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Synthesis of the Simplest Synthetic Porphyrins. Porphine and β-Octasubstituted Porphyrins

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Dedicated to the memory of Academician Oskar I. Koifman

The review presents methods known in the literature for the synthesis of the simplest synthetic β-octasubstituted porphyrins by monopyrrole condensation. The synthesis of pyrroles from non-pyrrole precursors by the most common Knorr and Barton-Zard methods and their further modification into derivatives capable of pyrrole condensation are presented. The methods of synthesis of the progenitor of porphyrins – porphine and randomomeric etioporphyrins, one of which (etiporphyrin III) has a structure close to natural porphyrins. The presented methods make it possible to obtain β-octasubstituted porphyrins with high yields in significant quantities for their use as model compounds of biochemical reactions, catalysts of various processes and medicines.

Keywords: Porphyrins, porphine, synthesis, pyrroles, dipyrromethanes.

Синтез простейших синтетических порфиринов. Порфин и β-октазамещенные порфирины

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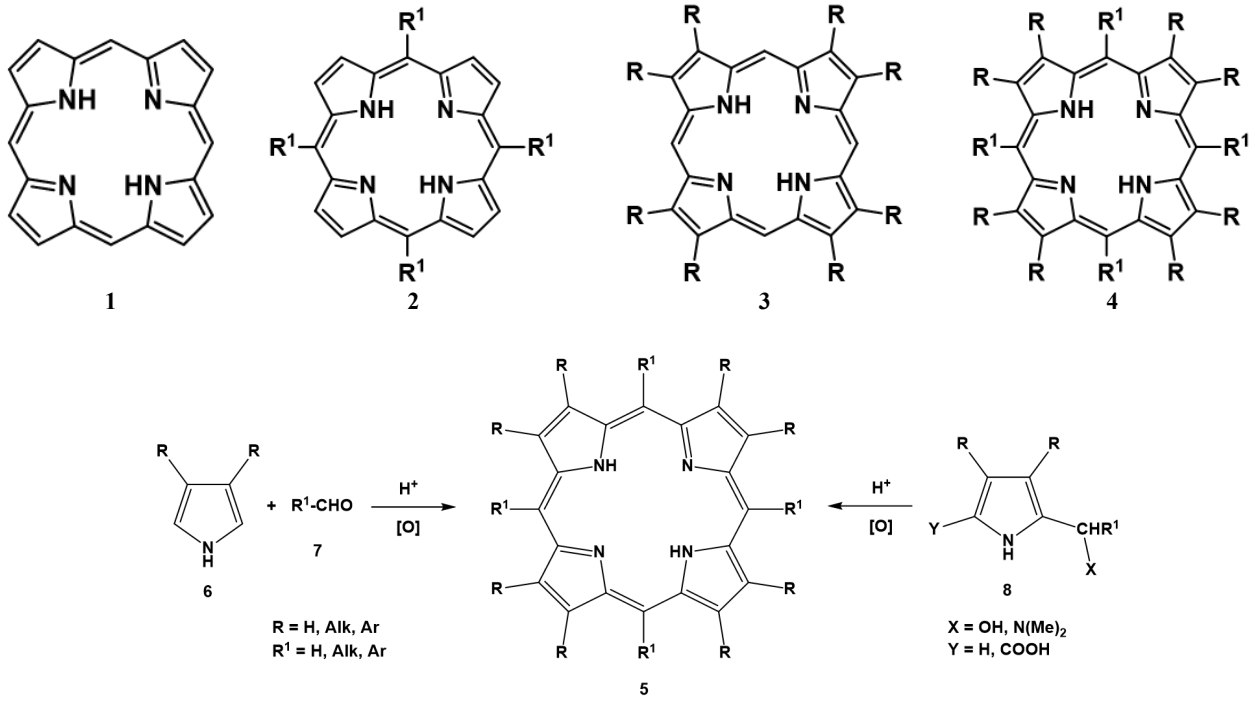
В обзоре приведены известные в литературе методы синтеза простейших синтетических β-октазамещенных порфиринов монопиррольной конденсацией. Представлены синтезы пирролов из непиррольных предшественников наиболее общими методами Кнорра и Бартона-Зарда и их дальнейшая модификация в производные способные к пиррольной конденсации. Приведены методы синтеза родоначальника порфиринов – порфина и рандомерных этиопорфиринов, один из которых (этиопорфирин III) имеет структуру близкую к природным порфиринам. Представленные методы позволяют получать β-октазамещенные порфирины с высокими выходами в значительных количествах для использования их в качестве модельных соединений биохимических реакций, катализаторов различных процессов и медицинских препаратов.

