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A novel and efficient synthesis of porphine

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Abstract—*meso*-Tetra(*n*-hexyloxycarbonyl)porphyrin was found to be converted into porphine, the mother compound of porphyrins, in a 77% yield when heated in aqueous sulfuric acid at 180 °C over 30 min under an inert atmosphere. The observation demonstrates that the substituted porphyrin serves as a novel and useful precursor for porphine.

1. Introduction

Heme is a vital pigment to constitute the essential component of hemoprotein. Natural porphyrins are peripherally substituted at the pyrrole rings, and the porphyrin in hemoglobin and myoglobin is protoporphyrin. Complete removal of the peripheral chains of porphyrins results in the most fundamental cyclic tetrapyrrole called porphine. Porphine serves not only as the starting material of various porphyrin derivatives,[1–3] but also as a unique molecular tool to perturb the heme–globin interactions in protein.[4] Neya et al. introduced iron porphine into myoglobin and found that the smallest heme was dynamically rotating around the iron–histidine bond.[5] Despite the simplest structure, the porphine synthesis is difficult[6] and the commercialized product is fairly expensive.[7] In view of the developing application as well as the fundamental importance, the facile porphine synthesis is to be explored.

Fischer and Gleim[8] and Rothemund[9] first noted the porphine formation in 1936. Their methods have been improved by Eisner and Linstead[10] and Krol[11] with the pyrrole derivatives containing α-methylene group as the *meso*-carbon source for porphine. Neya et al. reported a simple porphine synthesis with pyrrole and formalin.[12] Neya's reaction, though the yield is only 0.9%, is easily carried out on a large scale to afford more than 100 mg of porphine at one time. Taniguchi et al. devised a sophisticated porphine synthesis from tripyrrane and 2,5-dihydroxymethylpyrrole in a 31% yield.[13]

Another rational approach to porphine is the initial construction of substituted porphyrin followed by the deletion of the side chains. The methodology is advantageous over the direct porphine synthesis because substituted porphyrins are simpler to prepare than unsubstituted porphine. We have developed this strategy and synthesized porphine in a 60–75% yield from *meso*-tetra(*tert*-butyl)porphyrin[14] and β-tetra(*tert*-butyl)-porphyrin.[15]

Trova et al. have recently prepared new porphyrin derivatives, that is, *meso*-tetra(alkoxycarbonyl)porphyrins with carboxylate groups directly attached at the four *meso*-bridges.[16] The porphyrins are of interest because the metal complexes exhibit a strong activity of superoxide dismutase mimetics. The metal free compounds are available from pyrrole and alkyl glyoxylate esters with the yields >6% under the Lindsey condition.[17] The best yield of 15% is reported for *meso*-tetra(*n*-hexyloxycarbonyl)porphyrin (**1**).[16] We examined the conversion of **1** into porphine.

2. Results and discussion

The molecular structure of *meso*-tetra(alkoxycarbonyl)porphyrins implies that they may serve as precursors for porphine if the *meso*-substituents are cleavable. The removal of side chains was attempted under several

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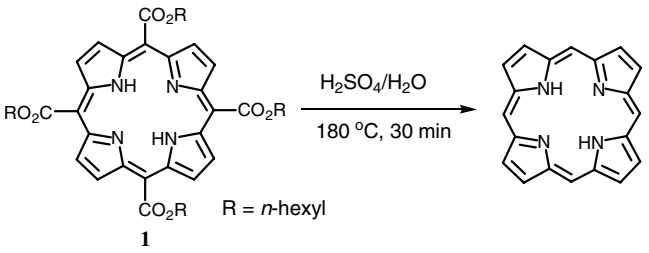

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Scheme 1. Porphine synthesis from *meso*-tetra(*n*-hexyloxycarbonyl)-porphyrin.

conditions. Andrews et al. reported that the ester groups in 1,4,5,8-tetramethyl-2,3,6,7-tetra(ethoxycarbony)porphyrin are removed to furnish 1,4,5,8-tetramethylporphyrin when the former is heated at 290 °C over 120 min in glycerin containing sodium hydroxide.[18] Application of the same condition to **1** under an inert atmosphere was unsuccessful to cause intensive decomposition. Shorter heating and/or lower temperature did not improve the result. We consequently set out the thermal decarboxylation of hydrolyzed **1** under acidic condition. It is expected that hydrolysis of the ester groups and subsequent decarboxylation will be carried out in one-pot if hot aqueous sulfuric acid was used. When we treated **1** with hydrated sulfuric acid under the optimized condition, the Soret peak shifted from 410 to 394 nm and the phyllo-type of visible spectrum of porphine appeared to reflect the removal of the ester side chains (Scheme 1). Water was indeed an essential additive because no porphine was obtained in neat sulfuric acid. After chromatographic purification, we obtained crystalline porphine in a 77% yield. The yield is comparable with or better than 65–75% reported for the previous porphine synthesis.[14,15]

It has now turned out that the side chains in **1** are deleted by using hot aqueous sulfuric acid to afford porphine. The reaction is straightforward and the work-up is easy. *n*-Hexylglyoxylate is readily accessible and gives **1** in a good yield under a mild condition. These observations, taken together, demonstrate that compound **1** is a novel and promising precursor for porphine. In conclusion, we have demonstrated that the initial construction of the substituted porphyrins followed by side-chain removal is a general instruction to the high-yielding synthesis of porphine.

3. Experimental

Porphyrin **1** (200 mg) was dissolved in sulfuric acid (40 ml), and water (8 ml) and anhydrous Na_2SO_4 (4.0 g) were added. The solution was kept in an oil bath at 180 °C over 20–30 min under argon until the effervescence of CO_2 due to the decarboxylation was over. The dark green solution was changed into dark purple during the incubation. Methanol (100 ml) and pyridine (120 ml) were added to the cooled reaction mixture on an ice bath, and the solution was diluted with water (600 ml). A saturating amount of sodium chloride was added to the aqueous solution, and the precipitates of the crude product were spun down. The precipitates were washed with small amounts of water and methanol with a centrifuge before being dried. The dry material was purified on a silicagel column with chloroform. The chloroform solution was evaporated down to leave copper-colored fine crystals of porphine (76 mg, 77% yield). Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.59; H, 4.74; N, 17.67. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.36 (s, 4H, *meso*-H), 9.53 (s, 8H, pyrrole–H), −3.88 (br s, 2H, NH). MS: *m*/*z*, 310 (M^+). Visible absorption spectrum was identical with that reported previously.[14]

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