

In Focus

Acid Catalysis in the Way to Porphyrins: Reaction of Pyrrole/Aldehydes in the Synthesis of *meso*-Substituted Porphyrins

Gomes, A. T. P. C.

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Catálise Ácida no Caminho para Porfirinas: Reação de Pirróis/Aldeídos na Síntese de Porfirinas *meso*-Substituídas

Resumo: Nos últimos anos as porfirinas adquiriram um papel muito importante em diversas áreas, tais como em catálise, na eletrônica, em células solares, na terapia fotodinâmica do câncer (PDT) ou na terapia fotodinâmica antimicrobiana (aPDT). Tendo em mente tais importantes aplicações, este manuscrito apresenta uma revisão de metodologias de síntese de porfirinas *meso*-substituídas através da condensação de pirrol com aldeídos, na presença de catalisadores ácidos.

Palavras-chave: Pirrol; aldeídos; catálise ácida; porfirina.

Abstracts

Over the past years porphyrins have acquired an important role as a result of their applications in diverse areas such as catalysis, electronics, solar-cells production, photodynamic therapy of cancer (PDT) or in antimicrobial photodynamic therapy (aPDT). Having in mind such significant applications, we have decided to review the procedures for the synthesis of *meso*-substituted porphyrins using the condensation of pyrrole and aldehydes in the presence of acid catalysts.

Keywords: Pyrrole; aldehydes; acid catalysis; porphyrin.

* University of Aveiro, Department of Chemistry and QOPNA, 3810-193 Aveiro, Portugal.

✉ ana.peixoto@ua.pt

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Acid Catalysis in the Way to Porphyrins: Reaction of Pyrrole/Aldehydes in the Synthesis of *meso*-Substituted Porphyrins

Ana Teresa P. C. Gomes

University of Aveiro, Department of Chemistry and QOPNA, 3810-193 Aveiro, Portugal.

* ana.peixoto@ua.pt

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Ana T. P. C. Gomes was born in Viseu, Portugal. She was graduated in Biochemistry and Food Chemistry by the University of Aveiro in 2005. She also got her Master of Science degree in Chemistry of Natural Products in the group of Professor José Cavaleiro in 2007 at the same University; her master thesis was based on functionalization of tetrapyrrolic macrocycles with diazo compounds.

Ana Gomes obtained her PhD degree in December/2011 with a working programme carried out in the same research group. Her PhD thesis describes the studies carried out in the same group on the synthesis and biological applications in photodynamic therapy of new porphyrin derivatives. Her working project was part of a collaborative action, funded by FCT—CAPES, between the Universities of Aveiro and Federal Fluminense.

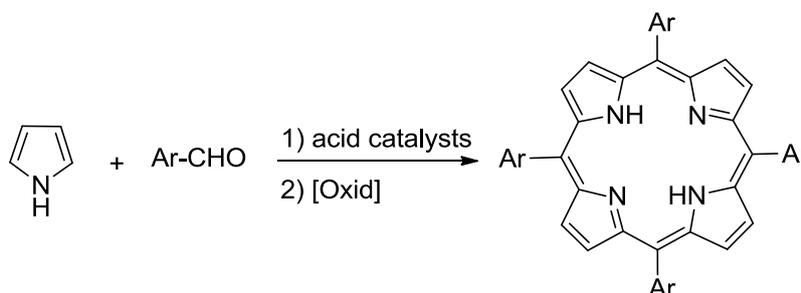
Nowadays she is a postdoctoral researcher in Organic Chemistry at the Chemistry Department of the University of Aveiro. Her scientific interests are based on the development of new porphyrin derivatives with potential applications in the photodynamic therapy of cancer cells and as new antimicrobial photodynamic therapy agents.

