DOI 10.5012/bkcs.2011.32.7.2465

Aldol-Like Carbon-Carbon Condensation for Pyridyl Substituted Chlorins

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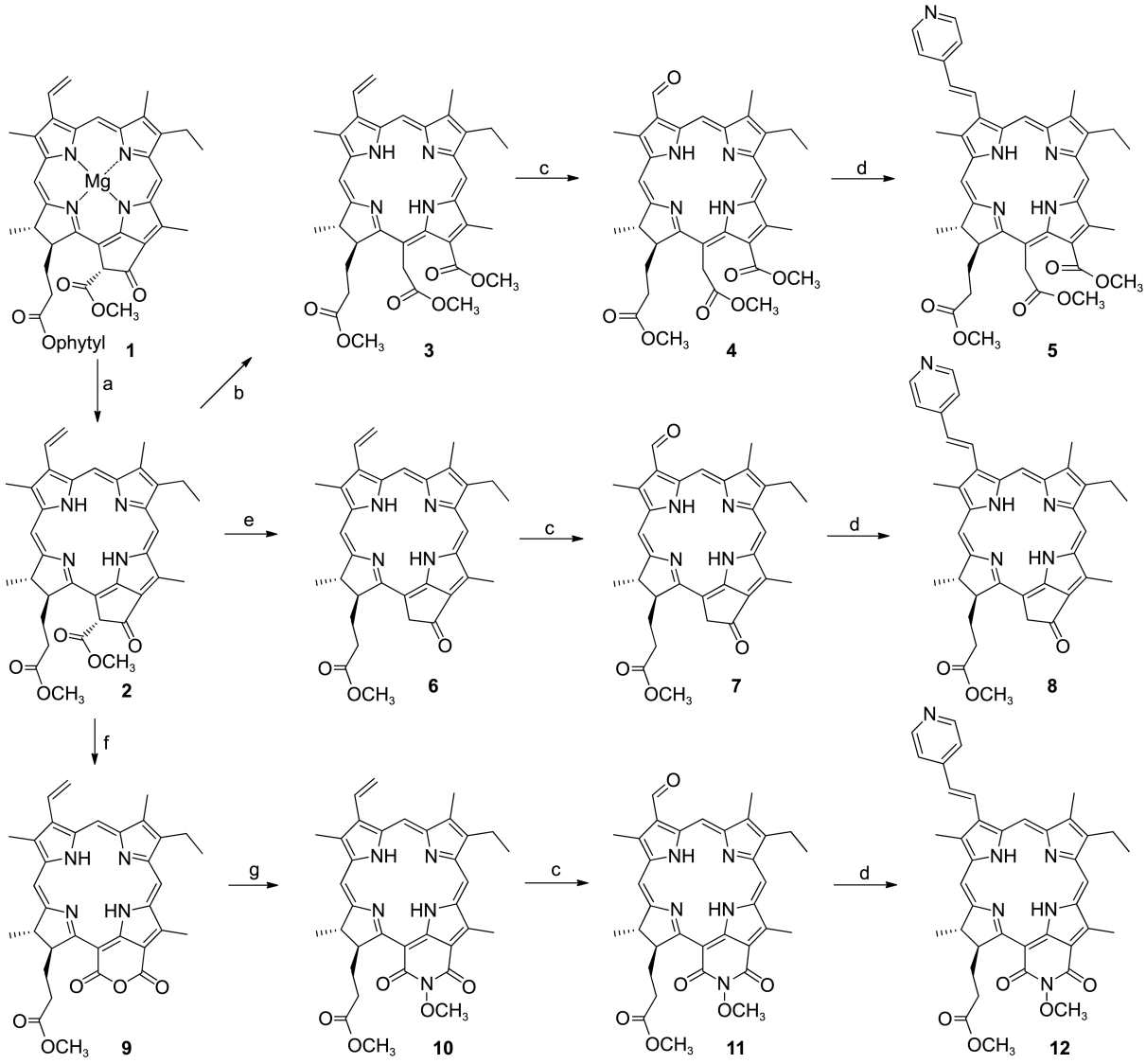
Received April 8, 2011, Accepted May 19, 2011

