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Total Synthesis of Hematoporphyrin and Protoporphyrin; a Conceptually New Approach

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In memoriam Prof. Dr. H. Prinzbach

Abstract: The total synthesis of protoporphyrin IX and its disodium salt using a new alternative method to the classical MacDonald condensation is reported. The key step is the reaction of the new unsymmetrical diiodo dipyrrylmethane **1** with the known dipyrrylmethane **2**. Coupling of the two fragments leads directly to porphyrin **3** without the need of an oxidizing agent. The new methodology is well suited for the synthesis of protoporphyrin IX derivatives on a multi-100 g scale in good quality without the need for chromatography. Furthermore, these preparations are completely free of any contaminant of animal origin, which represents a real improvement in the manufacturing of protoporphyrin IX derivatives.

Keywords: Development & scale-up · Novel porphyrin cyclization method · Process research · Protoporphyrin IX · Total synthesis

Introduction

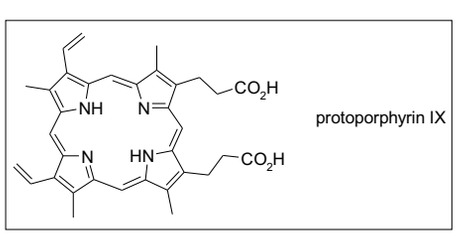
Protoporphyrin IX (Fig. 1) is most commonly prepared by semisynthesis starting from hemin, which in turn is isolated from ox or pork blood.[1,2] For medical applications, *e.g.* in cell culture media, this poses the problem of impurities of animal origin that may be present, in particular of agents in connection with transmissible spongiform encephalopathy. In order to meet the guidelines of the regulatory agencies,[3] it was necessary to provide a completely synthetic preparation process for the preparation of protoporphyrin IX that uses only products of synthetic origin.

Here, we describe the total synthesis of protoporphyrin IX and its disodium salt using a novel variant of the MacDonald condensation method. The key step is the reaction of the new unsymmetrical diiododipyrrylmethane **1** with the known dipyrrylmethane **2** (Scheme 1).[4] The two fragments are coupled without the presence of a metal leading directly to porphyrin **3** without the need of an oxidizing agent. The new methodology is well suited for the synthesis of protoporphyrin IX on a multi-100 g scale in good quality without the need for chromatography.

Synthetic Concept

The classical MacDonald condensation where a dipyrrylmethane unit is reacted with a dipyrrylmethane dialdehyde has been widely applied for the preparation of a variety of unsymmetrically substituted porphyrins.[5] The primary product is a dihydroporphin which must then be oxidized to obtain the corresponding porphyrin using either air[5] or a quinone such as DDQ.[6] In many cases, the oxidation step is rather problematic since the dihydroporphin is quite unstable and not easy to detect. Furthermore, the reduced quinone is difficult to remove from the reaction mixture requiring a chromatographic separation. For these reasons, scale up problems are unavoidable and, indeed, literature preparations are usually described in the mg range.

We reasoned that in order to avoid the formation of the dihydroporphin, one of the two dipyrrylmethanes should either be in a higher oxidation state or carry a nucleofuge which can be eliminated to form the required additional C=C double bond. We decided to prepare the diiodo derivative **1** and to react it under MacDonald conditions with dipyrrylmethane dialdehyde **2** (Scheme 1). To our delight and surprise, we directly obtained the desired porphyrin **3** in good yields. We postulate that the primary condensation product is intermediate **A** which spontaneously eliminates water as well as one mol of HI to give the iodinated porphyrin **B** which then is reduced by the HI formed in the first step to give **3** and I_2.[7] We consider the elimination of 2 mol of HI improbable since a rather thermodynamically unfavourable dehydroporphyrin would be formed.



protoporphyrin IX

Fig. 1.

