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REVIEW

Main Strategies for the Synthesis of *meso*-Arylporphyrins

O. I. Koifman[a] and T. A. Ageeva[a,*]

[a] *Ivanovo State University of Chemistry and Technology, Ivanovo, 153000 Russia*

**e-mail: president@isuct.ru; tageeva@isuct.ru*

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Abstract—*meso*-Arylporphyrins as most accessible tetrapyrrole macroheterocycles have always been the focus of attention from researchers concerned with practically useful properties of these compounds. The first syntheses of *meso*-arylporphyrins date back to about 90 years ago. Up to now, the yields of these compounds have been improved from 5 to 80%. The present review analyzes different ways and strategies for the synthesis of *meso*-aryl-substituted porphyrins. The most efficient methods that can be scaled up to an industrial level have been identified.

Keywords: *meso*-arylporphyrins, synthesis, pyrrole–aldehyde condensation, cyclotetramerization, synthetic strategy, mixed pyrrole condensation, alternative methods of synthesis, microwave-assisted synthesis, mechanochemical synthesis, ionic liquids

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1. INTRODUCTION

Tetrapyrrole macroheterocycles, the most widely known representatives of which are the "life pigments" such as chlorophylls, bacteriochlorophylls, and hemes, are involved in the most important life processes, including plant and bacterial photosynthesis, respiration, enzymatic catalysis, sulfite and nitro reduction, methanogenesis, and are a source of life support on our planet. Therefore, the constant and continuously growing interest in this class of compounds is not accidental. Over the past half century, the science of porphyrins and related compounds has become an independent field of research, and it has taken firm positions in chemistry, physics, biochemistry, and materials science. The accumulated vast material in this field of knowledge is reflected in the 45-volume edition of the Handbook of Porphyrin Science [1], which provides the necessary review and reference information on all key issues related to porphyrins.

Molecules of porphyrins and their analogs feature a combination of unique photophysical properties with extremely high stability, catalytic activity in chemical, photochemical, and electrochemical processes, and photo- and biological activity, which opens wide possibilities for creating new functional materials based thereon, in particular catalysts for practically important processes, materials for medical, technical, and agricultural purposes, highly efficient sensor and optoelectronic devices, optical limiters, photosensitizers, solar energy converters, optochemosensory materials, etc. [2–5]. Nowadays, of particular importance is the use of tetrapyrrole macroheterocycles for biomedical purposes. Apart from the well-established efficiency of porphyrin-based photodynamic therapy agents [6–17], the ability of these compounds to inactivate various viruses, including SARS-CoV-2, opens prospects of creating new alternative approaches to the treatment of drug-resistant viral and bacterial infections [18–20].

Successful development of any area of application of tetrapyrroles requires reliable methods for the synthesis and modification of porphyrin derivatives with necessary physicochemical and functional properties, which retain their stability to aggressive media and external conditions. Therefore, targeted synthesis of tetrapyrrole macroheterocycles with a specified structure or modification of existing porphyrins in order to endow them with necessary physicochemical or func-

tional properties is the first step in the formation of functional materials, and the creation of good synthetic strategies in porphyrin chemistry undoubtedly remains the main goal for many decades.

From the very beginning of research on tetrapyrrole macroheterocycles, special attention was paid to problems related to their synthesis, isolation, and modification [13–15, 21–29]. All natural porphyrins are unsymmetrically substituted macroheterocycles with peripheral alkyl, vinyl, formyl, and propionyl substituents ensuring their fixation in one way or another in the native polymer matrix. The synthesis of such compounds is very laborious and is characterized by low yields. The syntheses of chlorophyll by Woodward and of hemin by Fisher are of purely fundamental importance. The total syntheses of these macroheterocycles, each involving about thirty steps, are one of the greatest achievements in organic chemistry. Up to now, chlorophyll and vitamin B12 are the most complex porphyrins ever synthesized [21, 22]. Therefore, it seems reasonable to isolate bioporphyrins of the chlorophyll and heme groups from natural sources such as plants, algae, and animal blood and, if necessary, to modify them [22, 23]. Methods for the isolation of tetrapyrroles from plant and animal raw materials and their purposeful modification have been widely developed, and the variety of methodological approaches for their preparation from various sources can be the subject of a separate review [24–27].

Thus, the unique properties of chlorophyll *a* and bacteriochlorophyll *a* have opened up wide possibilities for creating photosensitizers for antimicrobial and anticancer photodynamic therapy [6, 7]. Chemical modification of the peripheral substituents of the original natural macroheterocycle can significantly increase the stability of its derivatives, increase the affinity for malignant neoplasms, and improve physicochemical properties [8–17]. Photosensitizers based on chlorophyll derivatives, e.g., *Fotoditazin* and *Fotoran E6* are successfully used today in the diagnosis and treatment of oncological diseases.

The blood pigment heme can also be modified by chemical transformations of peripheral substituents on the macroheterocycle [26–28]. A photodynamic therapy and fluorescent diagnostics agent, *Fotogem*, has been created on the basis of hematoporphyrin which as a heme derivative. Although heme-based porphyrins are more stable than green plants and algae pigments, due to the lack of macromolecular environment they become less resistant to the effects of the environment, light, and temperature. In this regard, the search for synthetic analogs and technological approaches to the synthesis of tetrapyrrole macroheterocycles has discovered a huge class of synthetic porphyrins and their analogs that are much more stable than natural ones.

The present review focuses on the key strategies for obtaining synthetic porphyrins, specifically *meso*-aryl derivatives, which are most used in the design of new functional materials for various fields of science, engineering, technology, and medicine [2–5].

Today, the synthetic chemistry of porphyrins and their analogs has reached such a level that makes it possible to purposefully obtain tetrapyrroles with almost any given structure and properties. Numerous data on the synthesis and chemical transformations of porphyrins have been summarized in a series of international publications such as “The Porphyrin Handbook” and “Handbook of Porphyrin Science.” The most important methodological approaches in the synthetic chemistry of porphyrins have been reviewed in [29–35].

All tetrapyrrole macroheterocycles (Fig. 1) consist of four pyrrole rings (*I–IV*) connected by methine bridges (α, β, γ, δ) that form the *meso* positions. Positions 2, 3, 7, 8, 12, 13, 17, and 18 of the macrocycle, often referred to as β-positions, can be occupied by various functional groups that determine the diversity of porphyrins. The tetrapyrrole macroheterocycle is characterized by multiloop conjugation, a powerful chromophore system, and high D_{4h} symmetry. The porphyrin coordination entity is formed by four pyrrole nitrogen atoms, and it has a characteristic cavity with a diameter of 4 Å, which is an ideal size for incorporating various metal ions to give highly stable coordination compounds. Up to now, complexes of porphyrins and their analogs with practically all metals of the Periodic Table have been synthesized and effectively used in various fields [36, 37]. On the other hand, any change in the macroheterocycle, on its periphery, or in the coordination center leads to change in the molecular structure and reactivity [38–40].

Tetraarylporphyrins that are synthetic analogs of natural porphyrins occupy a special place among tetrapyrrole macroheterocycles. The availability of *meso*-aryl-substituted porphyrins, their high stability, and the ability to undergo various chemical transformations makes them suitable for most applications [30]. The most common and well-studied representative of tetraarylporphyrins is symmetrically substituted

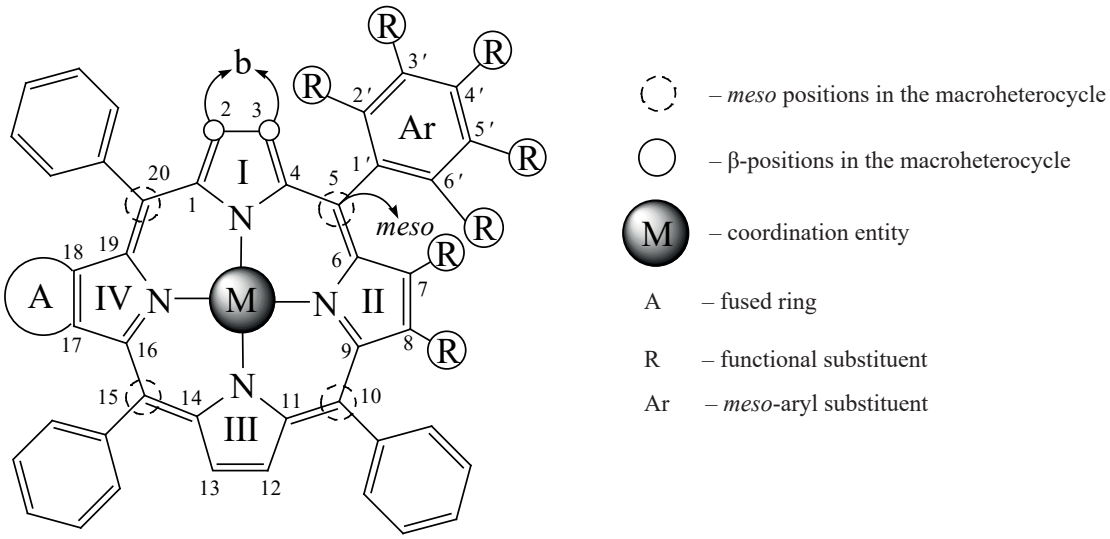


Fig. 1. Base structure of *meso*-arylporphyrin and possible ways of functionalization of the macroheterocycle.

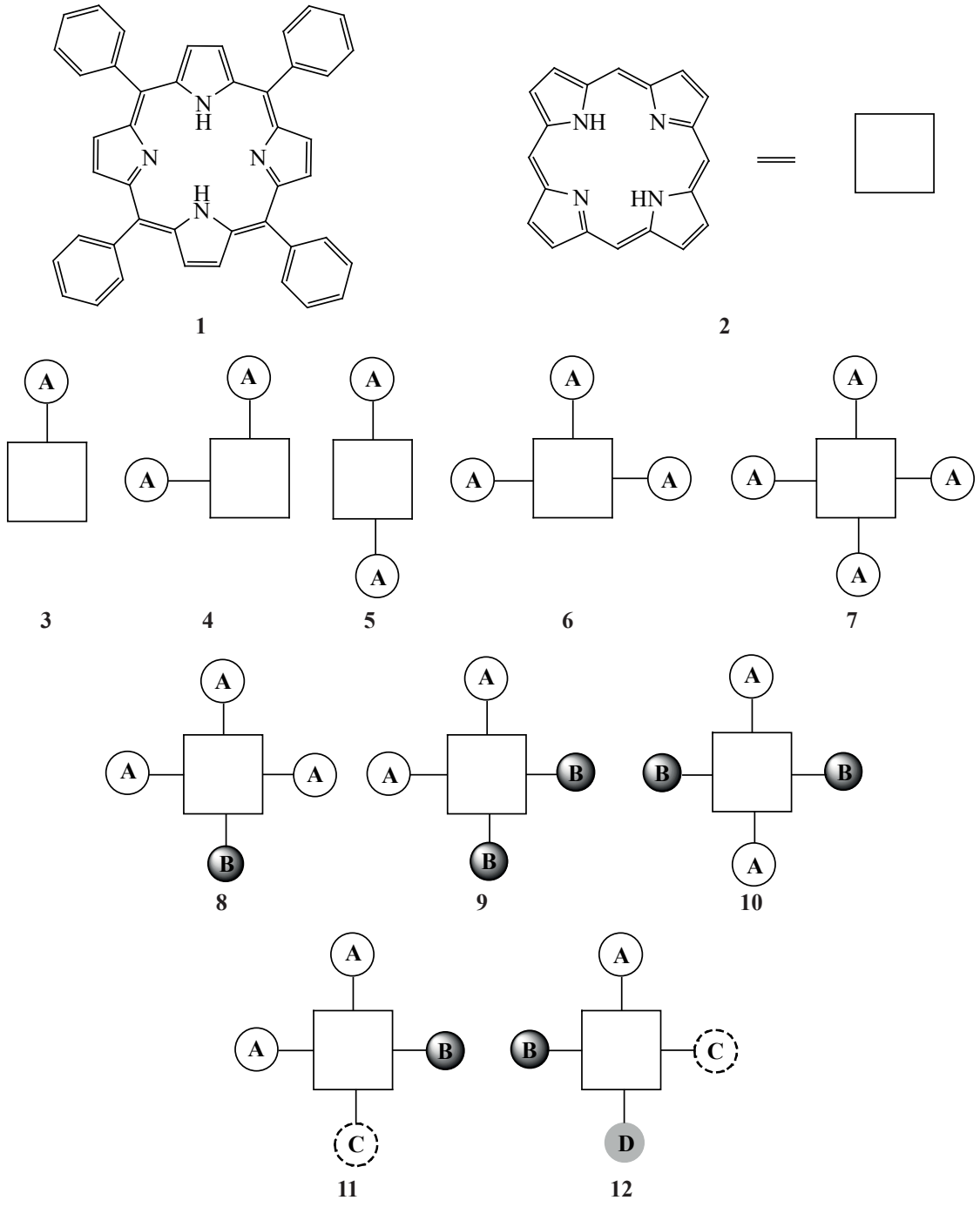
5,10,15,20-tetraphenylporphyrin (Fig. 2), and it is used as a standard for comparing photophysical properties of all other *meso*-arylporphyrins [41–43]. This compound is now the most demanded and tested in most areas of application of porphyrins and their metal complexes. Introduction of various substituents into the phenyl rings of *meso*-tetraphenylporphyrin makes it possible to purposefully change its properties such as solubility, thermal stability, photoactivity, and reactivity, and obtain necessary building blocks for functional materials in various fields of science, technology, and medicine. Symmetrically substituted tetraarylporphyrins, commonly referred to as A_4 type porphyrins [31], are the most frequently synthesized derivatives. However, advances in the applied chemistry of tetrapyrrole macroheterocycles and their use for various purposes generally require unsymmetrically substituted porphyrins. Unsymmetrically substituted derivatives are needed for most applications in optics, materials science, and photomedicine; examples are amphiphilic systems as photosensitizers [44, 45], donor–acceptor systems for solar energy conversion [45–48] and supramolecular chemistry [49, 50], and nonlinear optical materials [51–54].

Thus, interest in tetrapyrrole macroheterocycles has shifted toward *meso*-substituted porphyrins with mixed substitution patterns and less symmetrical systems, which are usually classified according to the arrangement of substituents relative to the macrocycle. According to this classification, 10 structural types of *meso*-substituted porphyrins are distinguished with different degree and symmetry of substitution (Fig. 2). Unsymmetrically substituted *meso*-arylporphyrins, especially monosubstituted ones, are convenient building blocks for their incorporation into various self-organized nanoscale systems [55, 56], porphyrin polymers [57–61], dendrimers [62, 63], hybrid materials [64, 65], electropolymerized films of porphyrins [64–69], and initiating systems for controlled radical polymerization [70–72].

2. PRINCIPAL METHODOLOGIES OF THE SYNTHESIS OF TETRAPYRROLE MACROHETEROCYCLES

The key point in the strategy for the synthesis of porphyrins is the formation of a tetrapyrrole macroheterocycle. Historically, the process of developing and optimizing methods for the synthesis of *meso*-arylporphyrins follows an almost century-long path, marked by certain milestones in the emergence of the most important strategic approaches to the formation of a tetrapyrrole macroheterocycle (Fig. 3).

