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Synthesis of Functionalized Corrphycene by Copper(II)-promoted Cyclization.

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Abstract: Corrphycene bearing two peripheral ethoxycarbonyl groups was formed in 19% yield *via* copper(II)-catalyzed cyclization of a linear tetrapyrrole. The reaction utilizes readily available precursors and is easily performed to provide a simple access to the functionalized corrphycene. © 1998 Elsevier Science Ltd. All rights reserved.

Shuffling of four pyrroles and four *meso*-carbons in the basic framework of porphyrin results in structural isomers with altered tetrapyrrole arrays. The porphyrin isomers have emerged as attractive synthetic targets owing to their potential chemical interest and biomedical application.[1] Corrphycene, an isomeric [18]porphyrin-(2.1.0.1), first appeared in 1994.[2,3] Two representative synthetic routes are known for it. The first approach by Sessler *et al.*[2] and Aukaullo and Guilard[3] involves preconstruction of a linear tetrapyrrole containing the direct pyrrole-pyrrole bond, formylation of the tetrapyrrole, and final formation of the ethene bridge after intermolecular McMurry coupling of the α,ω-dialdehyde. In the second procedure by Falk and Chen,[4] another type of a linear tetrapyrrole containing an ethane bridge is initially constructed. The direct pyrrole-pyrrole linkage is subsequently formed by a copper-catalyzed Ullmann reaction.[4] These corrphycene syntheses[2-4] require valuable pyrrolic precursors, tend to be long, and are best performed with the modern reactions under rigorously regulated conditions. The methodology used in porphyrin synthesis appears to hardly provide access to corrphycene.

We devised the third approach that stands on the conventional porphyrin synthesis to obtain corrphycene (**Scheme**). The key starting material is 1,2-*bis*(3-ethoxycarbonyl-4-methylpyrrol-2-yl)ethane **1**. This compound can be prepared in rather laborious manner through hydrogenating a precursory *bis*-pyrrolylethene obtained by self-coupling the formylpyrrole under the McMurry condition.[5] Fortunately, Fischer and Scheyer[6] reported a much simpler procedure in 1924. Treatment of the precursory pyrrolyhydrazine with copper(II) ammonium sulfate affords **1** in high yield. The classic method is attractive in that the reaction can be performed in a large scale without decreasing yield.

5,5'-Ethoxycarbonyl substituents in **1**, however, are not easy to remove because they are quite stable owing to the second ethoxycarbonyl groups in the same pyrrole rings. Decarboxylative sublimation of **2** at 170-200°C causes extensive fragmentation, and the reported yield[8] for **4**, 43%, is not always satisfactory. We note similar difficulty in preparing corresponding dipyrromethane.[7] Alternative iodinative decarboxylation[9] and subsequent reduction[10] were successfully applicable to compound **2**. The resultant **4** was readily transformed into diformyl derivative **5** by the Vilsmeiyer reaction.[11] The *a,c*-biladiene-like compound **6** was obtained by acid catalyzed condensation[12] of **5** with two equivalents of 3,4-dimethylpyrrole.[13] We found that copper(II) chloride successfully cyclizes **6** into copper(II) corrphycene **7** in refluxing

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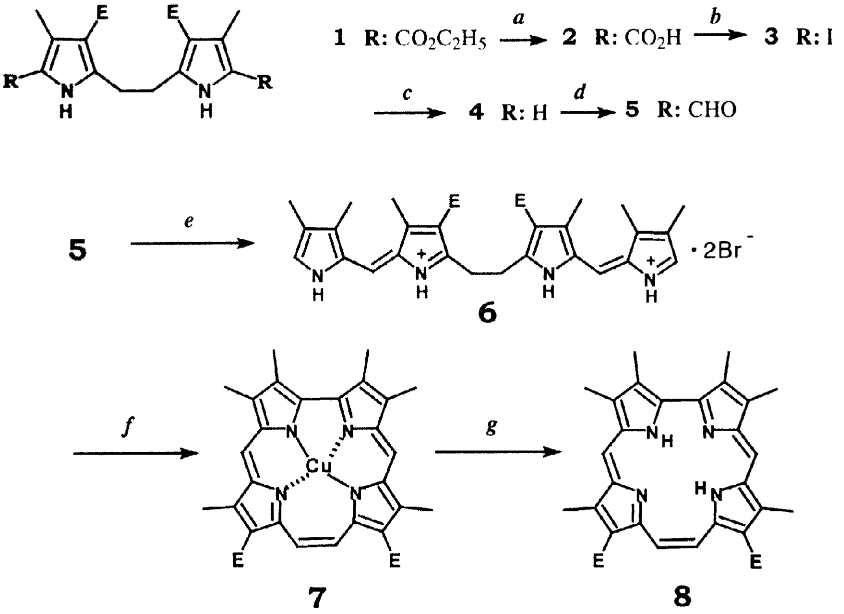
dimethylformamide.[14] Our reaction, at first sight, is similar to that of Falk and Chen[4] in that the direct pyrrole-pyrrole bond is formed in the cyclization step. However, the two methods are distinct from each other. We utilize an α,ω-free tetrapyrrole **6** and the cyclization is accomplished by copper(II) ion. On the other hand, they employ the α,ω-dihalogeno tetrapyrrole and the macrocycle is formed with the Ullmann-type reaction by metallic copper. Moreover, our copper(II)-mediated cyclization completes within one hour while their Ullmann-type reaction[4] proceeds over three days. Requirement for copper(II) ion suggests formation of a binary complex between the linear tetrapyrrole and copper(II) ion. The ring closure of the intermediary complex may be promoted by the excellent ability of corrphycene to coordinate a variety of metal ions.[1]