Synthetic Details[8]

The synthesis of the new diiodo dipyrrylmethane **1** was carried out as depicted

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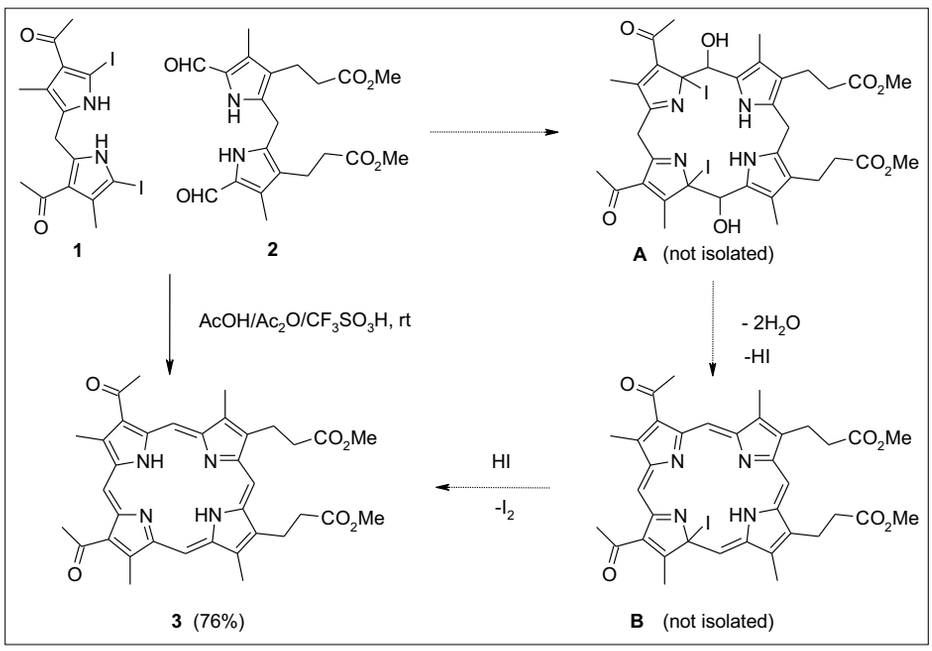
in Scheme 2. The partially optimized synthesis which delivered the desired intermediate in an acceptable over-all yield, starts with the silylated propyne **4** which is reacted with acetyl chloride in presence of $AlCl_3$ to give 3-pentyne-2-one (**5**). The phosphine-catalyzed reaction of **5** with benzyl isocyanoacetate gave the first pyrrole unit **6** which was obtained in pure form after chromatography in moderate yield. The second pyrrole moiety **9** was prepared starting from the commercially available pyrrole ethyl ester **7** which was first transformed to the corresponding benzyl ester **8** with Na/BnOH at 190 °C and then acetoxylated in presence of sulfuryl chloride to give **9** in moderate yield. The condensation of the two pyrrolo units **6** and **9** catalyzed by HBF_4 gave the desired dipyrrylmethane **10** in an acceptable yield of 68%. After removal of the benzyl groups *via* hydrogenolysis with Pd/C to give the diacid **11**, the novel diiodo dipyrrylmethane **1** was obtained in excellent yield and high purity as light red crystals.