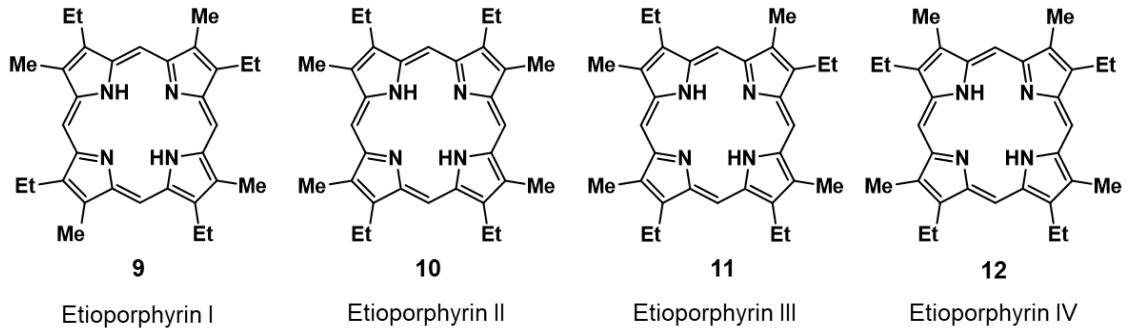
Ключевые слова: Порфирины, порфин, синтез, пирролы, дипирролилметаны.

Introduction

Porphyrins and metalloporphyrins are widespread in nature and have great biological significance. Their most important representatives are chlorophylls, which as part of the protein-lipid complex carry out the initial stage of photosynthesis in green plants, and blood hematin, which in combination with the protein globin reversibly binds and transports oxygen by blood to cells. Metalloporphyrins are also included in the composition of many enzymes based on chromoproteins – catalases, peroxidases and others. Porphyrins in the form of vanadyl and nickel complexes are found in oils. Along with the popular methods of obtaining porphyrins from natural sources, there are many ways to obtain synthetic porphyrins, some of which are commercially available.



Scheme 1.

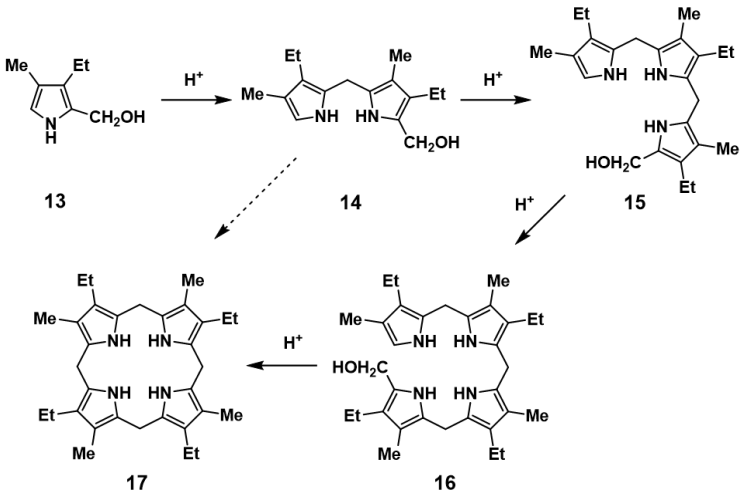


The progenitor of porphyrins is porphine (**1**), which has no substituents on the periphery of the tetrapyrrole aromatic cycle. The simplest ones are completely symmetrical. Porphyrins are usually obtained by tetramerization of monopyrroles. In these cases, the construction of a linear polypyrrole chain, its closure and further oxidation to porphyrin occurs automatically during the reaction without the release of intermediates. These methods make it possible to obtain porphyrins **2**-**4** with high yields, the most famous are *meso*-tetrasubstituted porphyrins (**2**, R^1=Alk, Ar),[1-4] β-octasubstituted porphyrins (**3**, R=Alk, Ar),[5,6] as well as hybrid *meso*,β-dodecasubstituted porphyrins (**4**, R=Alk, Ar, R^1 = Ar).[7]