Scheme: Synthesis of corrphycene **8**. *E* stands for $CO_2C_2H_5$. (a) 2 equiv. NaOH-water/Δ; (b) I_2/KI, $NaHCO_3$, 45°C; (c) H_2/Pd-C, tetrahydrofuran, room temp.; (d) $POCl_3$/dimethylformamide; (e) 2 equiv. 3,4-dimethylpyrrole, HBr; (f) $CuCl_2$, dimethylformamide, reflux, one hour; (g) C_2H_5OH/H_2SO_4.

The chelating copper(II) in **7** is readily removed by sulfuric acid. The yield of free base corrphycene **8**[14] is 19% based on tetrapyrrole **6**. This is indeed lower than 40% reported by Falk and Chen,[4] but significantly higher than 2 to 3% by Sessler *et al.*[2] and Aukauloo and Guilard.[3] Our corrphycene synthesis making use of the unrecognized ability of copper(II) ion is advantageous over the reported methods in that the ring closure is performed as easily as the copper(II)-catalyzed porphyrin synthesis from *a,c*-biladiene.[15] This feature combined with the fact that all of the precursors can be prepared in large quantities from readily available materials makes it possible for us to prepare corrphycene in a large scale. It is notable that the direct pyrrole-pyrrole link occurs between the pyrrole rings without ethoxycarbonyl group. The result suggests that the copper(II)-mediated cyclization is generally applicable to the other tetrapyrroles without the α,ω-substituents. Carboxylates affect the electronic absorption of corrphycene. Corrphycene **8** exhibits an etio-type spectrum[14] while alkyl corrphycene has phyllo-type bands.[2,3] The carboxyl groups allows us various chemical modification for **8**. Since a closely related porphyrin with carboxylates on the edge is capable of oxygen binding in myoglobin,[16] corrphycene **8** further provides possibility that the iron complex serves as a prosthetic group of hemoprotein.

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9. Preparation of compound **3**. Compound **2**[8] (1.73 g, prepared[6] in 87% yield from **1**) was dissolved in warm 1:1 (v/v) ethanol/water mixture (50 ml) containing sodium hydrogencarbonate (2.5 g). Iodine (1.1 g)/potassium iodide (2.0 g) in water (20 ml) was added dropwise over 15 minute period to the stirred solution at 45°C. After stirring for further 90 minutes at 45°C, the resultant precipitates were collected, washed with a large amount of water, and dried. The yield of pale-purple granular product **3** was 2.84 g (85%). MS: m/z, 586 (M^+). ^1H NMR (300 MHz, $CDCl_3$, δ): 9.03 (br s, 2H, NH), 4.32 (q, *J* = 7.2 Hz, $-C\mathit{H}_2CH_3$, 4H), 3.30 (s, 4H, $-C\mathit{H}_2C\mathit{H}_2-$), 2.18 (s, 6H, ring $-CH_3$), 1.36 (t, *J* = 7.2 Hz, $-CH_2C\mathit{H}_3$, 6H).
10. Preparation of compound **4**. The foregoing **3** (5.00 g) dissolved in tetrahydrofuran (100 ml) containing triethylamine (ten drops) and 10%-palladium on activated carbon (0.70 g) was stirred overnight under hydrogen atmosphere. After filtration and evaporation of the solvent, the residue was crystallized from ethanol/water. The yield of nice crystalline material **4** was 2.60 g (92%). Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 64.88; H, 7.55; N, 8.15. MS: m/z, 332 (M^+). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.72 (br s, 2H, NH), 6.33 (m, 2H, ring -H), 4.28 (q, 4H, *J* = 7.2 Hz, $-C\mathit{H}_2CH_3$, 4H),

3.26 (s, 4H, -CH_2CH_2-), 2.20 (s, 6H, ring -CH_3), 1.36 (t, J = 7.2 Hz, -CH_2CH_3, 6H).