Key Words : Chlorin, Aldol-like condensation, Photosensitizer, Photodynamic therapy

Pyridyl substituted porphyrins or chlorins and their metal complexes have recently attracted considerable attention among the great diversity of porphyrins with a specific pattern of substituents because of their applications in the construction of notable arrays which have been investigated as biomimetic models of photosynthetic systems.[1,2] Water-soluble quaternary salts derived from pyridylporphyrins or pyridylchlorins have been studied as photosensitizers in



Scheme 1. Synthesis of pyridyl substituted chlorins. Reagents and conditions: (a) 5% H_2SO_4 in MeOH, N_2, 12 h; (b) NaOMe, MeOH, 2 h; (c) OsO_4/$NaIO_4$, 3 h; (d) 4-picoline, Ac_2O, AcOH, reflux, 5 h; (e) 2,4,6-picoline, reflux, 2 h; (f) (1) KOH/pyridine/air, (2) CH_2N_2; (g) (1) Hydroxylamine hydrochloride, pyridine, 5 h, (2) CH_2N_2.

photodynamic therapy (PDT).[3,4] The high uptake and retention of such compounds and their DNA targeting capabilities have led to the synthesis of a number of novel cationic derivatives, such as *Tetra*-cationic *meso*-porphyrins,[5] tetrahydroporphyrin tetratosylate (THPTS),[6] and monocationic cycloimide derivatives of chlorin p_6 (CICD).[7] The main feature of the reactivity of alkylpyridines is deprotonation of the alkyl group at the carbon adjacent to the ring.[8] The 2- and 4-picolines are known to undergo stereoselective aldol-like condensations with carbonyl compounds upon treatment with acid or base.[9] Based on these intriguing results, in the present work we proposed the synthesis of a series of novel pyridyl substituted chlorins *via* stereoselective aldol-like carbon-carbon condensation between 4-picoline and formyl chlorins, and the optical properties of the synthetic compounds which were affected by the 3^2-pyridyl group. To the best of our knowledge, this is the first report about the synthesis of carbon-carbon bond linked pyridyl chlorins *via* aldol-like condensation.

In this study, 3-formyl chlorins (Scheme 1. **4**, **7**, **11**), obtained by a sequence of reactions[10-14] from chlorophyll a, were refluxed with 4-picoline in acetic anhydride and several drops of acetic acid to afford the desired pyridyl chlorins (**5**, **8**, **12**) with 60-65% yields.[15] The structure of the pyridyl chlorins was determined by ^{1}H NMR, HRMS, UV-vis spectra and elemental analysis.[16-18] It is suggested that dienamide (Fig. 1(c)) is the reacting nucleophiles in aldol-type condensations brought with acetic anhydride.

The structure changes between the intermediates and the final products were showed clearly by the resonance changes in the ^{1}H NMR spectrum. As shown in Figure 2, The 3-vinyl proton signals of methyl pyropheophorbide *a* (MPPa, **6**) appeared as a typical ABX system at δ 8.01 (dd, J = 17.8, 11.5 Hz, 3^1-H), 6.29 (d, J = 17.9 Hz, 3^{2a}-H), and 6.18 (d, J = 11.5 Hz, 3^{2b}-H) (**A**), the 3-formyl of methyl pyropheophorbide *d* (MPP*d*, **7**) showed its proton signal as singlet at δ 11.47 (**B**), while as shown in the ^{1}H NMR spectrum (**C**), the absence of the 3-formyl proton resonance at δ 11.47, the presence of two doublets at δ 8.60 (3^1-H) and δ 7.56 (3^2-H), as well as the proton resonances of the 4-substituted pyridine part showed as two doublets at δ 8.80 (2' + 6'-H) and δ 7.72 (3' + 5'-H) confirmed the structure of the pyridyl substituted compound **8**. It was also observed that the coupling constant (J) between the two vinylic protons 3^1 and 3^2 of compound **8** is about 16 Hz, typical of an *E*-geometry of the double bond. It is worth noting that in this condensation method only the *E*-isomer was formed, which was further confirmed by the ^{1}H NMR spectrum of the corresponding chlorin e_6, and purpurinimide condensational derivatives (**5**, **12**).

