Chinese Chemical Letters 27 (2016) 789–794

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

A facile synthesis of cyano-chlorins related to chlorophyll from formyl (pyro)-pheophorbide-*a* by a tandem transformation of the aldehyde into a nitrile group

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ARTICLE INFO

Article history:
Received 27 October 2015
Received in revised form 14 December 2015
Accepted 22 December 2015
Available online 12 January 2016

Keywords:
Chlorophyll-*a*
Chlorin
(Pyro)pheophorbide-*a*
Cyanation reaction
Beckmann rearrangement
Tandem transformation

ABSTRACT

A facile synthesis for cyanochlorin related to chlorophyll from a formyl-substituted chlorin, by the oxidation of methyl (pyro)pheophorbide-*a*, was accomplished. These readily available chlorin aldehydes were assembled together with hydroxylamine hydrochloride in a tandem process to produce the corresponding chlorin nitriles in moderate to good yields. The formation of chlorin nitrile was discussed and a possible mechanism for the corresponding cyanation reaction was tentatively proposed.

1. Introduction

Many naturally occurring [(bacterio)chlorophylls, (B)Chls] have a highly reactive formyl group attached directly to their tetrapyrrole macrocycles, such as Chl-*b*, Chl-*d*, and BChl-*e*. It is well known that these carbon–oxygen double bonds are readily modified to build various unique chemical structures capable of influencing the fundamental properties. From many quantitative structure–activity relationship (QSAR) studies it has been shown that the presence, variety and position of the substituents in the parent molecule made a remarkable difference in biological activity [1–5]. Introducing active functional groups around the porphyrin core has become an important strategy to produce useful tetrapyrrolic macrocycles. Among these, the transformation of an aldehyde into a nitrile group is a highly valued reaction because of the versatility of nitriles as starting materials for the synthesis of different heterocyclic structures generating a broad spectrum of biological activities [6,7]. However, relevant reports related to chlorophyllous chlorin are scarce except the synthesis of cyano-pyropheophorbide-*a* by a two-step reaction including oximation and cyanidation at the 12-positions in our early works [8], and at the 3-position in other's [9]. With regard to these works, chlorin oximes were firstly prepared from chlorophyll derivatives bearing an aldehyde group by condensation with hydroxylamine hydrochloride, then underwent the Beckmann rearrangement upon treatment with 2,4,6-trichloro-[1,3,5]triazine (TCT) in DMF or ethyl dichlorophosphate (EtOPOCl) and 1,8-diazabicyclo[5.5.0]undes-7-ene (DBU) in dichloromethane to afford cyanochlorins. Nevertheless, the reaction procedures suffer from various limitations, such as costly reagents, intricate manipulation and/or harsh reaction conditions. To expand and simplify this peripheral cyanation reaction of chlorin, herein, we report an efficient synthesis for chlorin nitriles from chlorin aldehydes by a tandem procedure combining an oximation reaction with a Beckmann rearrangement.

2. Experimental

In this study, the transformation of an aldehyde group linked to the chlorin chromophore into a nitrile was carried out by a one-pot, two-step reaction. As a starting material, methyl pheophorbide-*a* (MP*a*) **1a**, isolated from *Spirulina pacifica* [10], was oxidized with osmium (VIII) oxide in tetrahydrofuran containing a catalytic amount of pyridine at 0 °C followed by the glycol cleavage with

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http://dx.doi.org/10.1016/j.cclet.2016.01.008
1001-8417/