The synthetic chemistry of porphyrins originates from the preparation of symmetrical tetraarylporphyrins. Rothemund was the first to obtain a series of 5,10,15,20-tetraarylporphyrins by condensation of aliphatic, aromatic, and heterocyclic aldehydes with pyrrole in pyridine–methanol at 145–155°C under anaerobic conditions for several days [74–76]. This methodology proposed more than 85 years ago and subsequently developed by Adler and Longo [77, 78], Lindsey [79–81], and others underlies most methods leading to the formation of porphyrin macroheterocycle



1: 5,10,15,20-tetraphenylporphyrin; **2**: tetrapyrrole skeleton; **3**:A; **4**: *cis*-A_2; **5**: *trans*-A_2; **6**: A_3; **7**: A_4; **8**: A_3B; **9**: *cis*-A_2B_2; **10**: *trans*-A_2B_2; **11**: A_2BC; **12**: ABCD

Fig. 2. Structures of possible types of *meso*-arylporphyrins.

[29–35]. The key starting material is either unsubstituted pyrrole which is brought into condensation with compounds capable of forming methylene bridges or pyrrole having an α-methylene group, which undergoes cyclotetramerization (Scheme 1). The necessary functional peripheral substituents can be introduced by using appropriately substituted initial pyrrole or aldehyde. A huge number of porphyrins with a wide variety of substituents both in the β-positions of the pyrrole rings and in the *meso* positions of the macrocycle have been synthesized by the condensation of pyrroles with aldehydes.

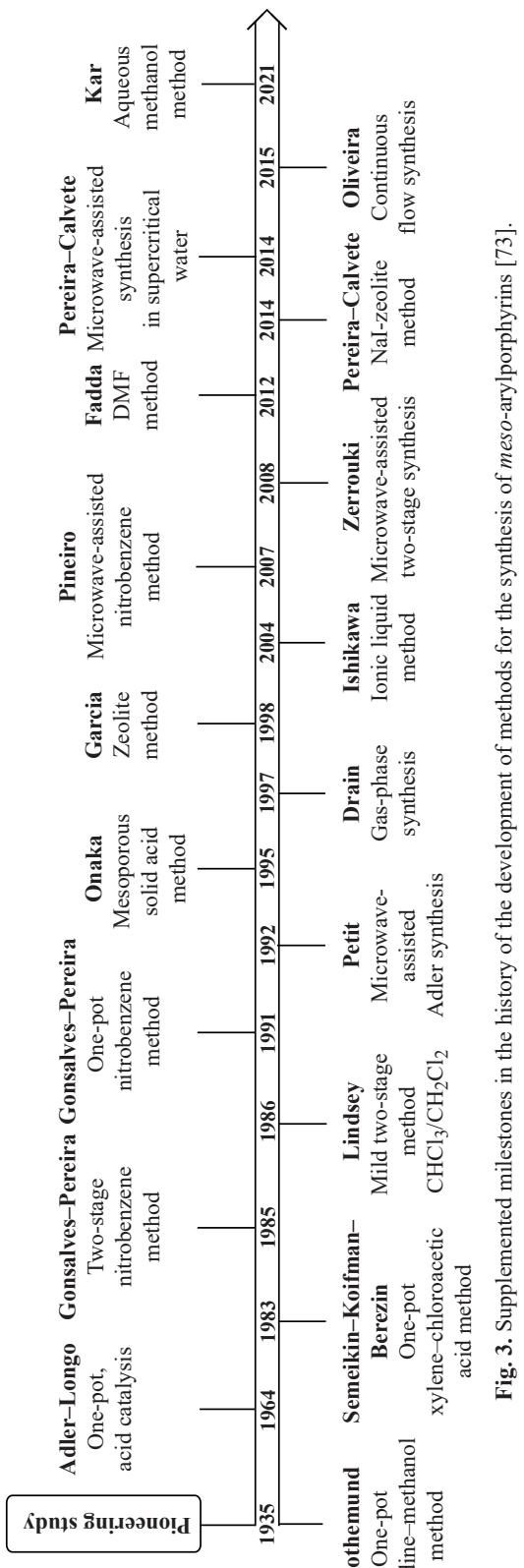


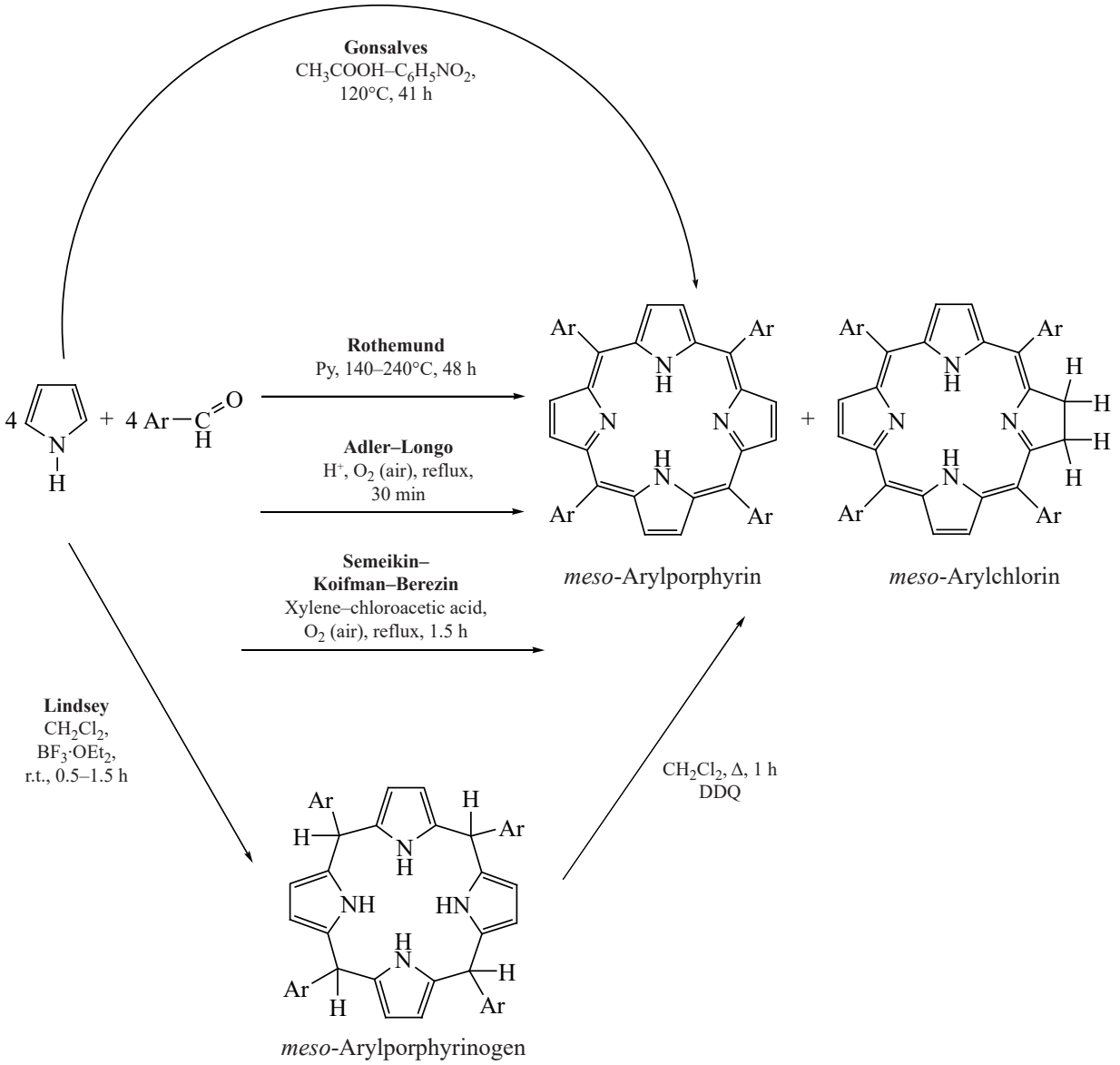
Fig. 3. Supplemented milestones in the history of the development of methods for the synthesis of *meso*-arylporphyrins [73].

In general, all synthesis strategies used to date are based on the improvement of the Rothemund reaction (Scheme 1). A porphyrin macroheterocycle is formed via cyclotetramerization of pyrrole or its derivatives; in this way, only substituted porphyrins can be obtained in good yield.

Despite the progress achieved in the synthesis of parent unsubstituted porphyrin, which now makes it possible to obtain its magnesium complex from 1-formyldipyrromethane in the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as oxidant and magnesium bromide in 30–40% yield [81], this synthesis remains the most difficult [82–85]. The isolation, purification, and studies of unsubstituted porphyrin are greatly complicated by its low solubility in organic solvents. Therefore, the most attractive synthetic porphyrin is *meso*-tetraphenylporphyrin, which is readily available through any of the existing methods and can be successfully modified at any position in both pyrrole and phenyl rings. In this regard, all new methods for the synthesis of *meso*-arylporphyrins, optimization of the conditions for the condensation of pyrrole and aldehyde, and studies of the formation of metal complexes begin with *meso*-tetraphenylporphyrin. Obviously, this trend will continue in the future, primarily in the design and study of new functional materials based on tetrapyrrole macroheterocycles. Therefore, the development of a convenient methodology for the synthesis of this compound, improvement of the yield in the condensation of pyrrole with benzaldehyde, facilitation of isolation and purification procedures, and safety and environmental friendliness of the process remain the most important challenges in the chemistry of tetrapyrrole macroheterocycles.

One of the main and accessible one-step methods for the preparation of *meso*-tetraphenylporphyrin and other symmetrically substituted *meso*-arylporphyrins is based on the Adler–Longo monopyrrole condensation (Scheme 1, Table 1) carried out in acidic medium on exposure to atmospheric oxygen. The optimal reaction medium is acetic or propionic acid, binary solvents like pyridine–acetic acid, or some other acidic media [86]. Optimization of the Adler–Longo method made it possible to largely direct the condensation toward the formation of tetrapyrrole. Thus, when using the Semeikin–Koifman–Berezin strategy, the yield of *meso*-tetraarylporphyrin in a xylene–chloroacetic acid mixture increased, on average, by a factor of two compared with the yield in propionic acid [87–91]. The reaction is usually carried out under reflux conditions,

Scheme 1.

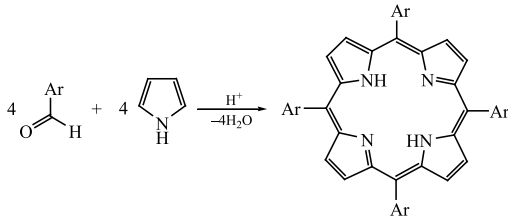


sometimes by passing atmospheric oxygen through the reaction mixture. The yield of tetraarylporphyrins depends on the aldehyde nature and reaction temperature, and the highest yield is achieved at about 140°C [87–91].

The Adler–Longo method proved to be excellent for preparative scale synthesis of porphyrins from fairly stable aldehydes. This quite accessible and convenient method provides rapid and easy synthesis of such porphyrins in ~20% yield. However, its scope is limited in the case of synthesis of *meso*-substituted porphyrins from aldehydes with substituents that are unstable to acids at high temperatures, many aliphatic aldehydes, and 2,6-disubstituted benzaldehydes. The synthesis of *meso*-arylporphyrins having acid-labile groups in the phenyl rings or containing some heterocyclic fragments (for example, furan or pyrrole) in the *meso* positions of the macroheterocycle requires high-boiling solvents such as pyridine, 2,4,6-trimethylpyridine (collidine), or quinoline at atmospheric pressure and the presence of atmospheric oxygen as an oxidant [92].

Apart from porphyrins, the corresponding chlorins can be formed under acidic conditions (Scheme 1), and in some cases the latter become the major products [90]. However, they can be easily converted to porphyrins by treatment with benzoquinone derivatives such as chloranil or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) [91].

Table 1. Main strategies for monopyrrole condensation in the synthesis of tetraarylporphyrins



Method Conditions	Rothemund [74]	Adler–Longo [76]	Semeikin–Koifman–Berezin [87]	Lindsey [80]	Gonsalves–Pereira [96]	Continuous flow [101]	Dimethyl-formamide [128]	Kar (aqueous methanol) [133]
Reaction medium	Pyridine	(a) Propionic acid; (b) Acetic acid	Xylene–chloroacetic acid (2–5%)	(a) CH_2Cl_2; (b) $CHCl_3$	(a) Propionic acid–nitrobenzene (30%); (b) Propionic/acetic acid–nitrotoluene	Propionic acid–nitrobenzene	DMF, TsOH, N_2	(1) H_2O–MeOH (1:2); (2) DMF
Temperature	220°C	a) 141°C; b) 120°C	Reflux	25°C	(a) 120°C; (b) reflux	140°C	150°C	(1) Reflux
Catalyst	–	H^+	H^+	TFA $BF_3 \cdot Et_2O$ $BF_3 \cdot Et_2O$/EtOH	H^+	H^+	H^+	H^+
Oxidant	–	O_2 (air)	O_2 (air)	DDQ; *p*-chloranil	(a) Nitrobenzene; (b) nitrotoluene		–	O_2 (air)
Reactant concentration	3.6 M	0.3–1 M	0.2–0.4 M	0.001–1 M	10 mM	0.3–0.6 M	1.44 mM	O_2 (air)
Reaction time	48 h	0.5–1 h	1–1.5 h (*meta*- and *para*-substituted) 2–2.5 h (*ortho*-substituted)	1 h	1–2 h	27 min	1 h	(1) 1.5 h; (2) 1.5 h + 10 h stirring in air
Number of steps	1	1	1	2	1	1	1	2
Isolation and purification method	Crystallization	Filtration	Filtration and chromatography	Chromatography	Filtration and chromatography	Precipitation, filtration	Precipitation, filtration, chromatography	Precipitation or chromatography
Yield, %	10	~20	Up to 45	Up to 55	(a) 45, (b) 38	31	80–90	10–40

The two-stage method for the synthesis of *meso*-substituted porphyrins under mild conditions, proposed by Lindsey et al. [76, 77, 92–94], involves the condensation of equimolar amounts of pyrrole and an aldehyde in chloroform or methylene chloride in the presence of trifluoroacetic acid or boron trifluoride–diethyl ether complex in inert atmosphere at room temperature to the corresponding porphyrinogen, followed by oxidation with a stoichiometric amount of DDQ or chloranil (Scheme 1). The formation of porphyrinogen is a self-assembly process sensitive to the reactant concentration, and the highest yield is usually obtained at a reactant concentration of 0.01 M. Currently, the Lindsey method is considered the best method for the synthesis of *meso*-substituted porphyrins with the highest yield and wide structural diversity [31–33].

Numerous studies of the condensation of pyrrole with benzaldehyde and other aromatic aldehydes have established the effect of solvents, temperature, and reactant ratio, mechanism of the process, and optimal conditions for the synthesis of *meso*-tetraarylporphyrins, and the results have been reviewed in detail in [29–35, 92–94]. The yield of *meso*-tetraphenylporphyrin in the one-pot two-stage Lindsey synthesis can reach 50–58% (Table 1) [95].

In order to modify the Adler–Longo method and obtain a chlorin-free product, Rocha Gonsalves et al. proposed a one-step nitrobenzene method for the synthesis of symmetrical *meso*-substituted porphyrins via condensation of pyrrole with aliphatic or aromatic aldehydes in acetic or propionic acid in the presence of nitrobenzene (30%) as an oxidant for intermediate tetraarylporphyrinogen [96–99] (Scheme 1, Table 1). This procedure is advantageous due to its versatility and the possibility of obtaining porphyrins by direct condensation of pyrrole with aldehydes, regardless of their nature and type of substituents. For example, 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin was obtained according to the nitrobenzene procedure in 40% yield [100] which cannot be achieved using the Adler–Longo methodology.