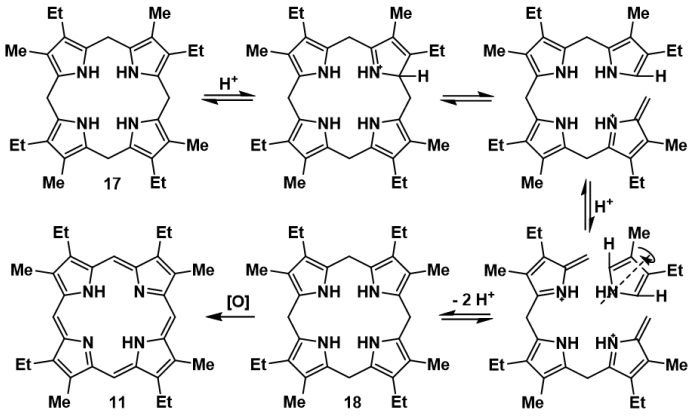
The synthesis of porphyrins **5** can be carried out by two methods: condensation of α-unsubstituted pyrroles **6** with compounds containing active carbon group **7** (usually aldehydes or their derivatives), which in the future will be the basis of the *meso*-methylene bridge, or self-condensation of pyrroles having a ready-made methylene component **8** in the α position (Scheme 1). The methods are similar to each other and are carried out under similar conditions, since in both cases the reaction passes through the stage of formation of a stabilized pyrrylmethylene cation.

But the situation is not as simple as it seems at first sight. If the substituents at 3- and 4-positions of pyrrole are not identical, a mixture of randomized porphyrins (for example, etioporphyrins **9**-**12**) is usually obtained.

Self-condensation of pyrrole, for example, such as **13** passes through dipyrrolylmethane **14**, tripyrran **15**, bilan **16** into cyclic porphyrinogen **17** (Scheme 2). Under these conditions, dimerization of dipyrrolylmethane **14** is also possible.



Scheme 2.

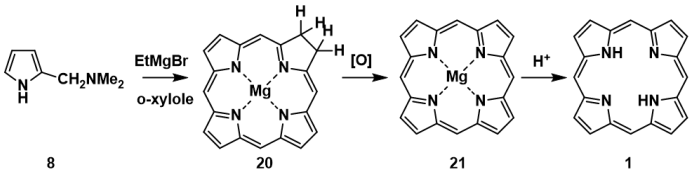


Scheme 3.

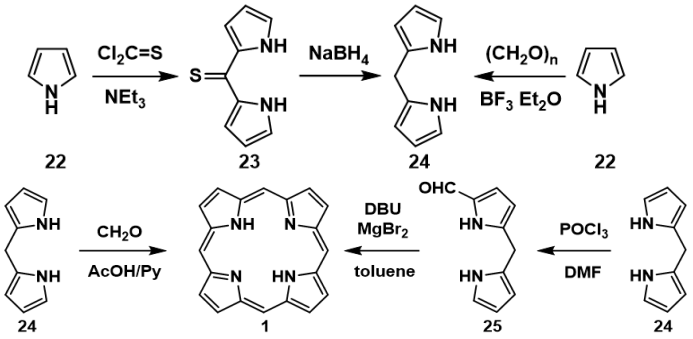
All of them, in acidic conditions, can regroup, giving after oxidation a mixture of randomized porphyrins **9**, **10**, **11** and **12** in the form of a statistical mixture 1:2:4:1, respectively. Scheme 3 shows the typical mechanism of formation of etioporphyrinogen III **18** from etioporphyrinogen I **17**.

1. Synthesis of porphine

The progenitor of porphyrins is porphine, first synthesized in 1935,[8] as it turned out is obtained in cyclocondensation reactions with very low yields (<1%),[9,10] although the initial products for its synthesis are commercially available and quite cheap.



Scheme 4.



Scheme 5.

The low yield of porphine is due to the high reactivity of the initial compounds in the condensation reaction, and the high probability of the growth of the polypyrrole chain, bypassing the stage of bilan, capable of cyclization, due to the absence of steric substituent factors in the pyrrole ring.