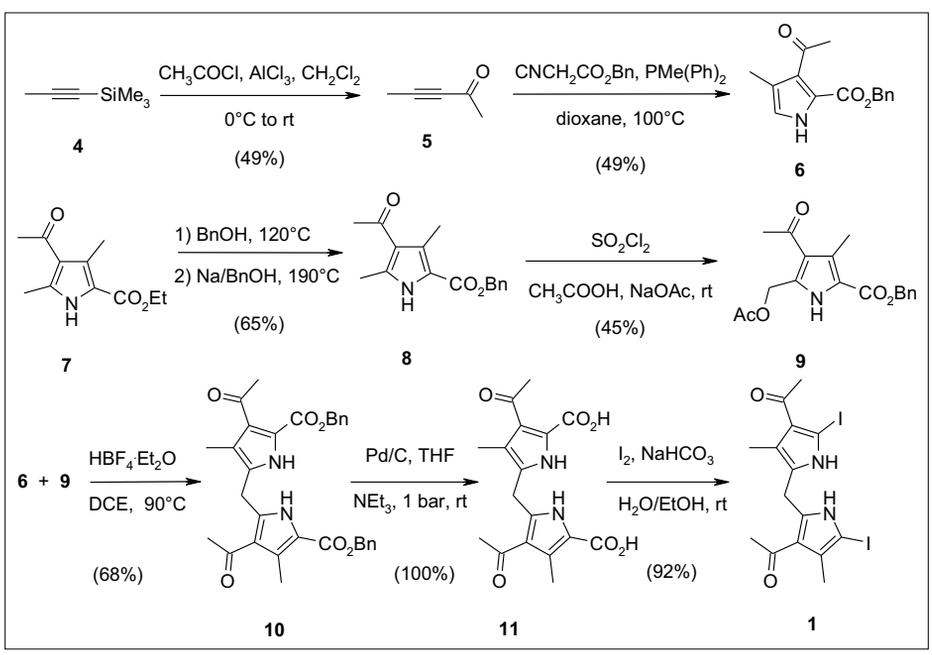
The synthesis of the second dipyrrylmethane moiety **2** was carried out as depicted in Scheme 3. Commercially available **12** was brominated selectively and then condensed with the loss of a C_1 unit to give dipyrrylmethane **13** in good yield. Dialdehyde **2** was then obtained in excellent yield *via* debenzylation with Pd/C to give **14**, followed by reduction with trimethyl orthoformate in presence of trifluoroacetic acid.

With the two dipyrrylmethane moieties **1** and **2** in hand, the condensation reaction was carried out in a mixture of acetic acid, acetic anhydride and trifluoromethyl sulfonic acid (Scheme 1). The desired porphyrin **3** was indeed obtained in excellent 76% yield. The target protoporphyrin IX (**16**) and its disodium salt **17** were obtained as shown in Scheme 4 *via* reduction of the two acetyl groups with $NaBH_4$ to give the hematoporphyrin ester **15**, followed by elimination of the intermediately formed dibenzoates in good to excellent yields. While **16** was obtained as violet-black crystals of high purity, the disodium salt was isolated as an amorphous powder.

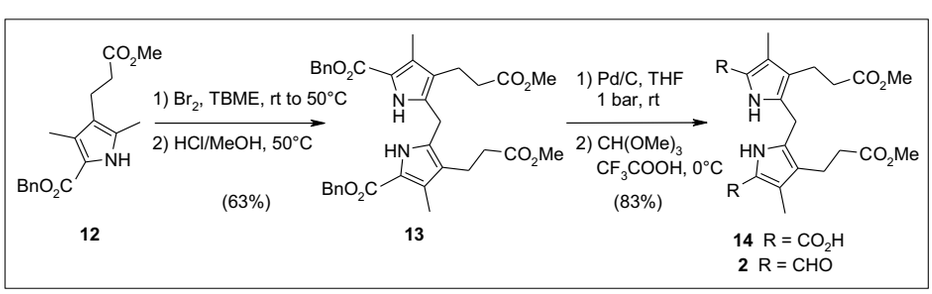
As can be seen from the detailed experimental part, the synthesis of **17** was first carried out on a 6 g scale. While most intermediates could be isolated *via* distillation or crystallization some compounds had to be purified by column chromatography. In an intensive process development, all of these chromatographic steps could be circumvented by relatively small variations of the experimental conditions. The improved procedure was then applied to the preparation of protoporphyrin IX derivatives on a 100 g scale with an overall yield in the range of 40% starting from **1** and **2**.



Scheme 1.