1. Introduction

Porphyrin macrocycles play an important role in areas such as photodynamic therapy of cancer (PDT), photoinactivation of microorganisms (aPDT), catalysis, electronics, solar cells production, and others.¹ The use of these tetrapyrrolic macrocycles is strongly dependent on their structures and that's why it is so important to develop or to improve synthetic strategies to reach novel derivatives by derivatization of the porphyrin macrocycle.² Having this in mind, the synthesis of porphyrins is the basis of many studies across a broad spectrum of scientific disciplines. The current use of *meso*-substituted porphyrins stems from their easy synthesis and amenability towards synthetic elaboration. A simple methodology to prepare these compounds consists in the condensation of pyrrole and aldehydes in the presence of acid catalysts (Scheme 1).

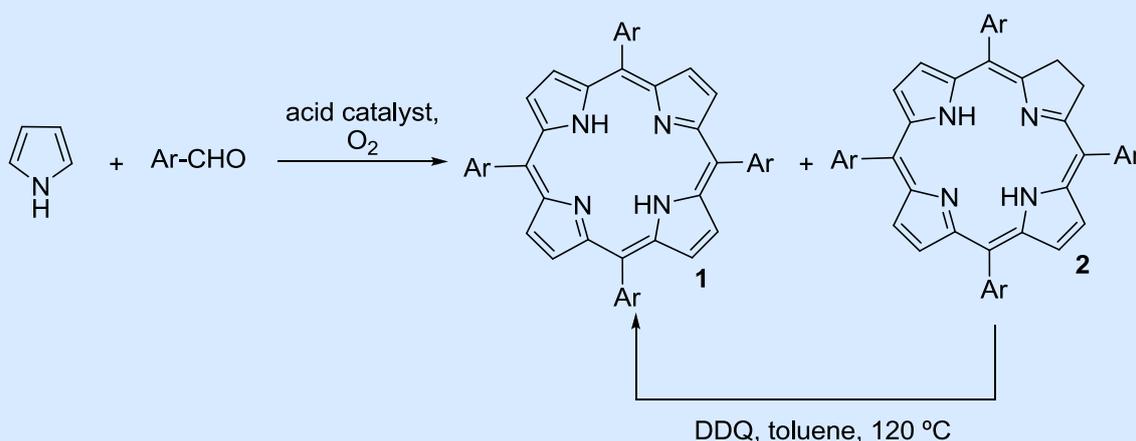
The use of acid catalysis is an important and efficient requirement for the synthesis of *meso*-substituted porphyrins. The acid catalyst is responsible for the protonation of the carbonyl group of the aldehydes, which are then attacked by pyrrole in an aromatic electrophilic substitution, leading to the formation of the tetrapyrrolic chain.

This In Focus manuscript reviews the procedures of the synthesis of *meso*-substituted porphyrins using the condensation of pyrrole and aldehydes in the presence of acid catalysts.



2. Experimental Procedures

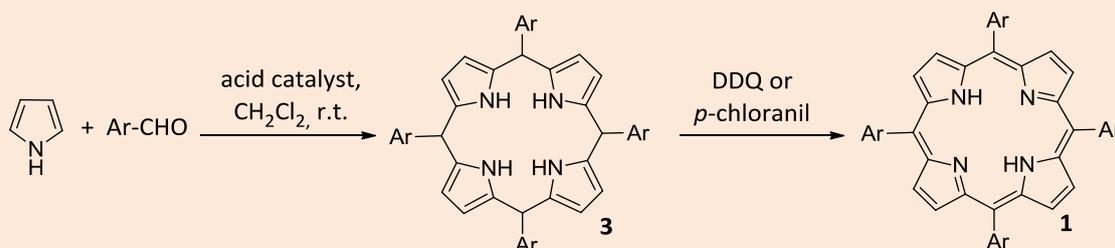
One of the first reports on the synthesis of *meso*-tetraarylporphyrins by condensation of pyrrole and aldehydes, in the presence of an acid catalyst, was performed by Adler and coworkers. In that methodology the condensation reaction of pyrrole and aldehydes took place in acid medium and under aerobic conditions.³ Several acids were used in these studies, such as acetic acid with or without a metal salt, chloroacetic acid or trifluoroacetic acid and propionic acid. The tetraarylporphyrin **1** (Scheme 2) was obtained in crystalline form directly from the reaction medium. However, the major disadvantage of this methodology is the contamination of the desired product with 2-10% of chlorin **2** (Scheme 2). However this compound can be easily oxidized to the correspondent porphyrin by treatment with DDQ in refluxing toluene.³