11. Preparation of compound **5**. Compound **4** (10.00 g) was dissolved in *N,N*-dimethylformamide (100 ml) and phosphorus oxychloride was added below 5°C in nitrogen atmosphere. The mixture was kept overnight at room temperature under protection of moisture and poured into water (500 ml). Concentrated aqueous sodium hydroxide was added until the smell of amine becomes apparent. The resultant precipitate **5** was collected, washed with water, and once crystallized from ethanol/water to yield pale yellow needles (10.10 g, 86%). MS: m/z, 388 (M^+). ^1H NMR (300 MHz, $CDCl_3$, δ): 10.48 (br s, 2H, NH), 9.38 (s, 2H, -CHO), 4.35 (q, 4H, J = 6.9 Hz, -CH_2CH_3, 4H), 3.36 (s, 4H, -CH_2CH_2-), 2.58 (s, 6H, ring -CH_3), 1.41 (t, J = 7.2 Hz, -CH_2CH_3, 6H).
12. Preparation of compound **6**. To the dialdehyde **5** (10.00 g) dissolved in acetic acid (90 ml), 3,4-dimethylpyrrole[13] (4.90 g) and 30% hydrobromic acid in acetic acid (20 ml) were added at 60°C. The mixture was heated for one hour and cooled. On placing the solution in ice bath for one hour, dark brown crystalline particles of **6** were formed. The material was collected, washed with methanol/water (1:1) mixture, and dried (11.12 g, 61%). Anal. Calcd for $C_{32}H_{40}Br_2N_4O_4$: C, 54.55; H, 5.72; N, 7.95. Found: C, 54.38; H, 5.50; N, 8.15. ^1H NMR (300 MHz, $CDCl_3$, δ): 13.46, 13.02 (each br s, 2H, NH), 7.72 (m, 2H, ring -H), 7.37 (s, 2H, =CH-), 4.30 (q, 4H, J = 7.2 Hz, -CH_2CH_3, 4H), 3.90 (s, 4H, -CH_2CH_2-), 2.61, 2.30, 2.07 (each s, 6H, ring -CH_3), 1.36 (t, J = 7.2 Hz, -CH_2CH_3, 6H).
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14. Synthesis of corrphycene **8**. Dimethylformamide (230 ml) containing compound **6** (2.70 g) and copper(II) chloride dihydrate (5.70 g) was stirred under reflux for one hour. The cooled solution was mixed with chloroform (500 ml), washed with water (500 ml x 4), and evaporated to dryness. The residue was repeatedly chromatographed on silica gel column with chloroform. The dark green fraction containing **7** was collected and evaporated to dryness (470 mg). MS: m/z, 600 (M^+) for $C_{32}H_{32}CuN_4O_4$. Visible (dichloromethane) λ_{max}, nm (ε): 437 (130,000), 525 (4,330), 557 (9,360), 600 (9,920). All of compound **7** was stirred overnight in 1:1 sulfuric acid/ethanol (100 ml) and mixed with chloroform (300 ml). The mixture was washed with water (400 ml x 2), 0.5 M sodium hydroxide (400 ml x 2), and water (400 ml). The solvent was evaporated off and the crude material was chromatographed on silica gel column with chloroform. Corrphycene **8** (402 mg, 19% from **6**) was crystallized as dark purple micro-needles with metallic luster (chloroform/methanol). Anal. Calcd for $C_{32}H_{34}N_4O_4$: C, 71.35; H, 6.36; N, 10.40. Found: C, 71.15; H, 6.50; N, 10.15. MS: m/z, 539 (M+1). ^1H NMR (300 MHz, $CDCl_3$, δ): 10.54 (s, 2H, -CH=CH-), 9.54 (s, 2H, -CH=), 4.86 (q, 4H, J = 7.2 Hz, -CH_2CH_3), 3.67, 3.30, 3.21 (each s, 6H, ring -CH_3), 1.76 (t, J = 7.2 Hz, -CH_2CH_3, 6H), -1.41 (br s, 2H, NH). Visible (dichloromethane) λ_{max}, nm (ε): 416 (102,000), 516 (6,450), 551 (5,750), 577 (4,650), 628 (2,500).
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