Momo et al. [101] tried to optimize the nitrobenzene method for the synthesis of *meso*-tetraarylporphyrins by using a continuous-flow technique. The continuous-flow synthesis of porphyrin was carried out in a heated stainless steel tubular reactor equipped with a two-channel syringe pump. The reactants, propionic acid and pyrrole–benzaldehyde–nitrobenzene mixture, were supplied from different pumps into the mixing zone and were then pumped into a high-temperature tubular reactor to prevent their early polymerization. The reaction conditions were optimized for monopyrrole condensation by varying the reactant concentrations, temperature, and flow rate (Table 1). The optimal flow rate of reactant solutions was estimated at 0.3–0.6 mL/min. Porphyrins were isolated by simple precipitation from methanol and further crystallization from methylene chloride and methanol. The proposed technology made it possible to obtain various *meso*-aryl- and *meso*-alkylporphyrins on a gram scale with a good reproducibility in a yield comparable with classical methods.

It was found that the acidity (pK_a) of the medium and the nature of acid catalyst (organic acid, Lewis acid) are crucial for the efficient cyclotetramerization of pyrrole with aldehyde [102]. In order to reveal the specific role of acid catalysis in combination with chemical oxidation of intermediate products, Sun et al. [103] found that the most effective acid activation of the starting compounds is achieved in a mixture of propionic and acetic acids using nitrobenzene or its derivatives to oxidize intermediate porphyrinogen [104–106]. Highly pure *meso*-tetraphenylporphyrin was thus obtained in 38% yield in the presence of *m*-nitrotoluene [103]. Furthermore, other nitrobenzene derivatives proved to be good oxidants providing more than 30% yield of tetraarylporphyrins containing no chlorin impurity [103] (Table 1).

In almost any of these methods, the yield of *meso*-tetraarylporphyrins strongly depends on the substituent in the benzaldehyde component, including its electronic effect and steric factor (Table 2). Numerous studies have shown that there is virtually no effect of steric factor in reactions with *para*- and *meta*-substituted benzaldehydes; therefore, only electronic effects of substituents can be taken into account. In the case of tetraarylporphyrins with *ortho* substituents at the phenyl rings, the steric factor prevails over the electronic one [107]. However, the rate of the condensation of pyrrole with aromatic aldehydes does not always correlate with the yield of porphyrin. Linear polymers or stable condensation products of pyrrole and aldehyde can be formed as by-products which do not undergo cyclotetramerization with the formation of tetrapyrrole macroheterocycle. For example, the condensations of *p*-nitro and *p*-aminobenzaldehydes with pyrrole gave tetrakis(4-nitrophenyl)porphyrin and tetrakis(4-aminophenyl)porphyrin in as low yields as 7 and 1%, respectively [107]. In order to obtain porphyrins with reactive functional groups at the phenyl rings, preliminary acylation of hydroxy or amino group in the initial aldehyde is necessary. The yield of

Table 2. Effect of substituent in the phenyl ring on the yield (%) of *meso*-tetraarylporphyrin

Porphyrin	Rothemund	Adler–Longo	Semeikin–Koifman–Berezin	Lindsey	Gonsalves–Pereira	DMF	Kar (water–methanol)
Tetraphenylporphyrin	10 [74]	20 [76]	43 [89]	20 [80]	20 [96]	20 [128]	21 [133]
Tetrakis(2-methylphenyl)porphyrin		11.5 [109]	20 [89]	45 [94]			
Tetrakis(3-methylphenyl)porphyrin		16.0 [109]	30 [89]				
Tetrakis(4-methylphenyl)porphyrin		14.9 [108]	39 [89]				
Tetrakis(2-methoxyphenyl)porphyrin	2.6 [111]	9.8 [108]	16 [89]	20 [94]	15 [96]		
Tetrakis(3-methoxyphenyl)porphyrin		14.0 [108]	25 [89]		45 [96]		
Tetrakis(4-methoxyphenyl)porphyrin	7.1 [110]	22.5 [109]	42 [89]		78 [98]		29 [133]
Tetrakis(2-chlorophenyl)porphyrin	8.3 [111]	3.26 [108]	16.8 [89]	28 [94]	4–9 [99]		
Tetrakis(3-chlorophenyl)porphyrin		18.2 [108]	26.8 [89]		22 [98]		
Tetrakis(4-chlorophenyl)porphyrin	2.6 [110]	23.3 [108]	34.6 [89]		49 [98]		20 [133]
Tetrakis(2-bromophenyl)porphyrin		2.1 [108]	13 [89]	24 [94]			
Tetrakis(3-bromophenyl)porphyrin			18,5 [89]				
Tetrakis(4-bromophenyl)porphyrin		12.0 [108]	19 [89]		25 [99]		9 [133]
Tetrakis(2-nitrophenyl)porphyrin		12 [109]	15 [89]	24 [94]	20 [96]		
Tetrakis(3-nitrophenyl)porphyrin			25 [89]		9 [96]		
Tetrakis(4-nitrophenyl)porphyrin	2.6 [111]	7 [109]	24 [87]	10 [94]	25 [96]	80 [128]	28 [133]
Tetrakis(3-hydroxyphenyl)porphyrin		10 [109]	5 [89]		40 [98]	70 [131]	
Tetrakis(4-hydroxyphenyl)porphyrin			1.7 [89]			72 [131]	
Tetrakis(3-aminophenyl)porphyrin						74 [131]	
Tetrakis(4-aminophenyl)porphyrin		<1 [109]				74 [131]	

porphyrins from aldehydes with protected groups is higher by a factor of 10, and the required amino- and hydroxyphenyl-substituted porphyrins can be easily obtained by hydrolysis of the corresponding tetraacetoxy or tetraacetamido derivatives.

Therefore, the strategy for porphyrin synthesis should always be selected taking into account the nature of substituents on tetrapyrrole macroheterocycle as the most important factor affecting both the yield and spectral, coordination, and other physicochemical properties of the resulting porphyrins [112, 113].

The combination of a rigid tetrapyrrole macroheterocycle and flexible peripheral substituents of various natures in tetraarylporphyrins and their metal complexes predetermines the tendency of these molecules to self-assemble into ordered supramolecular structures that easily respond to any external influences and thus determine the ways of forming modern functional materials and molecular devices based thereon. Symmetrically substituted tetraarylporphyrins were reported as promising liquid crystal materials [114–116]. To determine the relation between the structure of porphyrins and their mesogenic properties, a series of homologous 5,10,15,20-tetrakis(alkoxyphenyl)porphyrins (Alk = C_4H_9 to $C_{16}H_{33}$) were synthesized by alkylation of tetrakis(hydroxyphenyl)porphyrins with haloalkanes [117, 118]. Since the target porphyrins cannot be obtained with a good yield and required degree of purity according to the Adler direct condensation of pyrrole and hydroxybenzaldehyde, the above noted Rocha Gonsalves approach was employed. Correspondingly, the condensation of hydroxybenzaldehydes with pyrrole was carried out in a mixture of acetic acid and nitrobenzaldehyde (3:1) under reflux for 2 h, followed by keeping the reaction mixture at room temperature for 3 days [100]. 5,10,15,20-Tetrakis(4-hydroxyphenyl)porphyrin and 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin were obtained in 40 and 32% yields, respectively. Among 27 newly synthesized tetrakis(alkoxyphenyl)porphyrins and their metal complexes, four compounds exhibited thermotropic mesomorphism and one exhibited lyotropic mesomorphism in binary systems with toluene, benzene, and chloroform. The important role of the substituent position in the phenyl rings of porphyrins in the formation of mesophases has been determined. The phase transition temperature decreased in going from *p*-alkoxyphenyl-substituted porphyrins to their *meta* and *ortho* isomers. In the series of *ortho*-substituted porphyrins, mesogenic properties were found for homologs with a lower number of carbon atoms in the alkoxy groups than in the *para*-substituted analogs. Metal complexes derived from mesogenic porphyrins did not exhibit liquid crystal properties [100, 114].

A chiral nickel complex of 5,10,15,20-tetrakis[3,5-bis(2-methylbutoxy)phenyl]porphyrin was synthesized [119–121] (Scheme 2) and studied as a dopant in nematic mixtures based on strongly polar alkoxy cyano biphenyls and an eutectic mixture of weakly polar Schiff bases [119]. Anomalous temperature dependences of the components of the dielectric permittivity of liquid crystal solutions were found due to competition between the dopant which twists the mesophase and the magnetic field which tends to unwind the helix.

The nickel complex of 5,10,15,20-tetrakis[3,5-bis-(2-methylbutoxy)phenyl]porphyrin was used as a stationary phase for gas chromatography. It showed high structural selectivity in the chromatographic separation of isomeric 3,5- and 3, 4-lutidines over a wide operating temperature range from 20 to 350°C [120, 121].

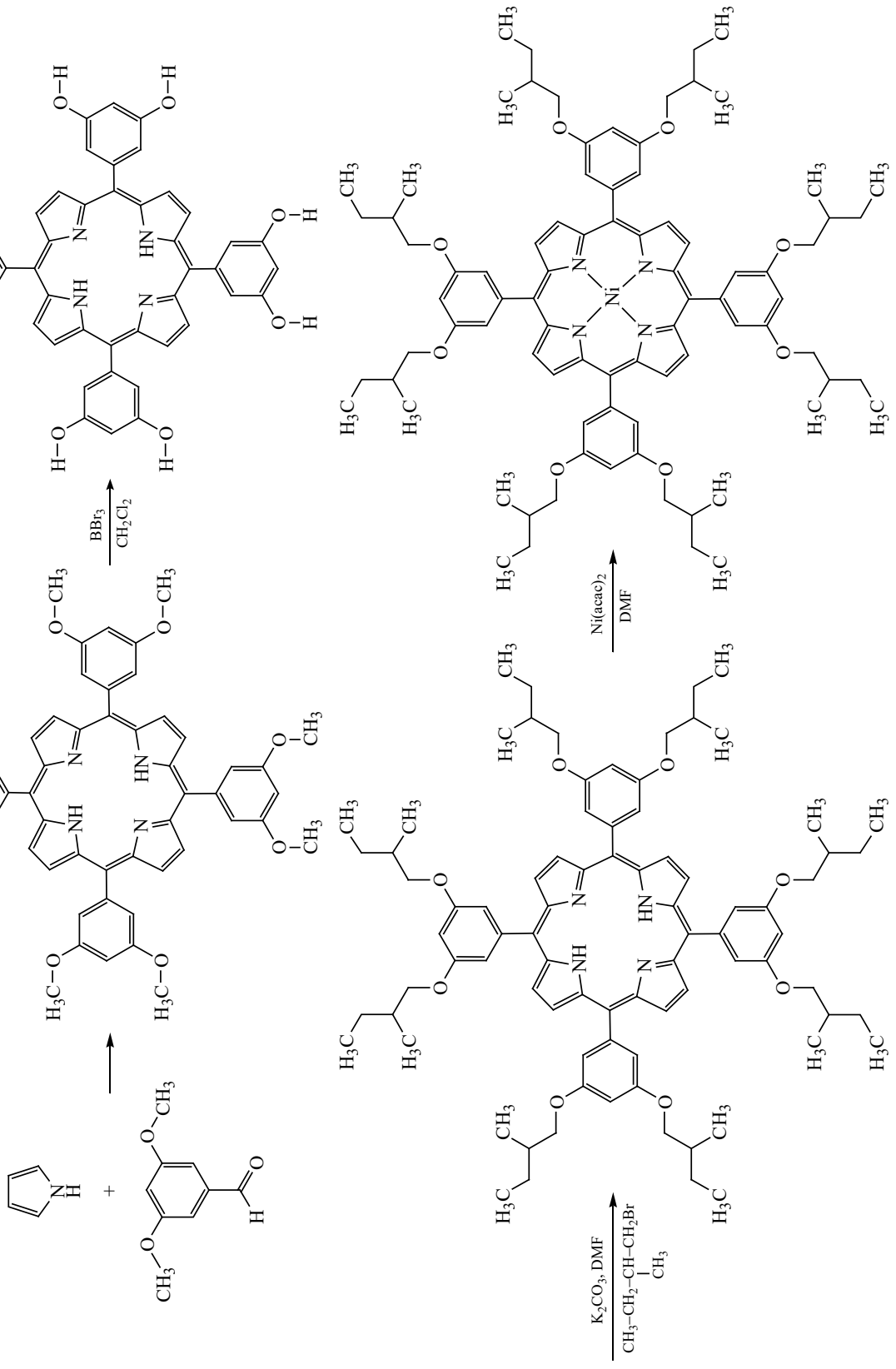
Thus, the one-pot strategy of monopyrrole condensation became the main one for the formation of tetrapyrrole macroheterocycles, and variation of its conditions made it possible to obtain various porphyrinoids [122] such as corroles [123, 124], inverted porphyrins [125], sapphyrins [126], and expanded porphyrins [127]. The Rothemund–Adler–Longo–Lindsey method can be considered universal for the preparation of synthetic porphyrins and porphyrinoids.

However, the disadvantage of any of the considered methods is the use of a large amount of rather aggressive organic solvents and laborious isolation and purification procedures. Therefore, simplification of any stage of the synthesis of porphyrins and their metal complexes is the most important problem.

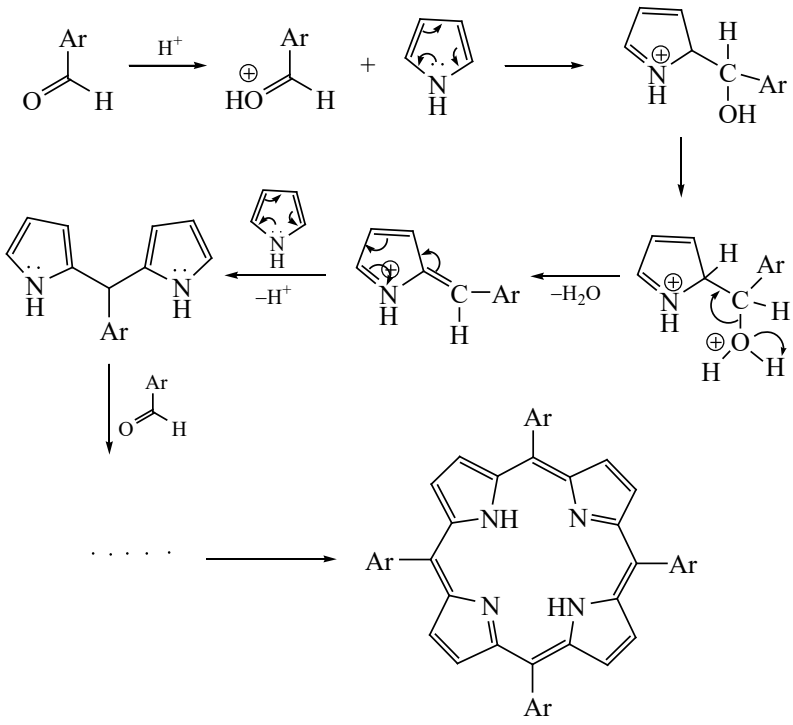
In order to obtain a large series of *meso*-substituted porphyrins exhibiting antioxidant and cytotoxic activity, Fadda et al. [128–130] proposed a new methodology based on the one-pot condensation of equimolar amounts of aromatic aldehyde and pyrrole in DMF in an inert gas atmosphere in the presence of an equimolar amount of *p*-toluenesulfonic acid (Scheme 3). The target porphyrins were formed within 1–2 min, the reaction mixture was kept at 150°C for an hour to complete the process, cooled, and poured into ice water, and the product was collected by filtration.

The yield and rate of the condensation were found to depend on the concentration of *p*-toluenesulfonic acid, solvent, temperature, and the presence of oxygen, as well as on the initial reactant concentrations.

Scheme 2.