The use of various changes during the condensation reaction (high dilution,[14] an increase in the duration of the process,[14] conducting it in a micellar matrix,[16] in a two-phase system,[12] *etc*.) can significantly increase the yield of porphine. The methods used are shown in Table 1.

Table 1. Methods of porphine synthesis.

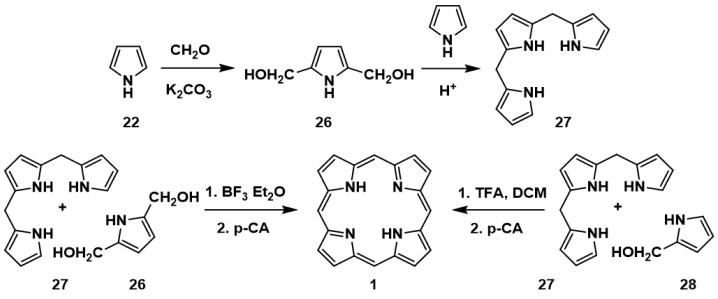
Pyrrole	Conditions	Yield (%)	Ref.
Pyrrole **22**	HCO_2H	<1.0	[10]
	CH_2O, EtCOOH	0.9	[11]
	CH_2O, AcOH/Py	1.0	[17]
2-Formyl-pyrrole	CH_2O, MeOH/Py	<1.0	[9]
2-Hydroxy-methylpyrrole **28**	1. Isobutylmethylketone/H_2O, AcOH 2. DDQ	15.3	[12]
	1. 0.5 M sodium lauryl sulfate, HCl 2. DDQ/THF	2.0	[16]
	AcOH, $Mg(OAc)_2$, $K_2S_2O_8$	5.3 3.7	[13] [18]
	Ethylbenzene, 11.5 days, 100 ºC	18.02	[14]
2-Dimethyl-aminomethyl-pyrrole **19**	1. 1,2-dichlorobenzene, EtMgBr, reflux 2. DDQ	3.9	[15]

It should be noted that the use of pyrrole **19** in high-boiling solvents in the presence of Grignard reagent forms a mixture of magnesium complex porphine **21** and chlorin **20**, which is easily oxidized to porphyrin **21** by benzoquinone derivatives,[15] however, chlorin itself is a difficult-to-obtain product (Scheme 4).

Based on all the above, porphine was synthesized from polypyrrole precursors, which makes it possible to significantly increase the yield of porphine, for example, dipyrrolylmethane **24** and formalin (4%, versus 1% from pyrrole)[17] and its 2-formyl derivative **25**, by self-condensation in the presence of magnesium bromide and DBU in toluene at boiling in an inert atmosphere (40%),[19] the latter was obtained by Wilsmeier formylation **24** (Scheme 5). However, the synthesis of unsubstituted dipyrrolylmethane **24** presents a certain problem. It is obtained by two developed methods, either by reducing dipyrrylthioketone **23** with sodium borohydride (87%),[20] obtained by condensation of pyrrole with thiophosgene in the presence of triethylamine (61%),[21] or condensation of excess pyrrole with paraform (40–60%).[22,23]

The use of unsubstituted bilatriene **27** for the synthesis of porphine also makes it possible to significantly increase the yield (with 2-hydroxymethyl-pyrrole **28** – 10%,[24] with 2,5-bis(hydroxymethyl)pyrrole **26** – 31%[25]) (Scheme 6). Bilatriene **27** is synthesized in two stages from pyrrole by condensation in an aqueous medium with formalin in the presence of potassium carbonate to **26** (84–92%), followed by its cyclization in water with an excess of pyrrole during acid catalysis (61%).[26]