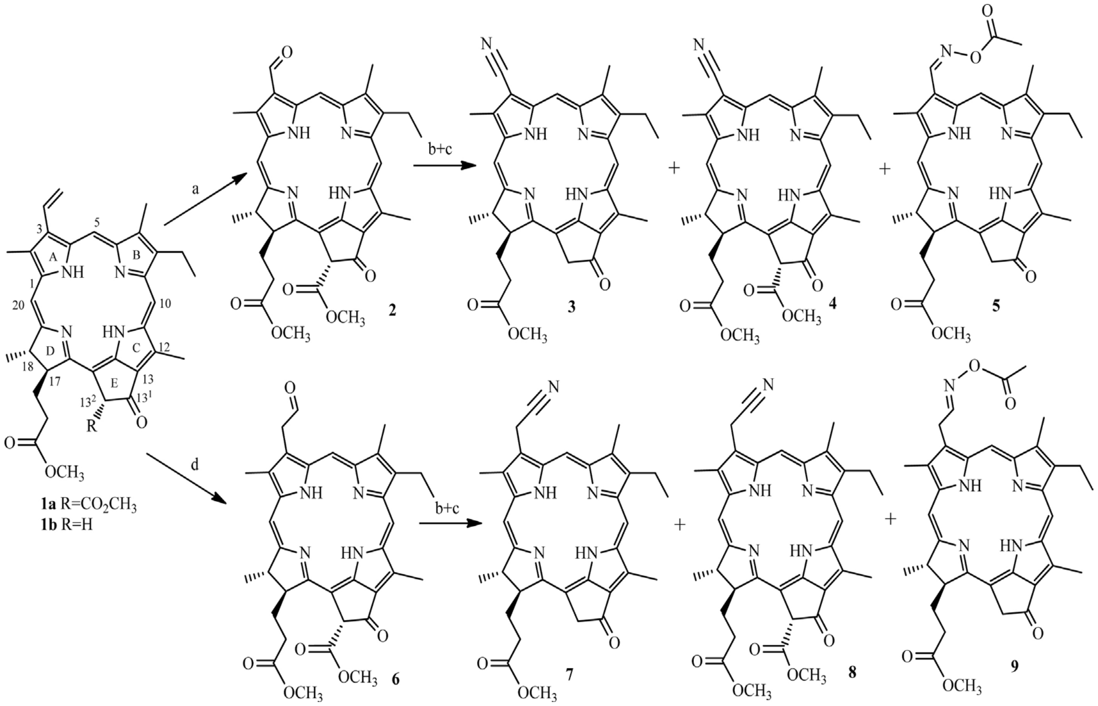
sodium periodate in aqueous tetrahydrofuran to give the methyl pheophorbide-*d* (MP*d*) **2** [11]. The oximation with hydroxylammonium chloride in acetic anhydride and the subsequent cyanation under reflux were combined into one step to give a complicated mixture from which the cyano-pyropheophorbide-*a* **3** was isolated in low yield (9%). This one-pot reaction implies that some reaction conditions for the oximation may be inappropriate such as temperature and acidity, therefore we attempted new protocol for the oximation *via* a modified procedure. As shown in Scheme 1, chlorin aldehyde **2** reacted with hydroxylammonium chloride in methyl alcohol in the presence of triethylamine at room temperature. After adding acetic anhydride the obtained crude product, upon being subjected to the Beckmann rearrangement by stirring at 90 °C for 6 h, was converted into cyano-chlorin **3** (47%) as a major product. In addition to this, acetylated chlorin oxime **5** (12%) and an inseparable mixture including **3** and a small amount C3-cyanized pheophorbide-*a* **4** were also obtained. The cyanation of 3-formymethyl pheophorbide-*a* **6** bearing an aliphatic aldehyde group at the 3-position, prepared from MP*a* **1a** by a thallium nitrate oxidation in tetrahydrofuran followed by hydrolysis in 88% formic acid [12], was implemented under same reaction condition to produce similar reaction result. Besides major product 3-cyano pyropheophorbide-*a* **7** (45%), trace amounts of pheophorbide-*a* **8** along with **7** and acetylated chlorin oxime **9** (9%) was separated from the reaction system.

Whether in one-pot reaction or tandem reaction, the methoxyformyl group at the 13^2-position was removed by decarbomethoxylation in acidic medium. Based on this result, we next attempted, using chlorin aldehyde derived from methyl pyropheophorbide-*a* **1b** (MPP*a*) which has no substituted groups in its exocyclic ketone [10], to form the oximido intermediate *in situ*. Aromatic chlorin aldehydes **10** (MPP*d*) and adipose homolog **11** were obtained from **1b** by the same oxidation procedure using $OsO_4/NaIO_4$ [13,14] and $Tl(NO_3)_3$ as the oxidizing agents [15], respectively. 12-Formylpyropheophorbide-*a* **12** and 15-formylchlorin-*f* dimethyl eaters **13** also were separated from a mixture from the isomerization of MPP*a* **1b** upon the treatment with saturated methanol solution of LiOH in the presence of oxygen (exposure of the reaction mixture to air) followed, by the acidification with AcOH and methylation with diazomethane [16,17]. The transformation of these carbon–oxygen double bonds to the carbon–nitrogen triple bonds were performed under the same *in-situ* conditions as the transformation of chlorin aldehyde **2** to homologic chlorin nitriles **3** (53%), **7** (58%), **14** (52%) and **15** (61%), respectively (Scheme 2).

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions. Reagents were purchased at the highest commercial quality and used without further purification. Reactions were monitored by thin layer chromatography (TLC). ^1H NMR spectra were recorded on a Bruker AV-400 instrument and calibrated using residual undeuterated chloroform ($\delta_H = 7.26$) as an internal reference. IR spectra were recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer. Mass spectra (MS) were recorded on a GC–MS Automass 120 or on a Kratos Concept instrument.

Representative procedure for the tandem cyanation reaction of chlorin aldehyde: An oven-dried 25 mL round-bottomed flask equipped with a magnetic stirring bar and a three-way stopcock was charged with chlorin aldehyde (0.3 mmol). The flask was evacuated and flushed with argon (three times), and then absolute methyl alcohol (2 mL) was added. To the solution were successively added grinded hydroxylamine hydrochloride (0.6 mmol) and triethylamine (0.5 mL), followed by stirring at room temperature. The oximation was complete within 1.5 h, monitored by TLC analysis, and then acetic anhydride (20 mL) was added to the reaction solution, which was directly subjected to Beckmann rearrangement by stirring at 90 °C for 6 h. The resulted mixture was poured into brine and extracted with dichloromethane (3 × 15 mL). The organic layers were combined, washed with water, concentrated in vacuo, and purified by chromatography on silica gel using EtOAc/petroleum ether (1:5–1:3) as an eluent to give the corresponding chlorin nitriles. All the compounds reported herein showed spectral data consistent with the assigned structures. Selected data are as follows:

For **3**: mp 191–194 °C; UV–vis (CH_2Cl_2) $\lambda_{max}(\varepsilon)$: 416 ($9.32 \times 10^4$), 514 ($1.51 \times 10^4$), 568 ($1.02 \times 10^3$), 645



Scheme 1. Reagent and conditions: (a) $OsO_4/Pyr/NaIO_4$; (b) $NH_2OH{\cdot}HCl/MeOH/TEA$; (c) $Ac_2O/90\ ^\circ C$; (d) $Tl(NO_3)_3$/88% formic acid.