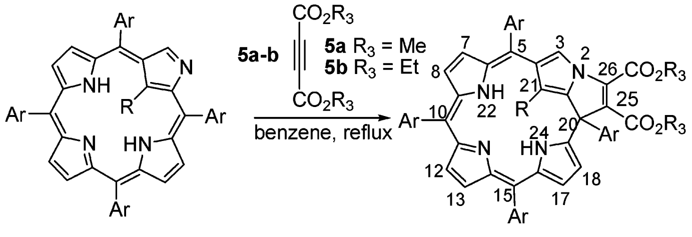
SCHEME 4. Synthesis of N-Confused Phlorins 6a−d



1a-b, 1d

6a-d

1d Ar = 3,4,5-trimethoxyphenyl, R = H

6a Ar = 3,4,5-trimethoxypheny, R = H, R_3 = Me
6b Ar = 3,4,5-trimethoxyphenyl, R = H, R_3 = Et
6c Ar = Ph, R = H, R_3 = Et
6d Ar = 4-CH_3Ph, R = H, R_3 = Et

various deformations of the macrocycle caused by six- and five-membered exocyclic rings and thus the different influence of the local aromatic ring current of *meso*-aryls.

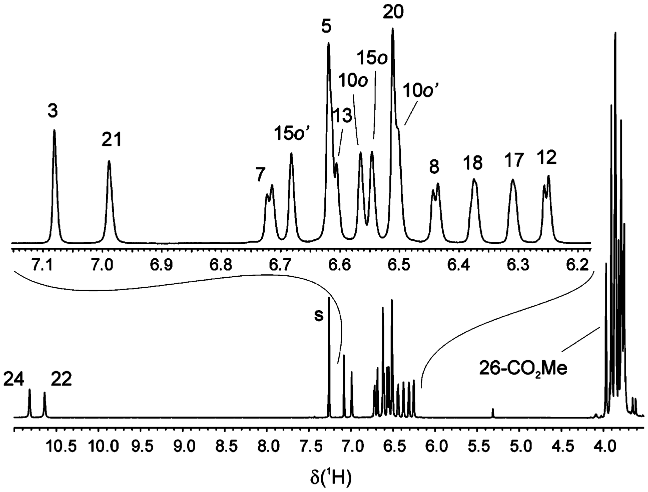


FIGURE 3. ^{1}H NMR spectrum (600 MHz, 223 K, $CDCl_3$) of **6a**. Resonance assignments (obtained from COSY and NOESY experiments) follow the numbering scheme given in Scheme 4.

In conclusion, two novel types of N-confused phlorin derivatives were obtained in a moderate yield by the reactions of NCP's with nitrile imines and with dialkyl acetylenedicarboxylates. Both reactions occur regioselectively on the external nitrogen and the neighboring *meso*-carbon through an addition/cyclization process. This work demonstrates the reactivity of the peripheral C═N bond of N-confused porphyrins and offers two easy ways for its modification. The facile synthesis as well as the structural diversity and flexibility of N-confused phlorins make them an attractive ligand systems for the wide study of organometallic complexes.