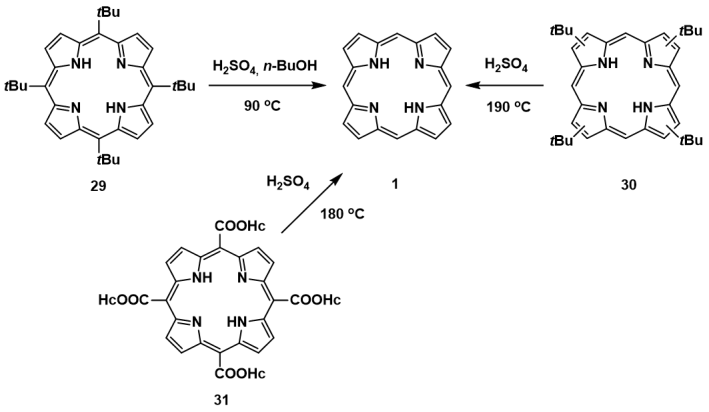
In addition, there is a synthesis method of **1** based on the degradation of porphyrin precursors containing *tert*-butyl or carboxyalkyl groups. So, in the interaction of 5,10,15,20-tetra(*tert*-butyl)porphine **29**[30,31] with sulfuric acid in the presence of *n*-butanol at 90 °C forms **1** with a yield of 74%.[27] Similarly, but under more stringent conditions, a mixture of randomomeric tetra(β-*tert*-butyl) is converted into porphine **30**[32] (sulfuric acid, 190–200 °C, 64%)[28] or 5,10,15,20-tetra(*n*-hexyloxy-carbonyl)porphine **31**[33] (sulfuric acid, 180 °C, 77%)[29] (Scheme 7). These methods are promising, but the yield of the initial porphyrins **29**-**31** does not exceed 15%.



Scheme 6.

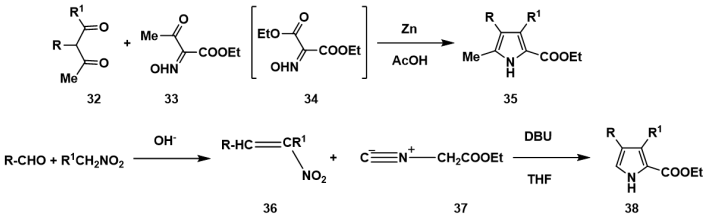
2. Synthesis of symmetric β-octasubstituted porphyrins

As mentioned above, symmetrical β-octasubstituted porphyrins are obtained by cyclocondensation of either 3,4-disubstituted pyrrole with formaldehyde, or similar pyrrole with an α-methylene component (Scheme 1, Table 2). The main task of these syntheses is to obtain the initial pyrroles. Of the variety of pyrrole syntheses for the construction of porphyrins, two main methods are of the greatest importance – the Knorr synthesis, known for more than a century,[5] consisting in the reductive cyclocondensation of β-diketones **32** with nitrozoacetoacetic ether **33** or nitrosomalon ether **34**, or a relatively recently discovered the Barton-Zard method,[34] consisting in the cyclo-condensation of nitroalkenes **36** obtained by condensation of nitroalkanes with aldehydes with isocyanacetic ether **37** in the presence of a strong non-nucleophilic base (usually DBU) (Scheme 8). These two methods complement each other and make it possible to obtain all the variety of porphyrins currently known. Other methods of pyrrole synthesis (for example, Paal-Knorr and Ganch) are of secondary importance and are used only in some cases.



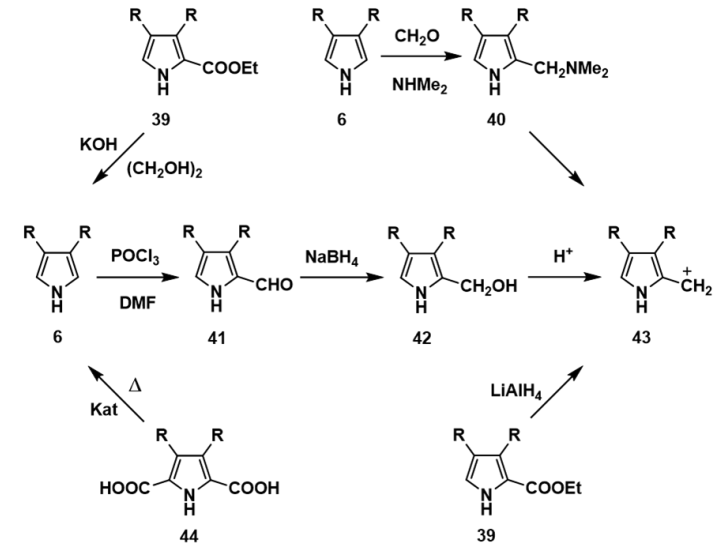
Scheme 7.

Further transformations of primary pyrroles **35** and **38** make it possible to obtain pyrroles with free α-positions or having an α-methylene component.[5]



Scheme 8.

