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A concise synthesis of monoazaporphyrin from 1,19-dideoxybiladiene-*ac*

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Abstract

1,19-Dideoxybiladiene-*ac* was found to be cyclized into monoazaporphyrin in 18–33% yield in the presence of iodine/potassium iodide mixture and ammonium hydroxide or sodium azide as the nitrogen source. The synthesis circumvents the tedious preparation of 1,19-dibromobiladiene-*ac* for monoazaporphyrin.
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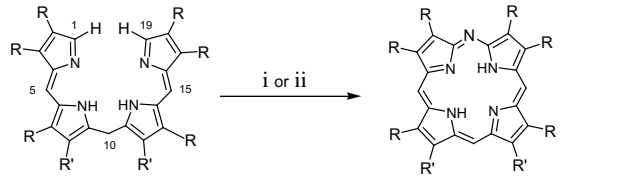
1. Introduction

Azaporphyrin is a porphyrin analogue derived from porphyrin after formal replacement of the *meso*-carbon atoms with nitrogen atoms.[1,2] The typical example is phthalocyanine bearing the four *meso*-nitrogens. Monoazaporphyrin is a molecular hybrid of phthalocyanine and porphyrin, and has a single *meso*-nitrogen atom. The molecule is currently of great interest, not only for the distinct physical properties, but also with respect to practical applications. Monoazaporphyrin has been a potential photosensitizer for photodynamic therapy.[3] Iron monoazaporphyrin causes a dramatic increase in the oxygen affinity of myoglobin, and induces an anomalous intermediate-spin ($S = 3/2$) state for the aquomet myoglobin.[4] Ogata and coworkers resolved the origin of the characteristic physical properties of monoazaporphyrin.[5]

Monoazaporphyrin has been prepared through the two representative routes. One is the ammonia treatment of verdoheme which is obtained from iron porphyrin after the coupled oxidation with oxygen.[6,7] Another route developed by Harries et al. is the cyclization of a linear tetrapyrrole 1,19-dibromobiladine-*ac*.[8] The second method has been improved by Pandey et al.[9] Singh et al., utilizing a phase transfer reagent, reported excellent yield of monoazaporphyrin from 1,19-dibromobiladiene-*ac*.[10]

The precursory 1,19-dibromobiladiene-*ac* is available from the coupling of dipyrromethane and 2-bromo-5-formylpyrrole.[9] Unfortunately, the bromoformylpyrrole for the biladiene is accessible only after a series of transformations staring from oxidation of 5-methyl group in pyrrole with sulfuryl chloride, hydrolysis of the dichloromethyl intermediate, protection of the resultant formyl functionality, brominative decarboxylation of the acid group, and regeneration of formyl group.[9,11] On the other hand, 1,19-dideoxybiladiene-*ac* (Scheme 1) is more conveniently prepared.[12,13] It is hence expected that



1: R = CH_3, R' = $CH_2CH_2CO_2CH_3$
3: R = R' = CH_2CH_3
2: R = CH_3, R' = $CH_2CH_2CO_2CH_3$
4: R = R' = CH_2CH_3

Scheme 1. Synthesis of monoazaporphyrin from 1,19-dideoxybiladiene-*ac*. Reagents and conditions: (i) KI/I_2, NH_4OH, dimethylsulfoxide, room temperature for **1**; (ii) KI/I_2, NaN_3, methanol, reflux for **3**.

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1,19-dideoxybiladiene-*ac*, rather than 1,19-dibromobiladiene-*ac*, may be utilized as a precursor for monoazaporphyrin. However, 1,19-dideoxybiladiene-*ac* is the precursor for corrole, a porphyrinoid missing one *meso*-carbon,[12,14] and the dideoxy compound cannot be applied to monoazaporphyrin synthesis. Nevertheless, the utilization of 1,19-dideoxybiladiene-*ac* is desirous because of the preparative ease. We report herein an efficient one-pot synthesis of monoazaporphyrin from 1,19-dideoxybiladiene-*ac*.

2. Results and discussion

We initially attempted the cyclization of 1,19-dideoxybiladiene-*ac* (**1**) at room temperature in the presence of aqueous ammonia as the nitrogen source. The result was discouraging to yield corrole as the sole product. Addition of iodine to the reaction mixture evidenced the formation of a trace amount of monoazaporphyrin. Concentrating our hope to this result, we optimized the condition and found that the addition of potassium iodide to the reaction mixture caused a satisfactory result. Monoazaporphyrin (**2**) was formed from **1** after incubation in dimethylsulfoxide containing ammonium hydroxide and the iodine/potassium iodide mixture at room temperature (Scheme 1). It is very likely that potassium iodide facilitates the formation of tri-iodide ion (I_3^-) from iodine, and reactive tri-iodide ion attacks the terminal 1,19-positions to afford 1,19-diiodobiladiene-*ac*. The in situ generated 1,19-diiodobiladiene-*ac* is then subjected to the nitrogen-mediated ring closure to monoazaporphyrin **2**. We obtained compound **2** in 33% yield. Compound **2** equipped with two propionyl groups is a close analogue of natural porphyrin, suggesting the potential application as a prosthetic group for hemoprotein, as has been demonstrated for monoazamesoporphyrin XIII.[4]