Scheme 2

The Adler methodology was extended to the condensation of pyrrole with several aldehydes or mixed aldehydes and even to the solid-phase synthesis. In all cases, the desired porphyrins were synthesized in good yields.³

Having in mind that the biosynthesis of natural porphyrins proceeds via porphyrinogen intermediates, Lindsey developed a new strategy for the synthesis of *meso*-substituted porphyrins using a sequential process of condensation and oxidation steps.⁴ This approach requires the condensation of pyrrole and aldehydes in dichloromethane, at room temperature, using trifluoroacetic acid, BCl_3 or BF_3 -etherate as Lewis acid catalysts. Then, in a second step a stoichiometric quantity of DDQ or *p*-chloranil is added in order to oxidize the porphyrinogen **3** into the corresponding chlorin-free porphyrin **1** (Scheme 3).⁴

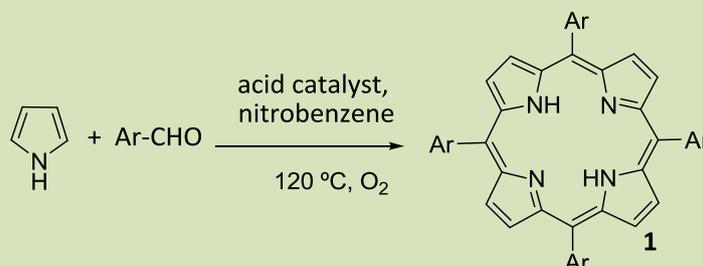


Scheme 3

This methodology has been applied for the synthesis of several *meso*-arylporphyrins, using several aldehydes and the overall yields can reach 50 % depending on the aldehydes used.⁴

The Lindsey method was extended to other modified approaches such as the ones using aerobic oxidation to avoid the contamination of reaction mixtures with the products from the reduction of DDQ and *p*-chloranil, to the one step process, using clays as catalysts, micellar synthesis and the condensations mediated by Grignard reagents.⁵