In some cases, α-diunsubstituted pyrroles **6** are used as starting materials, which are currently available through decarboxylation of pyrrole **39**, obtained in the Barton-Zard reaction, or by catalytic decarboxylation of α-dicarboxylic acid **44** – products of the Knorr pyrrole transformation. The Mannich reaction is used to synthesize α-dimethyl-aminomethyl pyrroles **40**,[39] or the reduction of α-formyl pyrrole **41**, which is obtained in the Wilsmeyer reaction by the interaction of α-substituted pyrrole with phosphorus chloride and dimethylformamide. Sodium borohydride is then used to reduce the α-formylpyrrole to α-methyl-carbinol **42**.[48] Another method has been proposed for producing α-methylcarbinol **42** directly from lithium-aluminium hydride and α-carbethoxypyrrole **39**[36,37] (Scheme 9, Table 2).



Scheme 9.

The second method is based on the use of 2-carbethoxy-5-methylpyrroles **45**, which are products of the Knorr pyrrole condensation and similar reactions (Scheme 10, Table 2). In this case, the initial methylpyrrole **45** is either brominated with bromine or chlorinated by the action of sulfuryl chloride, followed by the nucleophilic

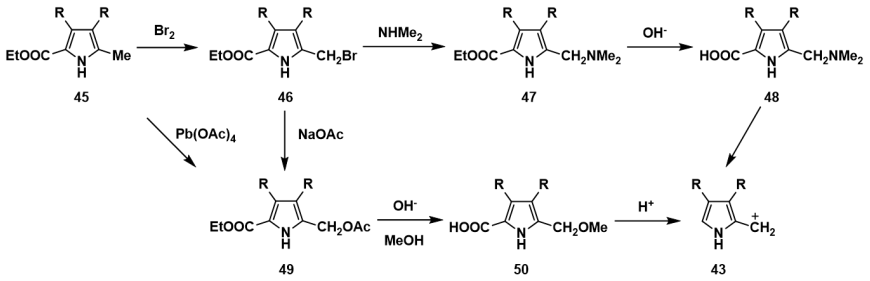
replacement of the bromine atom in **46** with a dimethylamino group. The carbethoxy group in **47** is then hydrolyzed to produce pyrrole **48**.[43] Alternatively, the methylpyrrole **45** can be oxyacetylated with lead tetraacetate in acetic acid, forming acetoxymethylpyrrole **49**,[46] which is then hydrolyzed into methanol to produce 2-carboxymethoxypyrrole **50**. Acetoxyethylpyrrole can also be produced by nucleophilic substitution of bromine in bromomethylpyrrole **46** with sodium acetate in acetic acid.[47] Both of these products, when subjected to the porphyrin formation reaction, give stabilized pyrryl-methylene carbocation **43** after decarboxylation.

In addition to the Barton-Zard syntheses (Scheme 8), its varieties are used, for example, the interaction of vinyl ketones **51** with isocyanoamethylene-*p*-toluylsulfonate **52** with further reduction of pyrrole **53** with lithium alumohydride to **6**[41] (Scheme 11, Table 2) or the interaction of isocyanoacetate **37**, instead of nitoalkene **36** with alkenesulfonates **56**, which are obtained by the interaction of alkenes with phenylchlorosulfinate to **54**, followed by oxidation to sulfonate **55** and dechlorination to **56** and further to pyrrole **39**,[50-52] the method is usually used for the synthesis of 3,4-cyclobutylene pyrroles from cyclohexenes.[53-57]

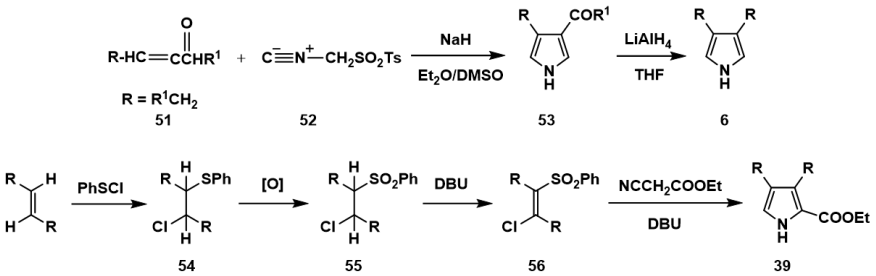
The Piloty-Robinson method is also used for the synthesis of 3,4-disubstituted pyrroles,[44] consisting in the preparation of dihydrazides **57** by the interaction of aldehydes with hydrazine, their acylation into imidines **58** and conversion to pyrroles **59** under microwave irradiation and further hydrolysis into pyrroles **6** (Scheme 12, Table 2)[44] and Paal-Knorr, in which esters enols **60** under anodic oxidation give 1,4-diacetals **61** interacting with benzyl ether of carbamine acid giving pyrroles **62** which are hydrogenated on a palladium catalyst to pyrroles **63**.[40]