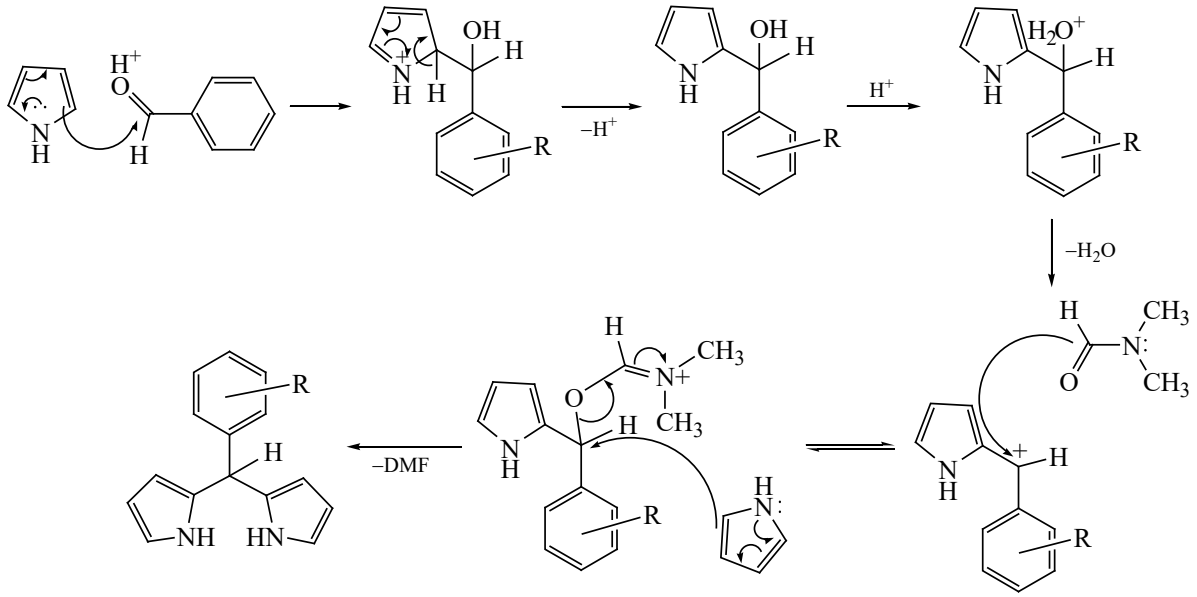
Scheme 3.



Dimethylformamide was convincingly shown to be the most appropriate solvent. The primary condensation product forms a complex with DMF (Scheme 4), which prevents the formation of polymeric pyrrole and eventually leads to the formation of tetrapyrrole macroheterocycle. When other solvents capable of acting as a protecting group were used, the intermediate complex polymerized predominantly into a resinous sparingly soluble material [128].

First of all, the proposed method attracts attention due to high yield and the possibility of direct condensation of aldehyde with pyrrole to afford porphyrins (e.g., tetrahydroxy and tetraamino tetraphenylporphyrins) that cannot be accessed by other methods (Table 2). All

Scheme 4.



porphyrins were obtained in 75–82% yield (Table 1), and, what is important, the procedure for the isolation of porphyrins by pouring the reaction mixture onto ice largely facilitates the process and simplifies and accelerates purification of the final products [131, 132].

Kar and co-workers [133, 134] have recently developed a new simple two-step method for the synthesis of symmetrical and unsymmetrical *meso*-arylporphyrins. The first step is the condensation of pyrrole or dipyrromethane with an aldehyde in aqueous methanol in the presence of HCl (Scheme 5). The solid product obtained in the first step was dissolved in dimethylformamide and oxidized with atmospheric oxygen under reflux for 1.5 h, followed by stirring overnight at room temperature. The subsequent purification by chromatography or recrystallization afforded the target porphyrins with a high purity.

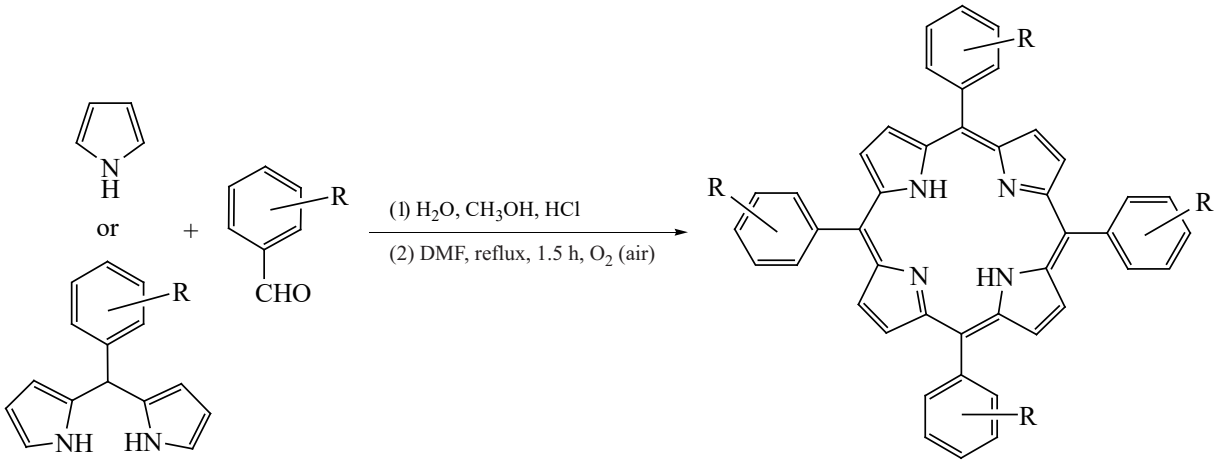
The advantage of the proposed method is that it does not require expensive or aggressive oxidants such as DDQ or chloranil and a large volume of dry chlorine-containing solvents. In contrast to previously used classical methodologies, the proposed method is highly scalable and ideally suitable for the synthesis of symmetrical and unsymmetrical *meso*-arylporphyrins on a gram scale. The yield of porphyrins is not high, and it ranges from 10 to 40%, depending on the initial aldehyde; however, it is well reproducible, and the resulting porphyrins are sufficiently pure, so that in some cases there is no need to resort to chromatographic purification.

Like phthalocyanines [135–137], it is possible to increase the yield of tetrapyrrole macroheterocycle in the condensation of pyrrole with benzaldehyde using metal salts as a template [138]. However, depending on the metal salt, the corresponding metal porphyrin complex can be obtained [139]. Following this approach, the two stages of metalloporphyrin synthesis, tetramerization of pyrrole and complexation, can be accomplished in a one-pot manner, which is advantageous when just a metal complex is required for further application. Metal-free porphyrin can be obtained by treatment of the complex with an acid. In this case, the metal salt chosen as a template should give a fairly labile metalloporphyrin which is capable of easily dissociating under mild conditions [140].

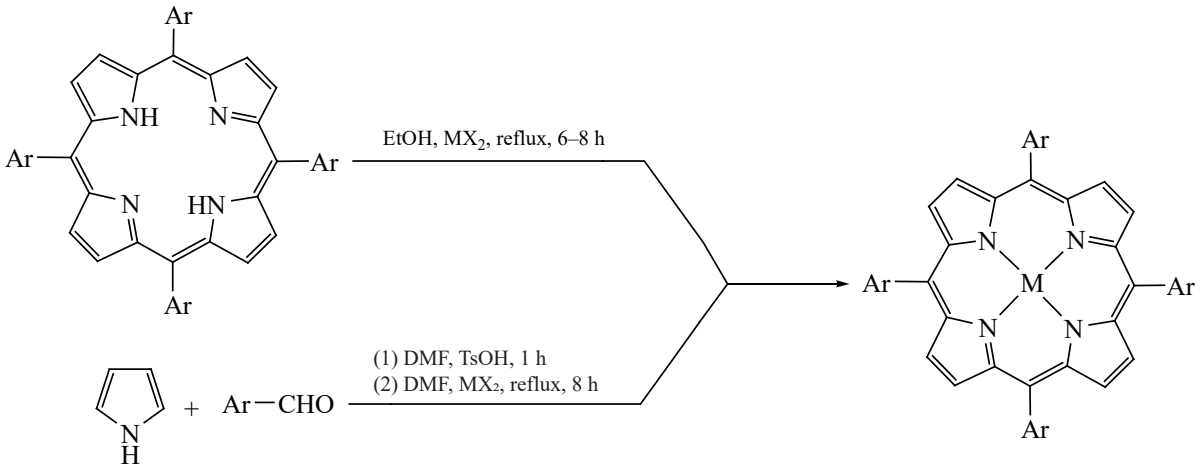
Gridnev and Nikiforov [141] proposed a one-pot method for the synthesis of a cobalt complex of tetrakis(methoxyphenyl)porphyrin with an up to 38% yield in a mixture of chlorobenzene and propionic acid at 130°C and in the presence of cobalt acetate. Kinetic study of the condensation of pyrrole with anisaldehyde showed that cobalt ion does not work as a template here and that it is necessary to add metal salt after the formation of tetrapyrrole. The mechanism of action of the metal salt in the synthesis of metalloporphyrins is not yet clear, but in the one-pot synthesis of metalloporphyrins in dimethylformamide [142–144], an increase in the yield of macroheterocyclic compound or its metal complex is achieved by sequential addition of reagents (Scheme 6).

Nevertheless, the template strategy remains the major one for the synthesis of tetrabenzoporphyrins and their *meso*-tetraaryl derivatives [145, 146]. It involves high-temperature template tetramerization of phthalic acid derivatives with nucleophilic reagents as a source of *meso*-carbon atoms [147, 148] (Scheme 7), as well as low-temperature assembly of the porphyrin system from stable saturated isoindole analogs and aldehydes with aromatization of the macroheterocycle

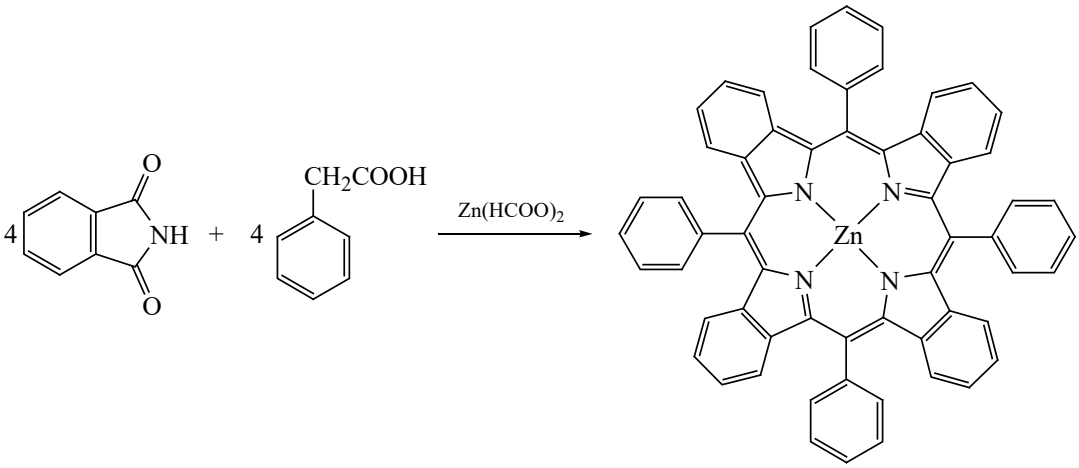
Scheme 5.



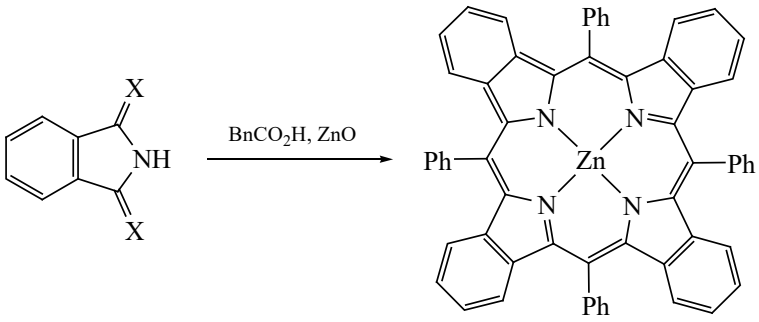
Scheme 6.



Scheme 7.



Scheme 8.



X = S, NH; 290°C (X = S) or 270°C (X = NH).

at the final stage [149–151] (Scheme 8). Template synthesis of symmetrical metal complexes of tetrabenzoporphyrins and their derivatives is carried out by heating a mixture of powdered phthalimide or its alkaline salt with zinc acetate in an inert atmosphere. Metal-free porphyrins can be obtained by treatment of a solution of the corresponding zinc complex with hydrochloric acid. The use of arylacetic acids in this methodology opened the way to tetraaryltetrabenzoporphyrins (TATBP) with various substituents on the

phenyl ring [152, 153]. The high-temperature template condensation of isoindole derivatives with arylacetic acids is generally suitable for the preparation of tetrabenzoporphyrins containing functional groups in the isoindole fragments. Some limitations of this method are mainly associated with inaccessibility of appropriately substituted phthalimides and their thermal instability. The yields of *meso*-substituted tetrabenzoporphyrin metal complexes in all template syntheses do not exceed 20%. To increase the yield, it was proposed to use dithiophthalimide and 1,3-diaminoisoindoline that are more active than phthalimide. The condensation of these compounds with phenylacetic acid and zinc oxide for 1 h afforded tetraaryltetrabenzoporphyrin [149] (Scheme 8).

Finikova et al. [150–152] proposed a simple and convenient method for the synthesis of tetraaryltetrabenzoporphyrins under mild conditions by the condensation of very stable (unlike isoindole) 4,5,6,7-tetrahydroisoindoles with aromatic aldehydes in the presence of a Lewis acid ($BF_3 \cdot Et_2O$), followed by oxidative aromatization of metal hexadecahydrotetrabenzoporphyrins (Scheme 9). This approach can be regarded as a modified Rothemund method. The aromatization stage also proceeds under mild conditions, at room temperature in the presence of DDQ [151].

The condensation of tetrahydroisoindole with aromatic aldehydes includes many steps. Although the yields of target products at each stage are fairly high, the overall yields of metal complexes with respect to the initial sulfolene do not exceed 50% [153]. Nevertheless, the practical value of this methodology is obvious since it makes it possible to obtain metal tetraaryltetrabenzoporphyrins on a gram scale in a single step without resorting to chromatographic purification. Furthermore, it opens an accessible route to a number of important *meso*-tetraaryltetrabenzoporphyrin metal complexes substituted both at the phenyl and fused benzene rings.