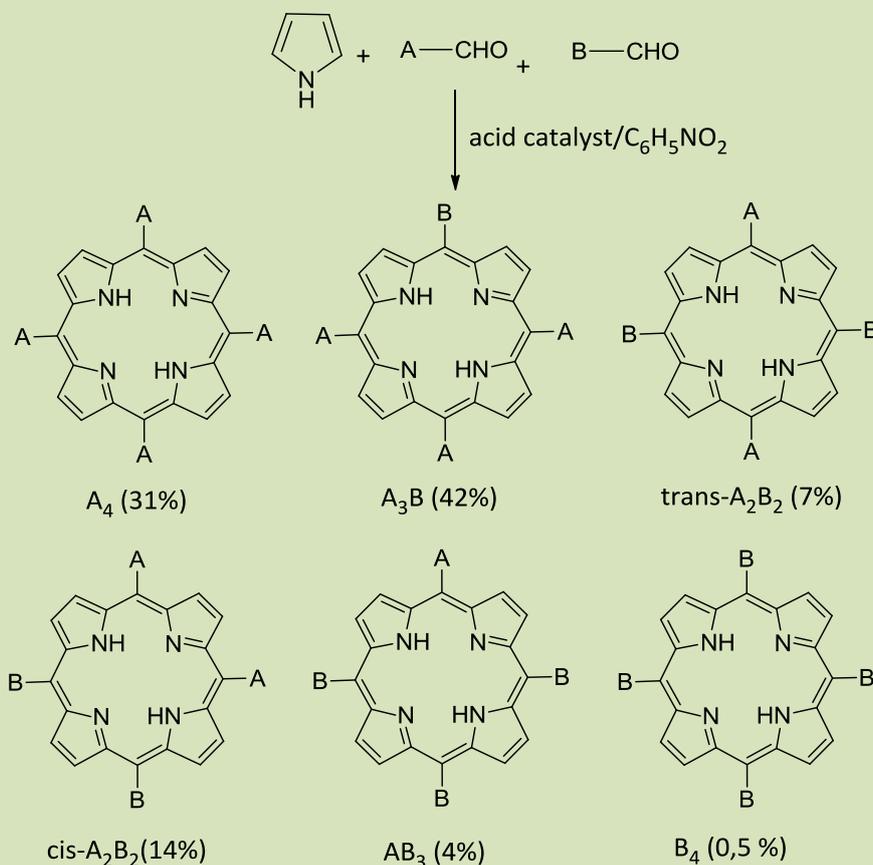
The oxidation process reported by Lindsey was studied and explored by other research groups. Gonsalves and coworkers developed a two step synthesis where the formation of porphyrinogen occurs through the condensation of pyrrole and aliphatic aldehydes in CCl_4 in the presence of trifluoroacetic acid at 60 °C. The oxidation of that intermediate occurs by the addition of DDQ or *p*-chloranil. Several *meso*-tetraalkylporphyrins were obtained using this approach. Latter studies demonstrated that it is possible to prepare chlorin-free *meso*-tetraarylporphyrins in good yields, in a one-step process.⁶ This process involves the condensation of pyrrole and aldehydes in a mixture of acid catalyst (acetic acid or propionic acid) with 30 % of nitrobenzene, at 120 °C in aerobic conditions (Scheme 4). Under such conditions chlorin-free porphyrins are obtained.



Scheme 4

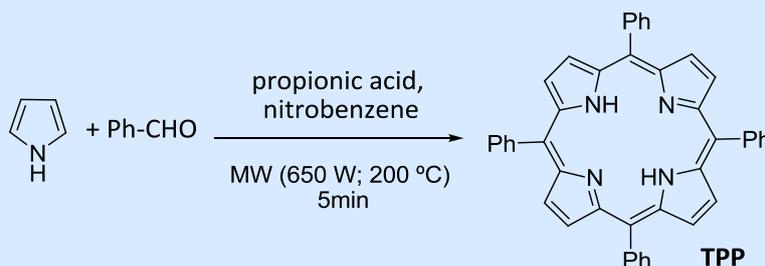
Such one-step process allows the synthesis of unsymmetrical *meso*-substituted porphyrins, through the condensation of pyrrole with a mixture of aldehydes. The amount of the different products formed depends on the proportion of each aldehyde present in the reaction mixture

and on the corresponding reactivity.⁶ Considering a mixture of two aldehydes with similar reactivities, A-CHO e B-CHO, in a 3:1 ratio, it is possible to obtain, in different yields, the porphyrins represented in Scheme 5. This is a good methodology when the reaction products can be easily separated.



Scheme 5

In recent years microwave (MW) assisted synthesis has been used in the synthesis of *meso*-tetraarylporphyrins. In fact during the last fifteen years new and important results on the application of MW irradiation on the porphyrin synthesis and functionalization have appeared. It has been demonstrated that, by using this type of irradiation, not only porphyrins but also their metal complexes can be synthesized.⁷ Also in this case, the acid catalysis is essential for the success of such syntheses. For example, 5,10,15,20-*meso*-tetraphenylporphyrin (**TTP**) has been efficiently prepared by condensation of pyrrole and benzaldehyde, in the presence of propionic acid as catalyst and under MW irradiation (Scheme 6).⁸



Scheme 6

Porphyrins with electron-donating and electron-withdrawing substituents at the *meso*-phenyl groups, and others with bulky substituents at the *ortho*-phenyl positions have also been synthesized in good yields by using MW irradiation for 5 minutes and stoichiometric amounts of pyrrole and aromatic aldehydes in propanoic acid and nitrobenzene.⁷

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