There are methods for the synthesis of individual pyrroles, for example, the synthesis of 3,4-dimethylpyrrole **6** (R=Me) by Diels-Alder reaction of the 2,3-dimethylbutadiene-1,3 **64** with N-ethoxycarbonylsulfinyl-imine **65** obtained by the interaction of urethane with thionyl chloride in the presence of pyridine, followed by conversion of the adduct **66** without isolation into the required pyrrole (35-40%)[58,59] (Scheme 13), or 3,4-diarylpyrroles **70** by condensation of benzyls **67** with dimethyl ether of acetyliminodiacetic acid **68** and subsequent hydrolysis and decarboxylation of the resulting pyrrole **69**.[42]

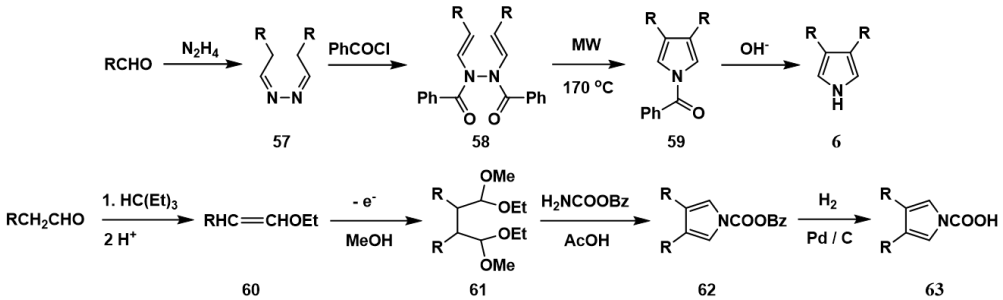
The most well-known porphyrin of this group is commercially available 2,3,7,8,12,13,17,18-octaethyl-porphine, which is highly soluble in many nonpolar organic solvents, unlike the practically insoluble 2,3,7,8,12,13,17,18-octamethylporphine. Some represent-tatives of this series are shown in Table 2.



Scheme 10.



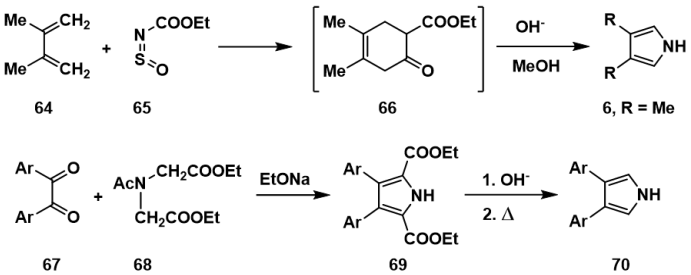
Scheme 11.



Scheme 12.

Table 2. Conditions of the synthesis and yield of symmetric beta-substituted porphyrins.