On the other hand, the ring-closure of octaethylbiladiene-*ac* (**3**) under the same condition was unsatisfactory to afford only a trace amount of octaethylmonoazaporphyrin (**4**). The observation suggests that the steric repulsion between the two ethyl groups in the 2,18-positions disturbs the reaction. We note a closely related observation by Franck and Krautstrunck on the porphyrin formation from a biladiene-*ac* bearing ethyl groups on the terminal pyrrole rings.[15] Transformation of **3** into monoazaporphyrin **4** necessitated a higher reaction temperature and sodium azide as the nitrogen source (Scheme 1). In addition, utilization of a two-equivalent of iodine was essential because an excess of iodine decreased the yield. This is in contrast with the condition for the synthesis of **1** where a 4.2-fold molar excess of iodine is employed. The rigorous control of the iodine amount in the preparation of **3** may come from enhanced reactivity of tri-iodide ion at higher temperature. We obtained **4** in 18% yield under the optimized conditions. Compound **4** has been conventionally derived from octaethylporphyrin after iron insertion, subsequent conversion into verdoheme and monoazaheme before iron removal.[6] Octaethylporphyrin itself is synthesized through the sequential steps from 3,4-diethylpyrrole.[16] In contrast, the cyclization of **3** directly affords **4** to avoid the treatment of octaethylheme and the synthesis of octaethylporphyrin.

In view of the easy preparation for 1,19-dideoxybiladienes-*ac*,[12,13] present methodology paves a simple and general route to various monoazaporphyrins.

3. Experimental

3.1. 15-Aza-3,7-bis(2-methoxycarbonylethyl)-2,8,12,13,17,18-hexamethylporphyrin (2)

1,19-Dideoxy-8,12-bis(2-methoxycarbonylethyl)-2,3,7,13,17,18-hexamethylbiladiene-*ac* dihydrobromide **1**[12] (620 mg), iodine (930 mg), and potassium iodide (1.86 g) were dissolved in dimethylsulfoxide (150 mL) before the addition of 28% ammonium hydroxide solution (15 mL). The mixture was stirred overnight at room temperature. Cold water (100 mL) was added to the solution, and the aggregated particles were spun down by centrifugation. The precipitates were washed with methanol (5 mL × 6) in the centrifugation tube to remove most of soluble tar. The dry residue was purified on silica gel column with chloroform containing 2% methanol. After solvent evaporation and recrystallization from methanol/chloroform, product **2** was obtained as purple needles with metallic luster (166 mg, 33% yield). Anal. Calcd for $C_{33}H_{37}N_5O_4$: C, 69.82; H, 7.03; N, 12.33. Found: C, 69.67; H, 7.14; N, 12.57. MS: *m*/*z*, 567 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.01 (s, 1H, *meso*-H), 9.82 (s, 2H, *meso*-H), 4.32 (t, 4H, $J = 7.6$ Hz, –C*H*$_2$CH$_2$CO–), 3.64 (s, 6H, –OCH$_3$), 3.53, 3.52, 3.48 (each s, 6H, ring –CH$_3$), 3.21 (t, 4H, $J = 7.6$ Hz, –CH$_2$C*H*$_2$CO–), −2.73 (br s, 2H, NH). Visible (chloroform) λ_{max}, nm (ε): 377 (108,000), 507 (500), 537 (22,200), 562 (7300), 613 (22,200).

3.2. 5-Aza-2,3,7,8,12,13,17,18-octaethylporphyrin (4)

1,19-Dideoxy-2,3,7,8,12,13,17,18-octaethylbiladiene-*ac* dihydrobromide **3**[13] (200 mg) was dissolved in 16 mL of methanol, and four drops of 28% ammonium hydroxide solution was added. Sodium azide (800 mg), iodine (162 mg), and potassium iodide (240 mg) were then added, and the solution was refluxed under vigorous stirring over 6 h. After evaporating off the solvent, the residue was purified on the silica gel column with chloroform. The fast-running purple band was collected and concentrated in vacuo. Crystallization from hexane/chloroform afforded dark-purple fine needles of **4** (31 mg, 19% yield). Anal. Calcd for $C_{35}H_{45}N_5$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.17; H, 8.64; N, 13.19. MS: *m*/*z*, 535 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.03 (s, 1H, *meso*-H), 9.89 (s, 2H, *meso*-H), 4.10–3.97 (m, 16H, –C*H*$_2$CH$_3$), 1.93–1.85 (m, 24H, –CH$_2$C*H*$_3$), −2.69 (br s, 2H, NH). Visible (chloroform) λ_{max}, nm (ε): 377 (127,000), 507 (8700), 537 (27,700), 560 (9200), 611 (28,400).

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