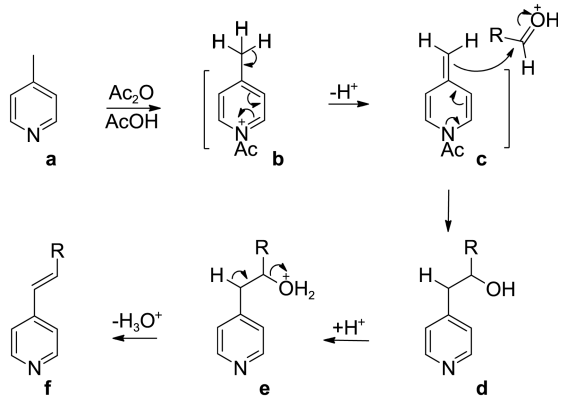


Figure 1. Mechanism of the aldol-like condensation. R represents different kinds of formyl substituted chlorins.

In the absorption spectra, the position and intensity of Q_y

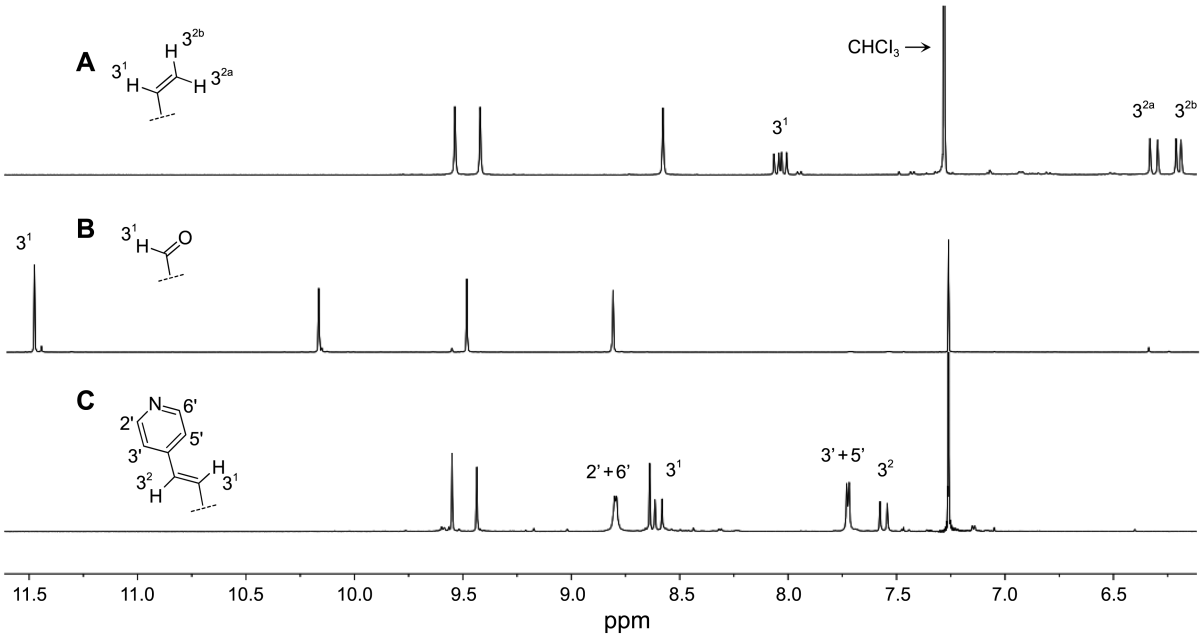


Figure 2. The comparative ^{1}H NMR spectra ($CDCl_3$, 500 MHz) in the region δ 6.0-11.6 ppm of (a) MPP*a* **6**, (b) MPP*d* **7**, (c) pyridyl substituted derivative **8**.