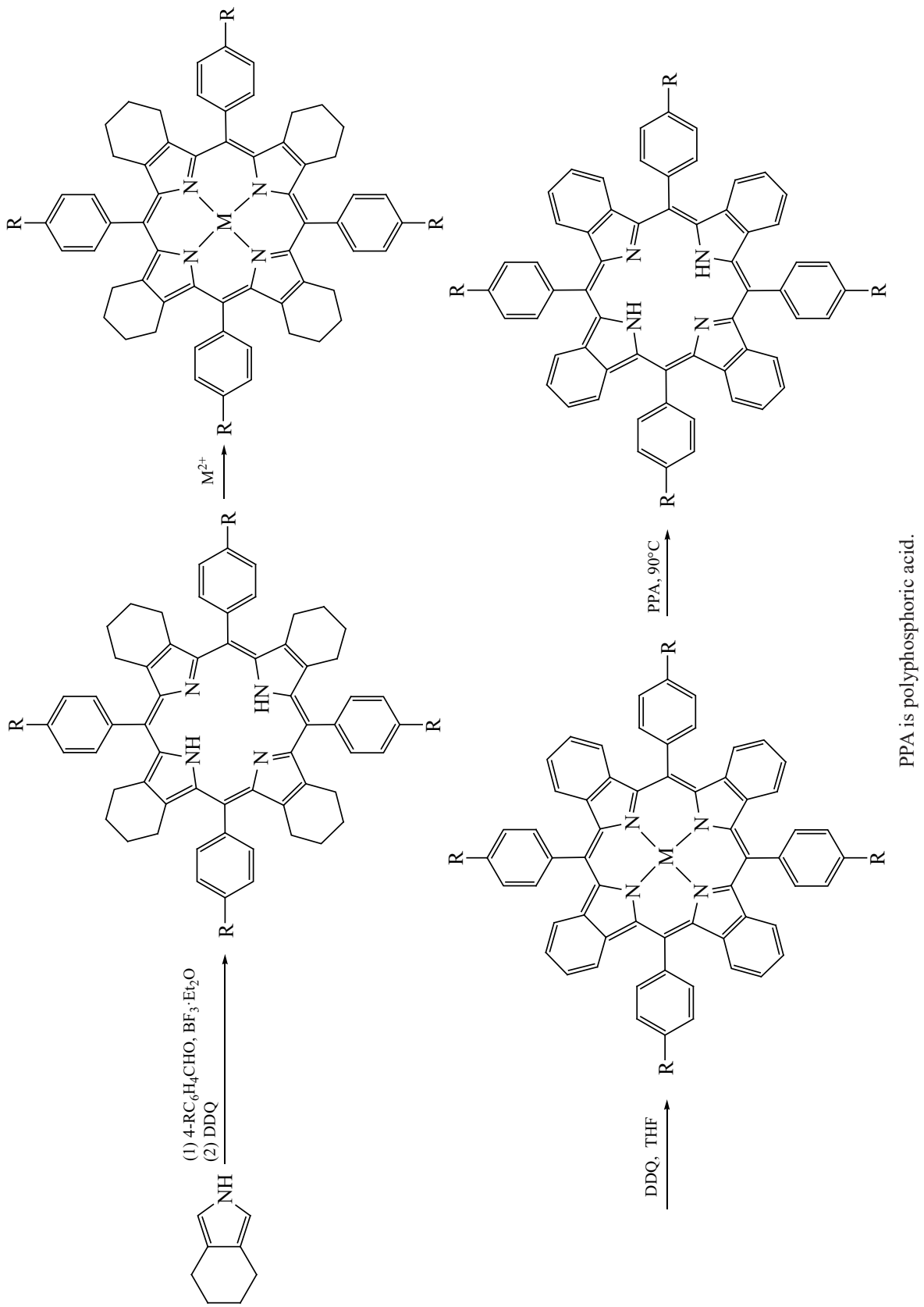
Both currently available strategies for the synthesis of tetrabenzoporphyrin and its *meso*-aryl derivatives are applicable to its symmetrical linear benzologs such as tetranaphtho- and tetraanthraporphyrins and their angular isomers, tetranaphtho[1,2]porphyrins and tetraphenanthro[9,10]porphyrins [154–156]. Interest in this group of highly conjugated fused porphyrins with an extended π-conjugation system has increased especially in the last two decades. Studies in this field have been largely stimulated by the need to develop long-wavelength chromophores for new functional materials such as infrared light-emitting devices [157], photovoltaics [158], oxygen sensors [159], photosensitizers [160], etc.

Undoubtedly, prospects related to this group of porphyrins require the search for more efficient methods for their preparation. Quite recently, Ruppel et al. [161] proposed a new general method for the synthesis of symmetrical tetraaryltetrabenzoporphyrins from a readily accessible isoindole synthon, 4,7-dihydro-2*H*-4,7-ethanoisoindole. This method provides high-yielding synthesis of metal-free porphyrins by condensation of isoindole with aromatic aldehydes and subsequent oxidative aromatization of the tetrapyrrole macroheterocycle, regardless of the aldehyde nature (Scheme 10).

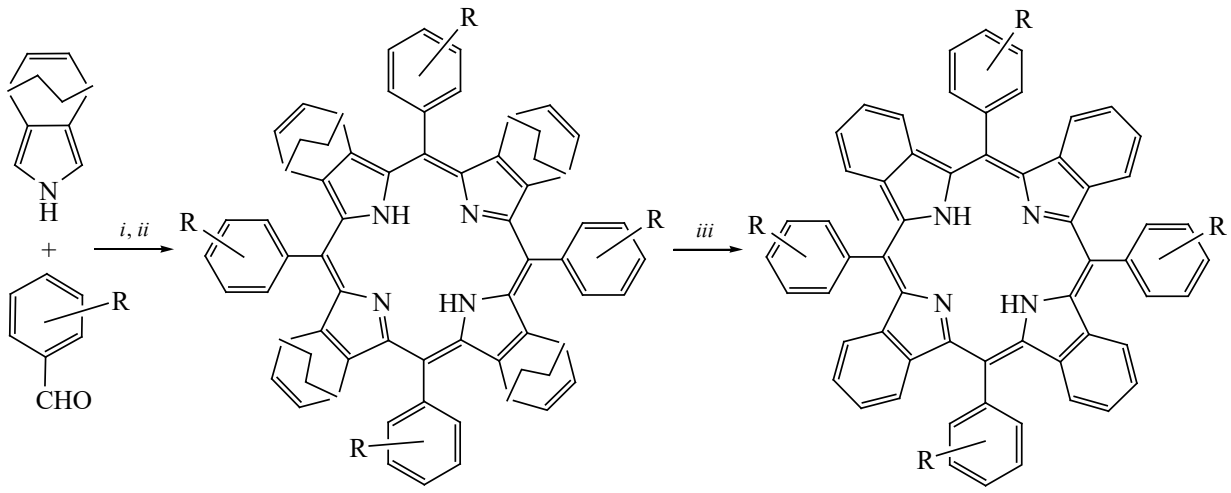
The condensation of 4,7-dihydro-2*H*-4,7-ethanoisoindole was described previously [162], but the yield of the corresponding tetrabenzoporphyrin was very low. Extensive studies of the reaction conditions showed that the yield depends on the reactant concentration, reaction time, and catalyst nature. The proposed strategy was used to obtain 30 symmetrical tetraaryltetrabenzoporphyrins whose yields exceeded those known to date by more than two times. The authors found that a thermodynamically favorable tetrapyrrole structure is formed in inert dichloromethane in the presence of a Lewis acid ($BF_3 \cdot Et_2O$) for 18 h at room temperature with protection from daylight. This Lewis acid works equally well regardless of the aldehyde nature. After completion of the condensation, aromatization was achieved by treatment with DDQ for 2 h under reflux. The mixture was washed with 10% sodium sulfate and sodium carbonate solutions, the solvent was removed, and the product was isolated by filtration and finally purified by reprecipitation without resorting to column chromatography. As a result, 30 metal-free tetraaryltetrabenzoporphyrins were obtained in 50 to 86% yield. If necessary, the corresponding metal complexes were easily obtained by traditional methods. The authors believe that the proposed methodology is quite general and commercially applicable.

The structural diversity of tetraaryltetrabenzoporphyrins was expanded by applying the proposed methodology in combination with mixed condensation [163]. The condensation of 4,7-dihydro-2*H*-4,7-ethanoisoindole with a mixture of two aromatic aldehydes or of two different isoindole derivatives with benzaldehyde was used to obtain low-symmetry TATBPs with various substituents either in the *meso*-aryl fragments or on the periphery of the macroheterocycle with

Scheme 9.


(1) 4-RC6H4CHO, BF3·Et2O
(2) DDQ
M2+
DDQ, THF
PPA, 90°C
PPA is polyphosphoric acid.

Scheme 10.



Reagents and conditions: *i*: CH_2Cl_2, $BF_3 \cdot Et_2O$, N_2, r.t., 18 h; *ii*: DDQ, N_2, reflux, 2 h; *iii*: reduced pressure, 205°C, 1 h.

an overall yield of 55–58%. The product mixtures were separated by column chromatography.

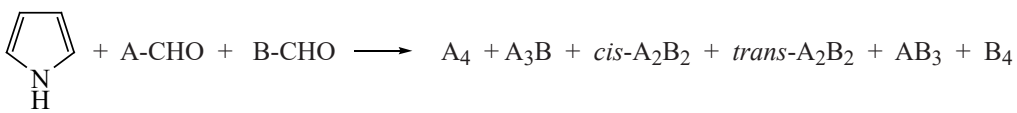
The symmetrical substitution pattern in *meso*-tetraarylporphyrins restricts the scope of their possible practical use for solving a number of problems related to both modeling the functions of natural porphyrins and designing effective hybrid materials for various fields of technology and medicine. In this regard, unsymmetrically substituted *meso*-tetraarylporphyrins are of particular interest. One of the simplest methods for the synthesis of such porphyrins is mixed-aldehyde condensation [164, 165] (Scheme 11). The reaction of pyrrole with a mixture of two aldehydes makes it possible to obtain a mixture of six porphyrins (Fig. 2): A_4, A_3B, *cis*-A_2B_2, *trans*-A_2B_2, AB_3, and B_4, which can be separated by thin-layer or column chromatography.

The statistically expected ratio of porphyrins in the mixed-aldehyde synthesis is given by the binomial distribution. Provided that the reactivities of aromatic aldehydes are similar and their ratio is 1:1, the quantitative distribution of the resulting tetraarylporphyrins is as follows: A_4, 6.25%; A_3B, 25%; *cis*-A_2B_2, 25%; *trans*-A_2B_2, 12.5%; AB_3, 25%; B_4, 6.25%.

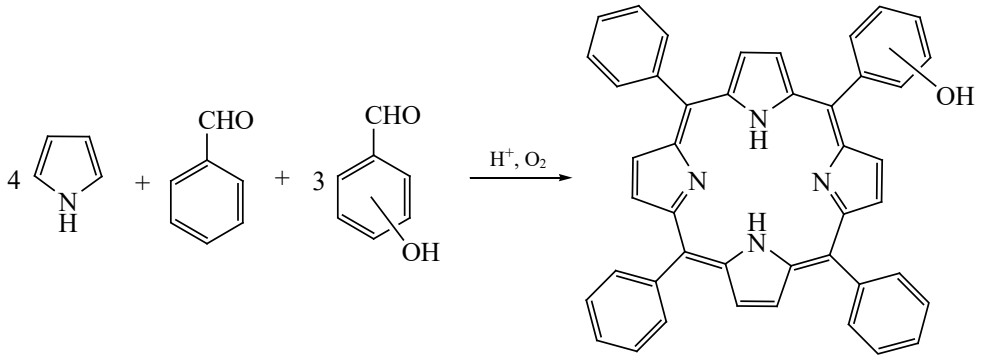
Most often, the mixed-aldehyde condensation method with an initial aldehyde ratio of 3:1 is used to obtain A_3B porphyrins; in this case, the mole fractions of A_4 and A_3B porphyrins are 31.64 and 42.19%, respectively. However, the optimal ratio of reacting aldehydes to achieve the highest yield of A_3B porphyrin depends on the actual reactivities of the aldehydes, as well as on the ease of separation of the resulting porphyrin mixture [166]. Despite the simplicity and accessibility of the mixed-aldehyde condensation method, its application is significantly limited by the need for time-consuming chromatographic separation of the products. This methodology is of interest when one of the aldehydes used cannot give rise to the corresponding symmetrical *meso*-arylporphyrin according to the classical monopyrrole condensation method or the yield of such porphyrin is very low. As shown in [167, 168], hydroxybenzaldehydes readily react with benzaldehyde and pyrrole to produce (hydroxyphenyl)-triphenylporphyrins (Scheme 12).

Syrbu and Semeikin [107, 167] modified the mixed-aldehyde condensation method with a view to improving the yield of unsymmetrically substituted porphyrin. For this purpose, the condensation of pyrrole with two different aldehydes was carried out in a mixture of xylene and chloroacetic acid without an oxidant in order to accumulate the corresponding arylporphyrinogen, in which the substitution pattern in the phenyl rings correlated with the initial aldehyde ratio. The subsequent oxidation with atmospheric oxygen

Scheme 11.



Scheme 12.



afforded the target A_3B porphyrin in a yield comparable with the yields of symmetrical tetraarylporphyrins.

Ezhov et al. [170] applied the mixed-aldehyde condensation method as an accessible and easily executable one to synthesize a series of zinc complexes of A_3B porphyrins as elements of photovoltaic devices.

To reduce the number of statistically possible condensation products formed by closure of the tetrapyrrole macroheterocycle, Lindsey et al. proposed a methodology for the synthesis of porphyrins containing up to four different *meso* substituents [171] via condensation of dipyrromethanes already containing the required substituents, followed by oxidation with DDQ (Scheme 13). As a result, pure porphyrins were obtained on up to a gram scale of pure with minimal use of chromatographic methods.

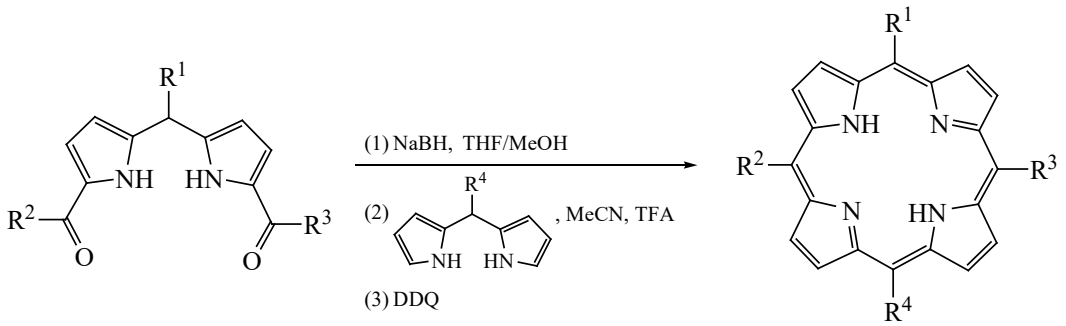
Detailed study of the formation of unsymmetrical *meso*-arylporphyrins showed that the reaction course depends mainly on the nature of the introduced substituents and acid catalyst [172]. In keeping with the obtained results, the reaction efficiency can be significantly increased, and planning of the synthesis of tetrapyrrole macroheterocycles can be facilitated, by proper choice of substituents in the initial reactants. The Lindsey methodology has become one of the most popular for the synthesis of unsymmetrically substituted *meso*-arylporphyrins. For example, it has been successfully used to obtain new catalytically active metal porphyrins [173] and to design new structural blocks for supramolecular systems [174].

Two convenient methods have been developed for the synthesis of 5,15-diphenylporphyrins with electron-donating and electron-withdrawing substituents on the phenyl rings. The first of these is the high-temperature condensation of dipyrromethanes with aromatic aldehydes (Scheme 14) in the presence of zinc acetate in nitrogen-containing heterocyclic solvents such as pyridine, collidines, lutidines, and quinoline [175].