Experimental Section

Synthesis of N-Confused Phlorin 4a. A solution of NCP **1a** (67 mg, 0.1 mmol), hydrazonyl chloride **2a** (46 mg, 0.2 mmol), and triethylamine (30 mg, 0.3 mmol) in dry benzene was stirred and refluxed under a nitrogen atmosphere for 26 h. The reaction progress was monitored by TLC. After reaction completion (full consumption of **1a**), the reaction mixture was cooled to the room temperature, and solvent was evaporated under vacuum. The residue was chromatographed on a silica gel column with CH_2Cl_2 as eluent. The fastest moving green band was collected and solvent was removed to give 60 mg (yield 70%) of the N-confused phlorin **4a**. ^{1}H NMR (600 MHz, $CDCl_3$, 223K) δ: 2.23 (s, 3H), 2.36 (s, 3H), 2.45 (m, 6H), 4.46 (s, 1H), 6.48 (m, 1H), 6.61 (m, 1H), 6.65 (d, J = 4.8 Hz, 1H), 6.82 (m, 2H), 6.93−6.96 (m, 3H), 7.01 (m, 2H), 7.10 (d, J = 4.8 Hz, 1H), 7.17−7.25 (m, 7H), 7.28−7.32 (m, 3H), 7.39−7.43 (m, 7H), 7.48 (m, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.62 (m, 2H), 7.78 (d, J = 7.8 Hz, 1H), 8.14 (s, 1H), 8.66 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K) δ: 21.0, 21.1, 21.2, 21.3, 66.0, 98.8, 107.4, 112.8, 116.2, 121.6, 121.8, 121.9, 127.6, 127.7, 127.9, 128.0, 128.5, 128.6, 128.7, 128.9, 129.0, 129.4, 131.1, 130.9, 132.2, 135.2, 137.3, 137.8, 141.9, 146.2, 146.6, 152.1, 167.1. UV−vis ($CHCl_3$) λ_{max}/nm (log ϵ): 399 (4.62), 698 (4.40). MS (MALDI-TOF): *m/z* 864.2 (864.4 for $C_{61}H_{48}N_6$). HRMS (SIMS): calcd for $C_{61}H_{48}N_6$ [M^+] 864.3940, found 864.3925.

Synthesis of N-Confused Phlorin 6a. A sample of **1d** (97 mg, 0.1 mmol) was placed in a flame-dried 25-mL two-neck round-bottom flask and dissolved in 10 mL of dry benzene under nitrogen. The dimethyl acetylenedicarboxylate **5a** (28 mg, 0.2 mmol) was added to the solution, which was stirred and refluxed for 3 h. Lack of the **1d** in the reaction mixture (TLC-controlled) indicated the reaction completion. The mixture was cooled to the room temperature, and solvent was evaporated under vacuum. The residue was chromatographed on a silica gel column with CH_2Cl_2/ethyl acetate (90:10 v/v) as an eluent. The fastest moving brown band was collected and solvent was removed to give 75 mg (67%) of the N-confused phlorin **6a**. ^{1}H NMR (600 MHz, $CDCl_3$, 223K) δ: 3.73 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 3.79 (s, 6H), 3.82 (s, 3H), 3.86 (s, 12H), 3.87 (s, 3H), 3.90 (s, 6H), 3.97 (s, 3H), 6.25 (d, J = 4.2 Hz, 1H), 6.31 (s, 1H), 6.37 (s, 1H), 6.44 (d, J = 5.4 Hz, 1H), 6.51 (m, 3H), 6.55 (s, 1H), 6.57 (s, 1H), 6.61 (m, 3H), 6.68 (s, 1H), 6.72 (d, J = 5.4 Hz, 1H), 6.98 (s, 1H), 7.08 (s, 1H), 10.64 (s, 1H), 10.82 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$, 298 K) δ: 51.8, 52.9, 55.6, 55.8, 55.9, 57.7, 59.8, 60.3, 60.4, 60.5, 101.4, 105.1, 107.5, 108.0, 108.5, 112.5, 117.5, 117.9, 122.7, 127.1, 128.0, 128.1, 128.3, 129.6, 130.2, 132.7, 134.7, 134.8, 134.9, 135.1, 135.9, 136.5, 137.3, 137.4, 137.8, 138.5, 142.1, 147.8, 151.6, 152.2, 152.4, 152.6, 159.7, 162.2, 168.4. UV−vis ($CHCl_3$) λ_{max}/nm (log ϵ): 412 (4.60), 760 (4.06). MS (MALDI-TOF): *m/z* 1116.6 (1116.4 for $C_{62}H_{60}N_4O_{16}$). HRMS (SIMS): calcd for $C_{62}H_{60}N_4O_{16}$ [M^+] 1116.4004, found 1116.4031.

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Supporting Information Available: Experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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