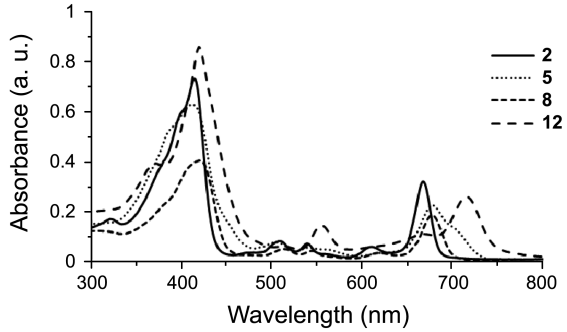


Figure 3. Electronic absorption spectra (10 μM in CH_2Cl_2) of MPa (**2**) and pyridyl substituted chlorins **5**, **8**, **12**.

bands of the final products were changed after the condensation (Fig. 3). It was found that all the substituted derivatives demonstrated bathochromic shifts (12-50 nm) and decreased intensities of their Q_y bands in various degrees compared to their starting materials MPa **2**. For example, compared to the parent molecule MPa **2**, the pyridyl substituted derivative **5** showed an intensity-dropped Q_y band at 678 nm with 12 nm red shift, while compound **12** showed its intensity-dropped Q_y band at 716 nm with 50 nm red shift compared to MPa **2**. Similar relationship was also demonstrated for compound **8**. When compared to the intermediates **4**, **7** or **11**, however, all the pyridyl substituted derivatives demonstrated hypsochromic shifts of their Q_y bands in various degrees (15-26 nm). These changes were ascribed to the combination of two adverse effects: (i) extension of conjugated system by introducing 3-vinylpyridine group, and (ii) loss of electron-withdrawing formyl group.

Further evidence for the structure determination came from the high resolution mass spectra (HRMS). It was found that the high resolution mass spectra of the pyridyl substituted derivatives showed the protonated molecular ion peak (*m/z*), for example compound **8** showed its protonated molecular ion peak (*m/z*) at 626.3130 (Calcd. for $C_{39}H_{40}N_5O_3$ [MH^+] 626.3131), in agreement with its corresponding theoretical value.

In conclusion, the synthetic methodology utilizing aldol-like condensation of formyl-substituted chlorins possessing chlorophyll-*a* skeleton with 4-picoline lays the groundwork for important peripheral functionalization of tetrapyrrolic ring systems. Such reactions constructed conveniently carbon-carbon bond linked pyridyl chlorins, and these modifications may be valuable in the generation of novel DNA intercalating agents and photosensitizers for PDT.

Acknowledgments. The authors appreciate the financial support by the second stage of the BK21 Project in 2010.