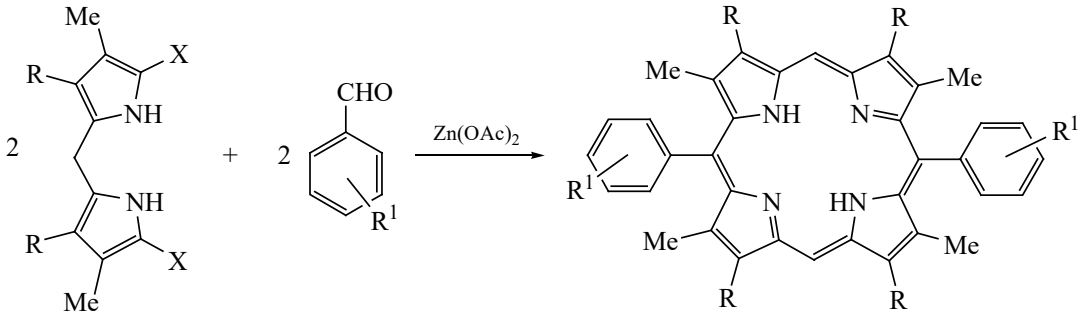
The second two-stage method is based on the condensation of α,α′-unsubstituted dipyrromethanes with benzaldehydes (Scheme 15) in halogen-containing solvents (chloroform or methylene chloride) at room temperature, followed by oxidation with benzoquinone derivatives (*o*- or *p*-chloranil, DDQ) [176 , 177]. The lower yields in the first method are compensated by the complete absence of acid rearrangement products of dipyrrolylmethenes, while in the second case the products contained up to 1–2% of monophenyloctaalkylporphyrins.

Natural porphyrins generally contain alkyl, carbonyl, vinyl, and carboxy groups in the β-positions of pyrrole rings, and each of these groups plays a certain

Scheme 13.

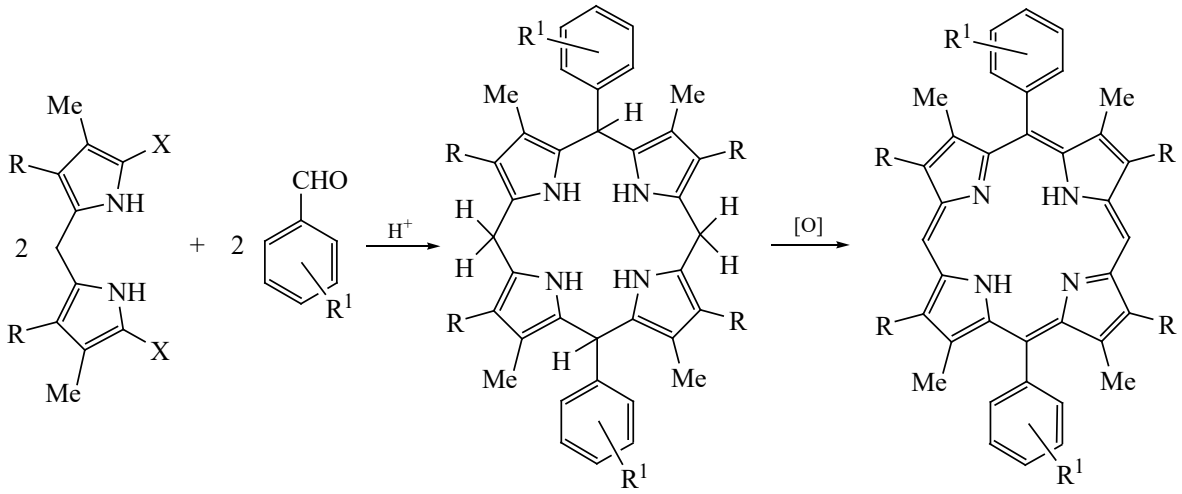


Scheme 14.



X = H, COOH.

Scheme 15.

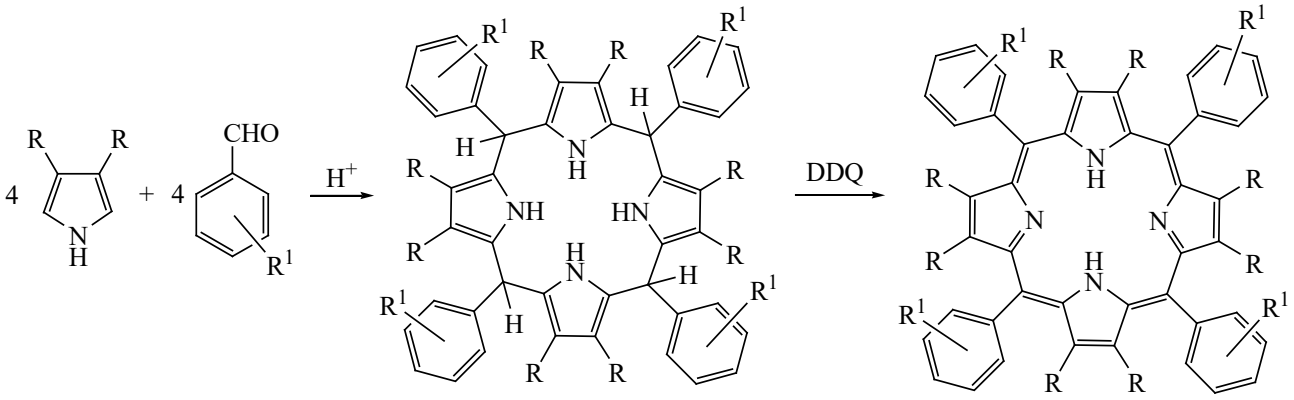


role as it is included in the native polymer system. Therefore, the synthesis of β-substituted porphyrins and their metal complexes is necessary to simulate natural processes [178]. Such porphyrins with a symmetrical structure can be obtained by the monopyrrole condensation method involving tetramerization of pyrroles with a methylene group in one of the α-positions as a source of *meso*-carbon atoms in the porphyrin macrocycle. Dolphin [179] used 3,4-dimethylpyrrole as a reagent more sensitive to electrophilic attack than pyrrole and showed that in this case the initial condensation stage will be faster, while the stage of oxidation of porphyrinogen to porphyrin will be slower due to steric hindrance.

A two-stage method was patented for the synthesis of tetraphenyloctamethylporphyrins [180]. It is based on the condensation of 3,4-dimethylpyrrole and benzaldehyde in methanol in the presence of hydrobromic acid, followed by oxidation of the resulting porphyrinogen with DDQ. The method makes it possible to obtain in good yields tetraaryloctaalkylporphyrins with both electron-donating and electron-withdrawing substituents in the phenyl rings (Scheme 16). For example, 5,10,15,20-tetrakis(4-*tert*-butylphenyl)-2,3,7,8.12,13,17,18-octamethylporphyrin and 5,10,15,20-tetrakis(3,5-di-*tert*-butylphenyl)-2,3,7,8.12,13,17,18-octamethylporphyrin were thus synthesized in a carbon dioxide atmosphere and purified by column chromatography on aluminum oxide with an overall yield of 60 and 15.2%, respectively [181]. The proposed method is quite versatile and is applicable to targeted synthesis of porphyrins with various *meso* substituents in order to endow them with the necessary functional properties. For instance, 5,10,15,20-tetrakis(thiophen-2-yl)-2,3,7,8.12,13,17,18-octamethylporphyrin obtained by the same procedure [182] absorbs in the near IR region; therefore, it can be considered as a promising molecular probe and photosensitizer in photodynamic therapy.

Thus, the strategy based on the condensation of pyrrole with aldehydes underlies the synthesis of all symmetrical and unsymmetrical *meso*-arylporphyrins as

Scheme 16.



the basis of most functional materials [2–5] and building blocks for supramolecular [49, 50, 56, 183, 184], self-organized [55], and porphyrin polymer assemblies [56, 57, 185, 186], which can be used to design modern hybrid materials and molecular devices.

On the other hand, the synthesis of porphyrin by classical methods often requires high temperatures and the use of toxic and/or dangerous reagents; the target products are obtained in very small quantities, and the procedures are poorly scalable.

3. ALTERNATIVE METHODOLOGIES FOR THE SYNTHESIS OF *meso*-ARYLPORPHYRINS

The recent solutions to improve the efficiency of methods for the synthesis of *meso*-arylporphyrins, namely the use of cleaner processes by replacing organic solvents with ionic liquids and supercritical water, increasing the yield through the use of solid microporous catalysts in combination with microwave irradiation, and reducing energy consumption by shortening reaction times, clearly pave the way for industrial technologies and expansion of the scope of application of tetrapyrrole macroheterocycles.

One of the most accessible alternative methods for the synthesis of *meso*-arylporphyrins is microwave-assisted synthesis [186, 187]. The use of microwave (MW) radiation in organic synthesis is now becoming a generally accepted synthetic methodology. It has been recognized that MW activation operates at the molecular level, and therefore reactions in a microwave reactor are usually faster than under conventional thermal heating, thereby reducing the reaction time and increasing the yield of porphyrins or their metal complexes.

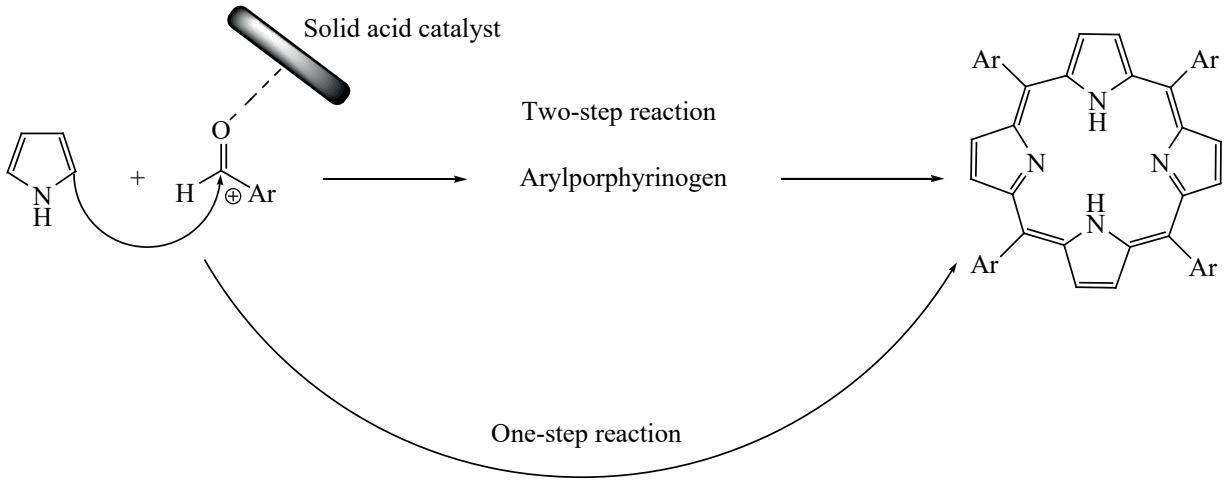
The simplicity and accessibility of classical one-pot methods for the condensation of pyrrole with aldehydes underlay the strategy of microwave synthesis of *meso*-arylporphyrins. For three decades, MW activation has been used to improve and optimize this process, and numerous publications on the synthesis of *meso*-substituted porphyrins using this methodology have been reviewed in [189–192].

Inorganic materials have recently been shown to offer a significant potential to replace organic acids as aldehyde activators in the synthesis of *meso*-substituted porphyrins [126–129]. Since it was unequivocally established that the choice of acid is the determining factor for the efficient catalysis of monopyrrole condensation, the use of solid acids in this process has opened a new environmentally friendly approach to the synthesis of tetrapyrrole pigments, especially in combination with microwave irradiation (Scheme 17).

Petit et al. [193] were the first to use MW radiation in the dry synthesis of *meso*-tetraphenylporphyrin. The condensation of pyrrole and benzaldehyde adsorbed on the surface of silica gel as an acid catalyst was carried out for 10 min in a domestic microwave oven (Table 3). Although the maximum yield of porphyrin under these conditions did not exceed 9.5%, the short reaction time, the high purity of the product, and the ease of its isolation showed that the proposed strategy is promising for obtaining small amounts of tetrapyrrole compounds.

The solvent-free methodology for the preparation of tetrapyrrole macroheterocycles was developed using zeolite catalysts [194]. The use of acid zeolite catalysts such as HZSM-5 and Al-MCM-41 in combination with microwave heating provided good yields and selectivity in the synthesis of tetraphenylporphyrin, tetra-

Scheme 17.



kis(4-methoxyphenyl)porphyrin, tetrakis(4-methylphenyl)porphyrin, and calixarene. In this case, a higher yield of tetraphenylporphyrin (Table 3) on the HZSM-5 molecular sieves was achieved due to the surface reaction and high acidity of the catalyst. The use of a TLC glass plate as a support for zeolites, which acts as a mini reactor in the microwave field, increased the efficiency of the condensation of pyrrole with benzaldehyde (Table 3) and simultaneously facilitated separation of the products [195]. Due to its efficiency, speed, and selectivity, the proposed methodology may be promising for high-performance parallel synthesis in combinatorial chemistry [195].

Unsymmetrical A_3B *meso*-arylporphyrins containing two different aryl moieties in the *meso* positions were synthesized by MW heating using a solid silica gel support. The microwave synthesis was based on the mixed-aldehyde condensation of 4-(methoxycarbonyl)-benzaldehyde, 3-hydroxybenzaldehyde, and pyrrole at a ratio of 3:1:4. The reactants were preliminarily adsorbed on the silica gel surface and heated in an open vessel in a domestic microwave oven at a power of 450 W for 12 min. Tetrapyrrole compounds were desorbed from silica gel with dichloromethane and separated by column chromatography. Unsymmetrically substituted 5-(3-hydroxyphenyl)-10,15,20-tris-[4-(methoxycarbonyl)phenyl]porphyrin and symmetrical 5,10,15,20-tetrakis[4-(methoxycarbonyl)phenyl]-porphyrin were obtained in 13 and 38% yield, respectively [196]. Likewise, 5-(2-hydroxyphenyl)-10,15,20-tris(4-acetoxy-3-hydroxyphenyl)porphyrin and 5-(3-hydroxyphenyl)-10,15,20-tris(4-acetoxy-3-hydroxyphenyl)porphyrin were synthesized under solvent-free conditions under microwave irradiation [197]. Six tetrapyrrole compounds were identified in the reaction mixture by thin-layer chromatography: A_4, A_3B, *cis*-A_2B_2, *trans*-A_2B_2, AB_3, and B_4 with a high content of 5-(2-hydroxyphenyl)-10,15,20-tris[4-(methoxycarbonyl)phenyl]porphyrin (A_3B). The yields of A_3B and A_4 porphyrins isolated by silica gel column chromatography were 33 (second eluted) and 48%, respectively (first eluted).

Zinc and copper complexes of all symmetrical and unsymmetrical porphyrins were obtained by the one-pot microwave-assisted synthesis method by adding the corresponding metal chloride to a mixture of pyrrole and aromatic aldehydes [197–199], and the yield of metal complexes derived from unsymmetrically substituted porphyrins significantly increased.

Nickel(II) tetraphenylporphyrin was synthesized in two ways, two-stage and one-stage [200]. In the first case, tetraphenylporphyrin obtained by monopyrrole condensation on silica gel under MW irradiation (Table 3) reacted with excess nickel(II) chloride in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a microwave oven at a power of 750 W in 6 min. The yield of the metal complex was 57%, and the overall yield was 38%.

The same metalloporphyrin was obtained in 60% yield following a one-step procedure, by the condensation of pyrrole and benzaldehyde in the presence of nickel(II) chloride and DBU under MW irradiation for 8 min. No metal complex was formed in the absence DBU, and the important role of the latter was also noted in the microwave-assisted syntheses of Mg, Cu, Tb(OAc), Lu(OAc), and La(OAc) complexes of 5,10,15,20-tetrakis(4-*tert*-butylphenyl)porphyrin [201].