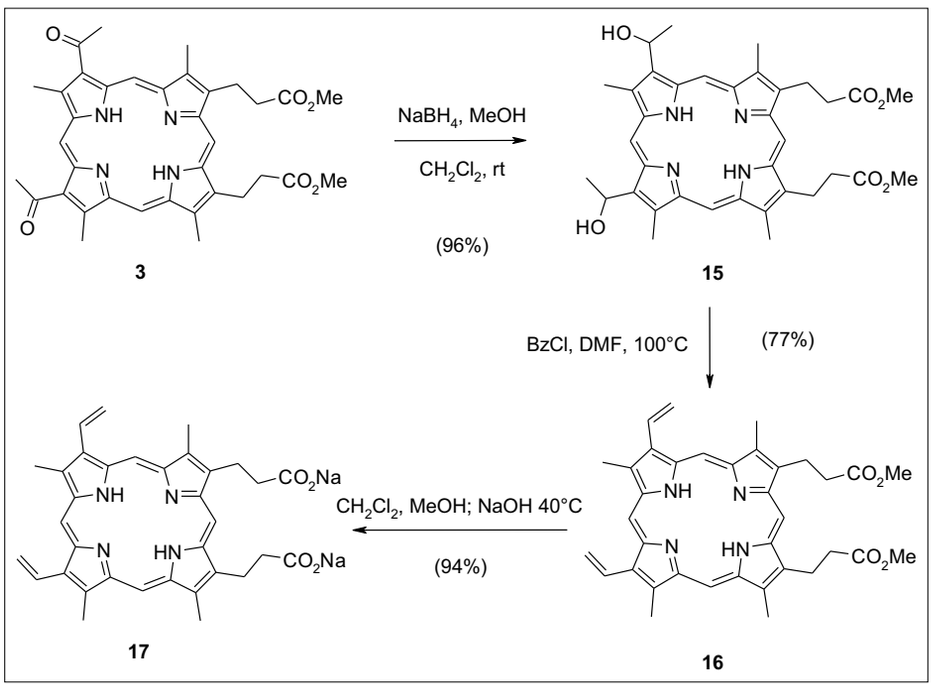
Scheme 2.



Scheme 3.

Conclusions

Protoporphyrin IX dimethyl ester **16** and its disodium salt **17** can be prepared from commercially available starting materials *via* a modified MacDonald procedure. The key step is the condensation reaction of the diiodo dipyrrylmethane **1** with the dialdehyde **2** which directly furnishes the porphyrin **3** without the need of oxidation



Scheme 4.

of a dihydroporphyrin intermediate. Both dipyrrylmethane units can be prepared on multi-100 g scale in excellent purity and satisfactory yield without the need of chromatography.

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[1] The original procedure was first reported by M. Schalfejew, *Hoppe Seylers Zeitschrift* **1900**, *30*, 390 (see also Ullmann, Encyklopädie der technischen Chemie, IV edition, **1976**, Vol. 11, p. 129). An improved procedure is described by H. Schulze, US-Pat. 4761472 (1988, assigned to BASF). About 3-4 g of heme are obtained from 1 l of oxblood.

[2] A. H. Jackson, K. R. Rao, M. Wilkins, *J. Chem. Soc., Perkin Trans. 1* **1987**, 307; W. Chen, H. Yang, D. Xu *Zhnongguo Yiyao Gongye Zazhi* **2000**, *31*, 293. *CAN 134*: 193262.

[3] *Official J. Europ. Union*, C24, 28.1.**2004**, p. 6.

[4] R. Chong, P. S. Clezy, A. J. Liepa, A. W. Nichol, *Austr. J. Chem*. **1969**, *22*, 229; A. H. Jackson, R. K. Pandey, *J. Chem. Soc., Perkin Trans. 1* **1987**, 299.

[5] G. P. Arenault, E. Bullock, S. F. MacDonald, *J. Am. Chem. Soc*. **1960**, *82*, 4384; M. Chakrabarty, *J. Ind. Chem. Soc*. **2001**, *78*, 761; P. S. Clezy, V. Diakiw, *Austr. J. Chem.* **1975**, *28*, 2703.

[6] C.-H. Lee, F. Li, K. Iwamoto, J. Dadok, A. A. Bothner-By, J. S. Lindsay, *Tetrahedron* **1995**, *51*, 11645.

[7] Indeed, I_2 could be observed when the reaction solution was heated in the rotovap. Furthermore, small amounts of a compound could be isolated *via* chromatography which showed the appropriate mass corresponding to intermediate **B** and reacted to give **3** in presence of HI.

[8] For experimental details see P. Martin, M. Müller, D. Flubacher, A. Boudier, H. U. Blaser, D. Spielvogel, *Org. Process Res. Devel.* **2010**, *14*, 799.