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15. General method for preparing pyridyl substituted chlorins: Formyl chlorin (1.0 eq.) and 4-picoline (1.5 eq.) were refluxed in Ac_2O (10 mL) with two drops of AcOH for 5 h under nitrogen atmosphere. The reaction mixture was evaporated to remove the solvent, and then dissolved with CH_2Cl_2 (30 mL), washed with H_2O (2 × 50 mL), organic layer obtained was dried over Na_2SO_4, concentrated, and purified over a silica gel column to yield the pure product as dark brown solid.
16. Data for **5**. Yield: 65%, UV-vis (CH_2Cl_2) λ_{max} ($\varepsilon \times 10^4$): 412 (6.31), 504 (0.78), 542 (0.56), 678 (2.26) nm. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (s, 1H, 10-H), 9.52 (s, 1H, 5-H), 8.80 (s, 1H, 20-H), 8.75 (d, J = 5.3 Hz, 2H, 2' + 6'-H), 8.53 (d, J = 16.2 Hz, 1H, 3^1-H), 7.64 (d, J = 5.6 Hz, 2H, 3' + 5'-H), 7.50 (d, J = 16.4 Hz, 1H, 3^2-H), 5.36 (d, J = 18.9 Hz, 1H, 15^1-H), 5.25 (d, J = 19.0 Hz, 1H, 15^1-H), 4.47 (q, J = 7.3 Hz, 1H, 18-H), 4.41 (d, J = 10.5 Hz, 1H, 17-H), 3.82-3.72 (m, 2H, 8^1-CH_2), 4.27, 3.78, 3.65, 3.57, 3.50, 3.28 (each s, each 3H, CH_3 + OCH_3), 2.64-2.53, 2.27-2.17 (each m, total 4H, 17^1 + 17^2-CH_2), 1.76 (d, J = 7.2 Hz, 3H, 18-CH_3), 1.71 (t, J = 7.6 Hz, 3H, 8^2-CH_3), −1.32, −1.55 (each br s, each 1H, NH). HRMS (FAB): Calcd. for $C_{42}H_{46}N_5O_6$ (MH^+) 716.3448; Found 716.3451. Anal. calcd for $C_{42}H_{45}N_5O_6$: C 70.47; H 6.34; N 9.78. Found C 70.50, H 6.35, N 9.80.
17. Data for **8**. Yield: 63%, UV-vis (CH_2Cl_2) λ_{max} ($\varepsilon \times 10^4$): 421 (4.05), 514 (0.51), 544 (0.43), 620 (0.35), 678 (1.86) nm. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H, 10–H), 9.44 (s, 1H, 5–H), 8.80 (d, J = 4.8 Hz, 2H, 2' + 6'–H), 8.64 (s, 1H, 20–H), 8.60 (d, J = 16.5 Hz, 1H, 3^1–H), 7.72 (d, J = 5.8 Hz, 2H, 3' + 5'–H), 7.56 (d, J = 16.5 Hz, 1H, 3^2–H), 5.29 (d, J = 19.5 Hz, 1H, 13^2–H), 5.14 (d, J = 19.5 Hz, 1H, 13^2–H), 4.52 (q, J = 7.4 Hz, 1H, 18–H), 4.35 – 4.30 (m, 1H, 17–H), 3.71 (q, J = 7.5 Hz, 2H, 8^1–CH_2), 3.69, 3.62, 3.51, 3.26 (each s, each 3H, OCH_3 + CH_3), 2.77-2.67, 2.64-2.54, 2.36-2.25 (each m, 4H, 17^1 + 17^2–CH_2), 1.83 (d, J = 7.4 Hz, 3H, 18–CH_3), 1.71 (t, J = 7.6 Hz, 3H, 8^2-CH_3), 0.34, –1.74 (each br s, each 1H, NH). HRMS (FAB): Calcd. for $C_{39}H_{40}N_5O_3$ (MH^+) 626.3131; Found 626.3130. Anal. calcd for $C_{39}H_{39}N_5O_3$: C 74.86; H 6.28; N 11.19. Found C 74.88, H 6.31, N 11.20.
18. Data for **12**. Yield: 60%, UV-vis (CH_2Cl_2) λ_{max} ($\varepsilon \times 10^4$): 370 (3.95), 420 (8.60), 510 (0.61), 555 (1.45), 669 (1.11), 716 (2.60) nm. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (s, 1H, 10–H), 9.39 (s, 1H, 5–H), 8.80 (m, 2H, Py–H), 8.60 (s, 1H, 20–H), 8.48 (d, J = 16.5 Hz, 1H, 3^1–H), 7.72 (dd, J = 5.2, 0.6 Hz, 2H, Py–H), 7.57 (d,

J = 16.5 Hz, 1H, 3^2–H), 5.28 (dd, J = 7.6, 2.2 Hz, 1H, 17–H), 4.39 (q, J = 7.5 Hz, 1H, 18–H), 4.38 (s, 3H, N–OCH_3), 3.66 (q, J = 7.6 Hz, 2H, 8^1–CH_2), 3.83, 3.59, 3.45, 3.19 (each s, each 3H, OCH_3 + CH_3), 2.87-2.79, 2.56-2.42, 2.05-1.92 (each m, total 4H, 17^1 + 17^2–CH_2), 1.74 (d, J = 7.3 Hz, 3H, 18–CH_3), 1.68 (t, J = 7.7 Hz, 3H, 8^2–CH_3), 0.15, 0.14 (each brs, each 1H, NH). HRMS (FAB): Calcd. for $C_{40}H_{41}N_6O_5$ (MH^+) 685.3138; Found 685.3142. Anal. calcd for $C_{40}H_{40}N_6O_5$: C 70.16; H 5.89; N 12.27. Found C 70.19, H 5.91, N 12.30.