Table 3. Alternative strategies for the synthesis of *meso*-tetraphenylporphyrin

Conditions	MW [193]	MW [200]	MW [202]	MW [205]	MW [208]	MW [147]	MW–H_2O [226]	NaY zeolite [211]	Protic ionic liquid [233]	Mechano-chemistry [227]
Reaction medium	SiO_2	SiO_2, $NiCl_2$, DBU	Propionic acid	Propionic acid	Propionic acid–nitrobenzene	CH_2Cl_2	H_2O	Acetic acid–nitrobenzene	CH_2Cl_2–protic ionic liquid	SiO_2
Temperature				120°C	200°C	30°C	200°C	130°C	22°C	Room temperature
Catalyst	H^+	H^+	H^+	H^+	H^+	I_2	H^+	NaY	H^+	H^+
Oxidant			O_2 (air)	*p*-Chloranil	Nitrobenzene	*p*-Chloranil	Supercritical water		DDQ	MnO_2
Reaction time	10 min	8 min +8 min	4 min	30 min	min	(1) 20 min; (2) 1 min	10 min	2 h	30 min	30 min
Isolation, purification							Precipitation	Precipitation, cromatog-raphy	Extraction	Crystallization, chromatography
Reactor	MW, 135 W	MW, 500 W			Monomode MW reactor	MW, 100 W	Monomode MW, 300 W	–		Mill, 25 Hz
Yield, %	9.5	60	41	30	46	47	27	41	41	10

Classical methods of monopyrrole condensation in solution, which are widely used for the synthesis of various symmetrically and unsymmetrically substituted tetraarylporphyrins, require large amounts of organic solvents and laborious isolation and purification procedures. Optimization of these methods with the use of microwave irradiation provided significant advantages in shortening the reaction time, increasing its efficiency, and reducing the amount of toxic solvents.

The cyclocondensation of equimolar amounts of pyrrole and various aromatic aldehydes in an open vessel under the Adler–Longo conditions [77] in propionic acid on exposure to atmospheric oxygen in a domestic microwave oven for 4 min afforded chlorin-free *meso*-tetrarylporphyrins with a yield of 20–43% [202] (Table 3). Furthermore, the amount of propionic acid used as a reaction medium was reduced to 5 mL, which increased not only the efficiency of the process but also its environmental friendliness.

The efficiency of this methodology has been repeatedly demonstrated by the synthesis of various *meso*-arylporphyrins [191, 192, 202–204]. First of all, in most cases the reaction time was reduced to 3–5 min compared to conventional heating. At the same time, the yields of porphyrins having bulky substituents in the phenyl rings, such as 5,10,15,20-tetrakis(4-*tert*-butylphenyl)porphyrins (56%) [203] and 5,10,15,20-tetrakis[4-(terpyridinyl)phenyl]porphyrin (12%) [204] increased by several times under MW irradiation.

Detailed studies of the influence of the conditions on the condensation of pyrrole with benzaldehyde in propionic acid under MW irradiation showed that the highest yield of *meso*-tetraphenylporphyrin (30%) was obtained in the reaction carried out at 120°C at an initial reactant concentration of 4.0 mmol/mL for 30 min in the presence of *p*-chloranil as an oxidant [205] (Table 3) under controlled MW heating in a SynthWAVE 402 Prolabo microwave reactor with an open rotating system (maximum power 300 W, frequency 2450 MHz). Despite the fact that this porphyrin can be obtained in a high yield by other methods (Table 1), the proposed approach is promising due to severalfold reduction in the reaction time, 250-fold decrease in the amount of solvent, and exclusion of toxic reagents. The authors noted [205] that modification of the monopyrrole condensation method through MW activation makes it possible to synthesize porphyrin on an unlimited scale and conforms to the green chemistry principles.

Studies of the kinetics of the condensation of pyrrole with benzaldehyde in propionic acid and systematic assessment of the effect of each process parameter on the yield of tetraphenylporphyrin in the closed vessel system of a microwave reactor showed [206] that the optimal conditions (yield 35%) include temperature 200°C, reaction time 5 min, and the use of nitrobenzene as an oxidant.

Adaptation of another (Gonsalves–Pereira) classical one-pot strategy to MW technologies [191, 192, 207, 208] demonstrated advantages of an alternative energy source for increasing the yield of tetraarylporphyrins and their metal complexes with a significant reduction in the reaction time to 5 min and decrease in the amount of solvents used (Table 3). The use of a monomode or multimode microwave reactor for organic synthesis makes it possible to obtain porphyrins in a controlled manner with good reproducibility.

Following the proposed methodology, Gao et al. [209] synthesized 5,10,15,20-tetrakis(4-fluorophenyl)-porphyrin, 5,10,15,20-tetrakis(3-fluorophenyl)porphyrin, and 5,10,15,20-tetrakis(2-fluorophenyl)porphyrin in propionic acid in the presence of nitrobenzene; the yields were 36, 30, and 28%, respectively.

While developing alternative methods for the synthesis of *meso*-arylporphyrins, Pereira et al. [210] found that Al-MCM-41 is the most efficient among various aluminosilicate mesoporous materials as a solid acid catalyst for the condensation of aromatic aldehydes with pyrrole. The yield of fluorine-containing porphyrin encapsulated inside the catalyst cavities was 54%, while the same porphyrin was synthesized in solution with a yield of only 9% [211]. The yield of porphyrin is significantly affected by both the acidity of the solid catalyst and the size of its pores [211]. The use of NaY zeolite as a solid catalyst in combination with the classical nitrobenzene methodology significantly improved the efficiency of pyrrole cyclotetramerization [211]. The proposed method for the synthesis of *meso*-arylporphyrins involved condensation of equimolar amounts of aldehyde and pyrrole (concentration 0.42 M) in a mixed solvent (acetic acid–nitrobenzene, 7:5) in the presence of heterogeneous NaY zeolite (0.016 M). The reaction mixture was heated at 130°C for 2 h and filtered, and the resulting porphyrin was isolated either by direct precipitation with methanol or by column chromatography. After thermal activation at 500°C, the zeolite catalyst can be reused without loss of catalytic activity. Using this methodology, Pereira et al. [212] obtained a series of unsymmetrical *meso*-arylporphyrins, including halogen-substituted ones; their yields were almost two times higher than those obtained by the classical

nitrobenzene method. The versatility of the proposed methodology using a solid NaY zeolite catalyst was confirmed by the data of [213–215], according to which a number of unsymmetrically substituted porphyrins were synthesized to create a platform for various biomedical applications, including their use as photosensitizers and diagnostic agents. This methodology turned out to be especially attractive for the one-step preparation of hybrid functional materials based on *meso*-arylporphyrins encapsulated in a zeolite matrix [191].

The use of microwaves to intensify other traditional methods for the synthesis of *meso*-arylporphyrins also gave good results. Microwave activation of the reaction mixture in the two-stage synthesis of tetraphenylporphyrin in dichloroethane in the presence of molecular iodine and *p*-chloranil as oxidants increased the yield to 47% [216] (Table 3). Subsequently, the same research team successfully applied the proposed methodology to synthesize unsymmetrical A_3B porphyrins by mixed-aldehyde condensation [217].

The statistical synthesis of unsymmetrical *meso*-tetraarylporphyrins always requires expensive and time-consuming methods for separation and purification of the products [218]. Therefore, to reduce consumable costs, save time, and minimize waste, a semi-automated modular process was developed that includes a monomode MW reactor equipped with an autosampler, an instant purification device by medium-pressure liquid chromatography with a UV/visible detector, and a reusable glass column filled with silica gel. This technique made it possible to synthesize and purify several random mixtures of porphyrins simultaneously, thus greatly reducing the environmental factor (*E* factor) compared to traditional syntheses of porphyrins.

Statistical mixed-aldehyde condensation of pyrrole with two different arylaldehydes (Fig. 4) leads to the formation of a mixture of six tetrapyrrole macroheterocycles in different amounts, not counting other side products. In most cases, this methodology is justified by the fact that it provides quick access to unsymmetrical porphyrins which are difficult or even impossible to synthesize by other methods.

Hölzel et al. [218] performed a two-stage mixed-aldehyde monopyrrole condensation in a microwave reactor following the Zerrouki methodology (Fig. 5). Depending on the ratio of benzaldehyde and 4-(methoxycarbonyl)benzaldehyde, low-symmetry tetraarylporphyrins of types A_3B, *cis*-A_2B_2, *trans*-A_2B_2, and AB_3 were isolated in different yields (Table 4).

In addition to the target low-symmetry porphyrins, some other products such as ring-expanded and ring-contracted porphyrinoids, linear oligomers, and polymers were formed in small amounts. Furthermore, symmetrical A_4 and B_4 porphyrins were always present as undesirable products. These compounds can easily be obtained in high yield by monopyrrole condensation with only one aromatic aldehyde.

The classical methods for the synthesis and isolation of porphyrins require huge amounts of organic solvents that are very harmful to both human health and the environment. In this regard, the key factor that should be taken into account when developing new synthetic strategies is the environmental factor (*E* factor) which is defined as the ratio of the total mass of all waste generated in the process to the mass of a useful product; this parameter gives a quick quantitative assessment of how much the process is environmentally friendly [219]. For example, the lowest value of the *E* factor is typical for oil refining processes (<0.1), while pharmaceutical industry processes are characterized by an *E* value of 25 to 100. The value of the environmental factor for the synthesis of unsymmetrically substituted porphyrins using the proposed modular system is reduced to 530–624 [218].

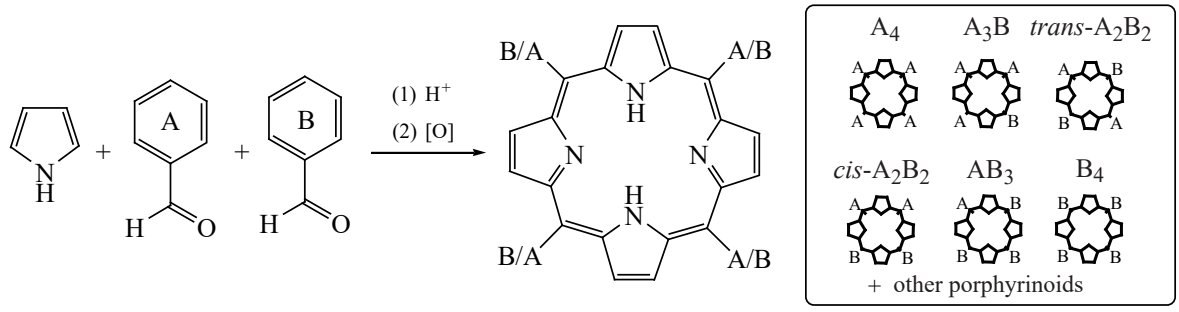


Fig. 4. Statistical mixed-aldehyde condensation of two aromatic aldehydes and pyrrole [218].

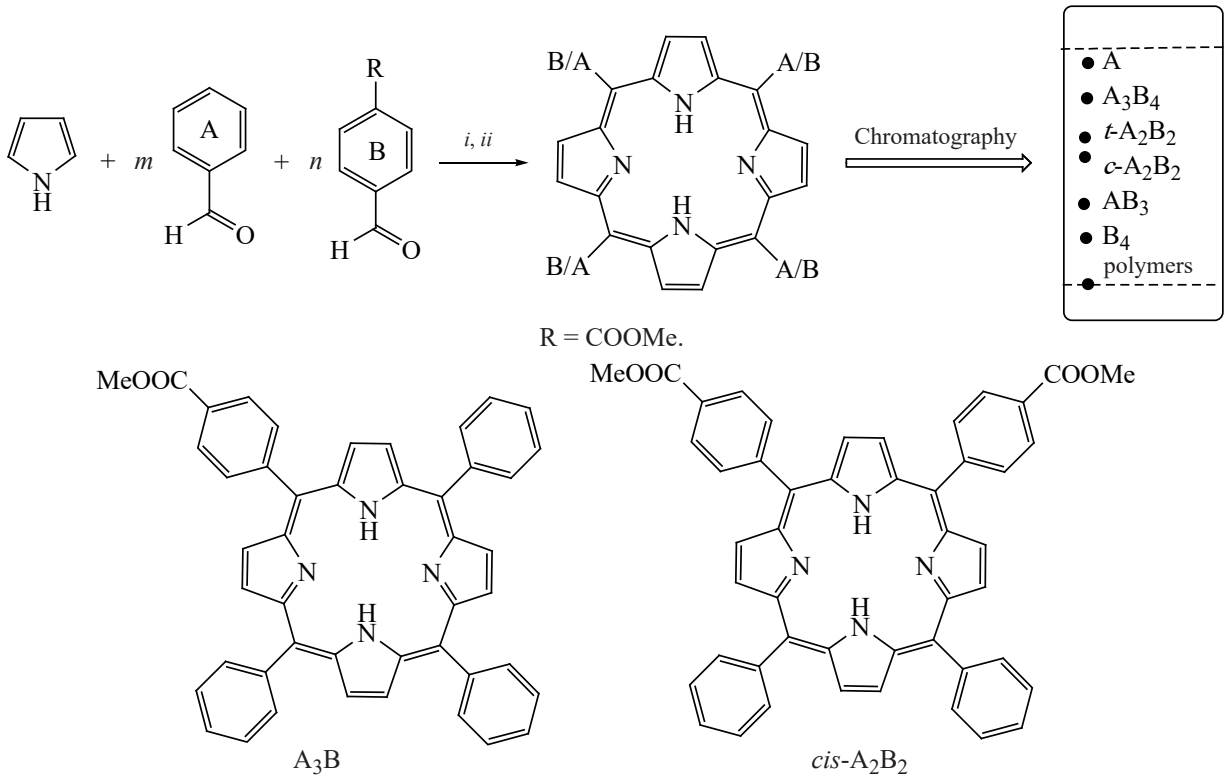


Fig. 5. Statistical microwave-assisted synthesis of 5-[4-(methoxycarbonyl)phenyl]-10,15,20-triphenylporphyrin: *i*: CH_2Cl_2, 10 mol % I_2, 40°C, 100 W, 5 min; *ii*: addition of *p*-chloranil, 40°C, 100 W, 1 min.

Therefore, at present, the development of automated systems can become a powerful tool for creating environmentally friendly technologies. These systems could minimize the interaction between the operator and reaction system, as well as increase the reproducibility and reliability of processes while reducing the required time and costs for chemical and human resources.

Thus, numerous studies on the use of MW for the intensification of monopyrrole condensation process have shown the possibility of applying this approach to any classical method for the synthesis of *meso*-arylporphyrins. In relation to any strategy for the synthesis of porphyrins, MW irradiation is superior to conventional thermal methods due to much shorter reaction time, increased yield, improved selectivity, and minor formation of the corresponding chlorins.

Over the past decade, green chemistry has become a major scientific discipline [219, 220]. Research and application of its basic principles has led to the development of cleaner and safer chemical processes. Undoubtedly, as applied to the chemistry of tetrapyrrole macroheterocycles, the green chemistry approach is of great importance in connection with the growing range of applied problems solved today with the use of this class of compounds [2–5]. Therefore, there is a growing demand for the development of new synthetic processes based on more stable chemical principles, which could replace hazardous organic solvents with alternative ones, reduce the time of

Table 4. Overall yields of 5-[4-(methoxycarbonyl)phenyl]-10,15,20-triphenylporphyrin under microwave irradiation

Ratio *m*/*n*	Yield,[a] %				Overall yield, %
	A_3B	*trans*-A_2B_2	*cis*-A_2B_2	AB_3	
1.1/0.9	8.9	4.1	19.0	12.0	44.0
3/1	22.0	1.5	3.1	0.9	27.5

[a] Based on the initial pyrrole.

energy-consuming procedures, and replace laborious chromatographic isolation and purification methods by crystallization from solution.

One of the most environmentally friendly approaches in organic synthesis involves replacement of organic solvents by water as ubiquitous, safe, and environmentally friendly solvent. At temperatures above the boiling point and pressure above 16 bar, water becomes a supercritical fluid which can be used as a potential solvent for hydrophobic organic compounds [221, 222] and acid or base catalyst. Under certain conditions, it can also act as an oxidant [223, 224]. The properties of water as a solvent change due to changes in its dielectric constant, electrical conductivity, ionic product, and the structure of hydrogen bonds [225]. A simple, fast, and safe way to obtain superheated water is microwave irradiation in an apparatus designed for organic synthesis [222, 224].

Pereira and co-workers were the first to perform microwave synthesis of *meso*-tetraphenylporphyrin in supercritical water. The maximum yield in the condensation of pyrrole with benzaldehyde was obtained by mixing pyrrole (9.8 mmol), benzaldehyde (9.8 mmol), and water (0.2 mL, 50 M) in a 10-mL vessel under MW irradiation (300 W) at 200°C for 10 min. As shown in [226], supercritical water acted as not only solvent but also acid catalyst and oxidant. The yield of *meso*-tetraphenylporphyrin precipitated from the cooled reaction mixture with ethanol was 27%, and the product contained less than 2% of *meso*-tetraphenylchlorin (Table 3).

Comparison of different methodologies for the synthesis of *meso*-tetraphenylporphyrin showed that the microwave synthesis in water featured the best quantitative environmental friendliness characteristics (Table 5) ever obtained for this process.

The wide versatility of this methodology is demonstrated by good yields of symmetrical aryl- and alkyl-substituted porphyrins [226], unsymmetrical *meso*-arylporphyrins, and their metal complexes characterized by low melting points [227], the synthesis, isolation, and purification of which by traditional methods is a serious problem. The use of new environmentally friendly technologies for the synthesis of new tetrapyrrole macroheterocycles opens the way for the creation of functional materials for various applications, including catalysis, biomedicine, nonlinear optics, and photovoltaics [228].

Alternative solvents that meet the green chemistry principles become increasingly attractive in the synthetic chemistry of porphyrins. These solvents include ionic liquids which have been widely used as a medium for various organic reactions since the beginning of this century [229, 230]. A special group consists of protic ionic liquids which combine the properties of an acid and ionic liquid. Such ionic liquids are characterized by a high catalytic activity which exceeds the activity of organic and mineral acids in similar processes [231].

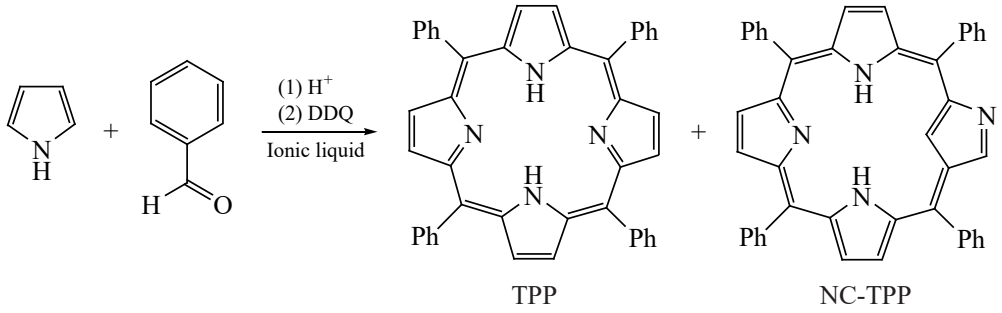
Ishikawa and coworkers were the first to use an acidic ionic liquid, 3-butyl-1-(4-sulfobutyl)imidazolium trifluoromethanesulfonate as a solvent and catalyst for the condensation of pyrrole and benzaldehyde [232]. The proposed methodology was based on the two-stage Lindsey method where dichloromethane was replaced by the two-phase system ionic liquid–dichloromethane (3:10). The reaction was carried out in the presence of methanesulfonic acid at 22°C at 30 min, followed by oxidation with DDQ, to obtain *meso*-tetraphenylporphyrin (TPP) and its confused isomer (NC-TPP) (Scheme 18).

Table 5. Calculated *E* factors and EcoScale scores for the syntheses of *meso*-tetraphenylporphyrin by different methods [191]

Entry no.	Method of synthesis	*E* factor	EcoScale score	Reference
1	Adler–Longo[a]	158	28	[77]
2	Gonsalves–Pereira[a]	300	20	[98]
3	Lindsey[a]	2252	–19	[79]
4	Zerrouki[b]	2393	4.5	[216]
5	Chauhan[b]	278	5.5	[202]
6	Pineiro[b]	600	12	[207]
7	Henriques[b]	35	50.5	[226]

[a] Traditional method.
[b] Microwave-assisted synthesis.

Scheme 18.



The use of a two-phase system is advantageous compared to the synthesis under homogeneous conditions. The target porphyrins are collected in the dichloromethane layer which and can be easily separated from the ionic liquid; they are isolated and purified by chromatography, and the ionic liquid can be reused up to 10 times [233] without loss of catalytic activity. The maximum yield of tetraphenylporphyrin was 41%, and the yield of NC-TPP was 7% [233] (Table 3). The use of ionic liquids in the Lindsey methodology greatly reduced the amount of chlorinated solvents.

Later, Ishikawa's group used protic ionic liquids as a reaction medium and catalyst instead of propionic acid [234]. The condensation of pyrrole with benzaldehyde in a protic ionic liquid at 120°C for 60 min gave *meso*-tetraphenylporphyrin with the same yield as in the synthesis in propionic acid under the traditional Adler–Longo conditions [77] (Table 3). The products were easily isolated from the reaction mixture by extraction into chloroform, and ionic liquids after regeneration could be reused up to three times without losing their activity.

The same authors [235] extended this method to other *meso*-aryl-substituted porphyrins, in particular 5,10,15,20-tetra(pyridin-4-yl)porphyrin, the synthesis and purification of which is complicated by its high solubility in acids. The yield of that porphyrin was 14%, as in the Adler synthesis, the isolation procedure was simplified.

Babu et al. [236] proposed a fast and efficient method for the synthesis of *meso*-arylporphyrins by the Rothemund condensation of pyrrole with aromatic aldehydes at 100°C for 2–3 h using the protic ionic liquid l-butyl-3-methylimidazolium tetrafluoroborate as a catalyst on exposure to atmospheric oxygen as an oxidant. As a result, pure *meso*-tetraphenylporphyrin was obtained in 26% yield, which exceeded the yield in pyridine–acetic (propionic) acid. The product contained neither the inverted isomer nor chlorin. Unlike other methods, the proposed procedure for the synthesis of *meso*-arylporphyrins does not utilize chlorinated solvents, toxic catalyst, or additional oxidant. The ionic liquid used in this method acts as a solvent and Lewis acid catalyst, providing a fast and efficient route for the synthesis of *meso*-substituted porphyrins with higher yields than in the Rothemund method.

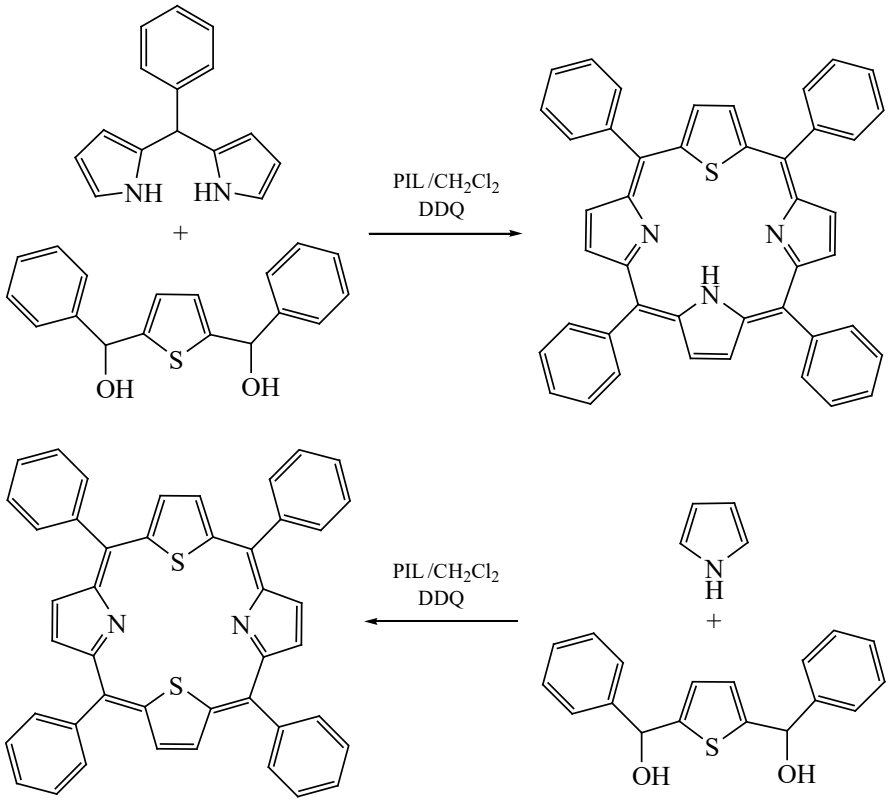
Thus, the synthesis of porphyrins in protic ionic liquids provides a simple alternative way to obtain various *meso*-substituted porphyrins under environmentally friendly conditions with up to 33% yield.

Rawat et al. [237] synthesized thia analogs of *meso*-tetraphenylporphyrin (Scheme 19). The reaction of 2,5-bis(α-hydroxybenzyl)thiophene with 5-phenyldipyrromethane in the presence of an ionic liquid afforded 30% of 21-thia-5,10,15,20-tetraphenylporphyrin, and the condensation of the same substituted thiophene with pyrrole produced 35% of 21,23-dithia-5,10,15,20-tetraphenylporphyrin in 35% yield. It was shown [237] that protic ionic liquid as a catalyst and reaction medium provides better results in the synthesis of modified porphyrins than do other acid catalysts in organic solvents.

Methods for the synthesis of porphyrin metal complexes that are important in the preparation of functional materials based on tetrapyrrole macroheterocycles [2–5] require large amounts of organic solvents and are often limited by the solubility of one or another reagent in the reaction medium. In this respect, the use of ionic liquids for the introduction of a metal ion into the porphyrin coordination center is of great interest.

Kitaoka et al. [238] studied a number of ionic liquids as a medium for obtaining *meso*-tetraphenylporphyrin copper complex. It was shown that the optimal ionic liquid is 1-hexyl-3-octylimidazolium bromide. The efficiency of this ionic liquid medium for the complexation of porphyrins with metal salts is largely increased by microwave heating. Transition metal complexes of *meso*-arylporphyrins were obtained

Scheme 19.



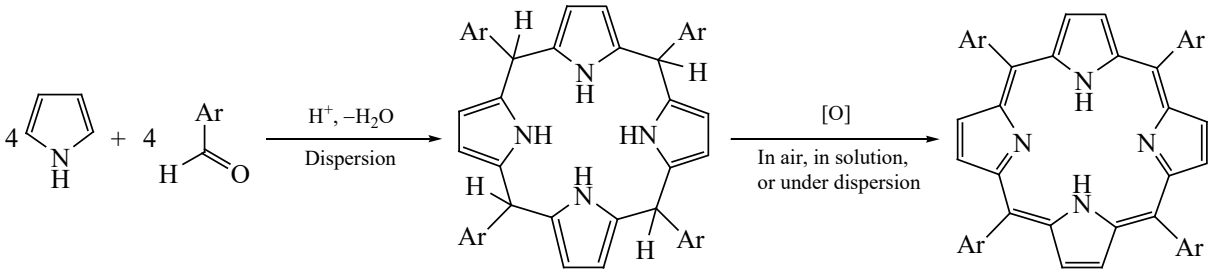
in 71–98% yield within 5 min in imidazole ionic liquids under MW irradiation [239].

Thus, protic ionic liquids can be a good substitute for volatile, toxic, and flammable organic solvents used in traditional methods for the synthesis of metal *meso*-arylporphyrins.

The formation of tetrapyrrole macroheterocycles requires efficient catalysis and appropriate physical activation of the reaction medium. The development of new strategies for the synthesis of *meso*-arylporphyrins has shown that mechanochemical and sonochemical methods can significantly facilitate macrocyclization of pyrrole with aromatic aldehydes under heterogeneous conditions using environmentally friendly solvents or under solvent-free conditions, in particular via mechanical activation of solid-phase reactions by grinding the reactants in ball or planetary mills. In this case, the supplied mechanical energy induces a chemical reaction. In addition to rapid macrocyclization, these technologies provide safer synthetic procedures and reduced energy costs and waste [240–242].

Shy et al. [243] reported a two-stage mechanochemical synthesis of *meso*-tetraphenylporphyrin by dispersing equimolar amounts of benzaldehyde and

Scheme 20.



"Pink powder" containing arylporphyrinogen

pyrrole without a solvent in the presence of an acid catalyst to obtain a solid pink powder of porphyrinogen in 6 min (Scheme 20). Without additional purification, this powder was oxidized either in air or in chloroform with an organic oxidant.

This synthetic method was also applied to substituted benzaldehydes and naphthaldehydes to obtain various *meso*-substituted porphyrins [244] in 3–33% yield within 20 min. A grinding agent such as sodium chloride, silica, or magnesium sulfate was added to the reaction mixture to facilitate dispersion of the reactants as a result of increased friction and/or accelerate the condensation process by removing of water from the reaction zone. The subsequent oxidation can be achieved either by treatment with an oxidant in solution to provide a yield comparable to that reported for traditional methods or mechanochemically; in the latter case, the yield was somewhat lower. Sublimation was proposed as a "green" method for porphyrin isolation and purification [245].

While searching for sustainable synthetic methodologies, the mechanochemical approach was studied as a new tool for one- and two-step syntheses of *meso*-aryl-substituted porphyrins [246]. The two-step synthesis was found to be the best method. In the first stage, mechanical activation of equimolar amounts of pyrrole and aromatic aldehyde was carried out in the presence of *p*-toluenesulfonic acid as a catalyst by dispersion in a mill for 30 min. The resulting pink powder of porphyrinogen was oxidized with manganese(IV) oxide in an environmentally acceptable solvent (2-methyltetrahydrofuran) while stirring in an open vessel; this heterogeneous oxidant proved to be efficient for hydrogenated porphyrins [208]. The yields of porphyrins synthesized in this way were lower than in other methods (Table 3), but the simplicity and safety of the mechanochemical synthesis make it promising for use in the synthetic chemistry of porphyrins.

Thus, alternative methodologies that allow the synthesis of porphyrins to be accomplished under mild conditions with good yields and convenient isolation procedures attract increasing attention of synthetic chemists. So far, these methods have been most widely utilized to obtain the simplest and most accessible group of *meso*-arylporphyrins which nevertheless are the most needed in various fields of their application. All these synthetic approaches will undoubtedly contribute to the availability and safety of methods for the preparation of porphyrins and their metal complexes as the most important components of new-generation functional materials for various molecular devices and medicine.

4. CONCLUSIONS

The scope of application of *meso*-arylporphyrins will expand due to increasing demand for functional materials based on tetrapyrrole macroheterocycles for modern technologies, medicine, and materials science. Self-assembly of these compounds as convenient "building blocks" for various supramolecular systems, their inclusion as a functional basis in hybrid materials, and availability of changes in the structure and properties via numerous modifications of the macroheterocycle provide almost unlimited possibilities for the design of new materials and devices.

Therefore, the demand for these compounds, as well as for convenient methodologies for their preparation, will only grow. The given analysis of methods for the synthesis of *meso*-aryl-substituted porphyrins shows that researchers have ample opportunity to choose the necessary method for their preparation, taking into account, among other things, the conditions of "green chemistry."

AUTHOR INFORMATION

O.I. Koifman, ORCID: https://orcid.org/0000-0002-1764-0819

T.A. Ageeva, ORCID: https://orcid.org/0000-0001-9445-4262

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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