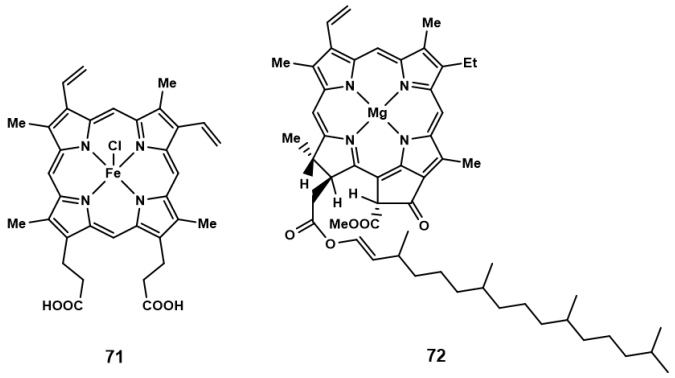
Porphyrin **3**	Pyrrole	Conditions	Yield (%)	Ref.
R = Me	**6**, R = Me	AcOH-Py, CH_2O, reflux, air	77.5	[17]
		CH_2O, 1N HCl, EtOH, 60 ºC, air	47.0	[49]
	41, R = Me	1. $NaBH_4$, MeOH 2. MeOH, 48% HBr, CA	78.0	[48]
R = Et	**39**, R = Et	1. $LiAl_4$, THF 2. AcOH, reflux, air	40.0	[36]
		1. $LiAl_4$, THF 2. CH_2Cl_2, PTSA, $CH_2(OMe)_2$ cat; CA	55.0	[37]
		1. $LiAl_4$, THF 2. CH_2Cl_2, PTSA, $CH_2(OMe)_2$ cat; CA	69.0	[38]
	40, R = Et	AcOH, reflux, air	52.0	[39]
	63, R = Et	AcOH-Py, reflux, air	59.0	[40]
	47, R = Et	1. KOH, H_2O, MeOH, reflux 2. AcOH, air	52.0	[43]
	49, R = Et	1. KOH, H_2O, MeOH, reflux 2. AcOH, $K_3[Fe(CN)_6]$	44.0	[46]
	45, R = Et	1. Br_2, AcOH, NaOAc, rt 2. KOH, H_2O, MeOH, reflux 3. AcOH, air	25	[47]
	48, R = Et	1. KOH, H_2O, EtOH, reflux 2. Benzene, PTSA, CH_2O, reflux, air	51.0	[44]
R = *i*Pr	**39**, R = *i*Pr	1. $LiAl_4$, THF 2. AcOH, reflux, air	45.0	[41]
R = Pr	**6**, R = Pr	EtOH, 48% HBr, CH_2O, reflux, air	32.0	[41]
	49, R = Pr	1. KOH, H_2O, MeOH, reflux 2. MeOH, 48% HBr, air	23.0	[45]
R = *n*-Bu	**6**, R = *n*-Bu	EtOH, 48% HBr, CH_2O, reflux air	33.0	[41]
		AcOH, reflux, air	35.0	[41]
R = *n*-C_5H_{11}	**6**, R = *n*-C_5H_{11}	EtOH, 48% HBr, CH_2O, reflux, air	40.0	[41]
R = *n*-C_6H_{13}	**6**, R = *n*-C_6H_{13}	EtOH, 48% HBr, CH_2O, reflux, air	11.0	[41]
R = *n*-C_7H_{15}	**6**, R = *n*-C_7H_{15}	EtOH, 48% HBr, CH_2O, reflux, air	11.0	[41]
R = *n*-C_8H_{17}	**39**, R = *n*-C_8H_{17}	1. $LiAl_4$, THF 2. AcOH, reflux	25.0	[36]
R+R = $(CH_2)_4$	**39**, R+R = $(CH_2)_4$	1. $LiAl_4$, THF 2. AcOH-Py, reflux	35.0	[35,36]
		1. $LiAl_4$, THF 2. CH_2Cl_2, PTSA, $CH_2(OMe)_2$ cat; CA	53.0	[37]
		1. $LiAl_4$, THF 2. CH_2Cl_2, PTSA, $CH_2(OMe)_2$ cat; CA	65.0	[38]
R = Ph	**6**, R = Ph	AcOH-Py, reflux	20.0	[17]
	39, R = Ph	1. $LiAl_4$, THF 2. AcOH, reflux	15.0	[36]
	40, R = Ph	1. Xylene; EtMgBr, reflux 2. AcOH	48.0	[42]
R = *n*-$MeOC_6H_4$	**40**, R = *n*-$MeOC_6H_4$	1. Xylene; EtMgBr, reflux 2. AcOH	87.7	[42]



Scheme 13.

3. Synthesis of etioporphyrins

β-Tetramethyltetraethylporphyrins (etioporphyrins) are the most well-known of the octaalkylporphins associated with natural porphyrins. As previously reported, there may be four isomeric etioporphyrins **9**-**12** differing in the position of β-substituting methyl and ethyl groups. Etioporphyrin III is closest to natural gemin **71**, which, as part of a protein complex, carries oxygen in the human body and higher animals and chlorophyll *a* **72**, which carries out photosynthesis by algae and plants.



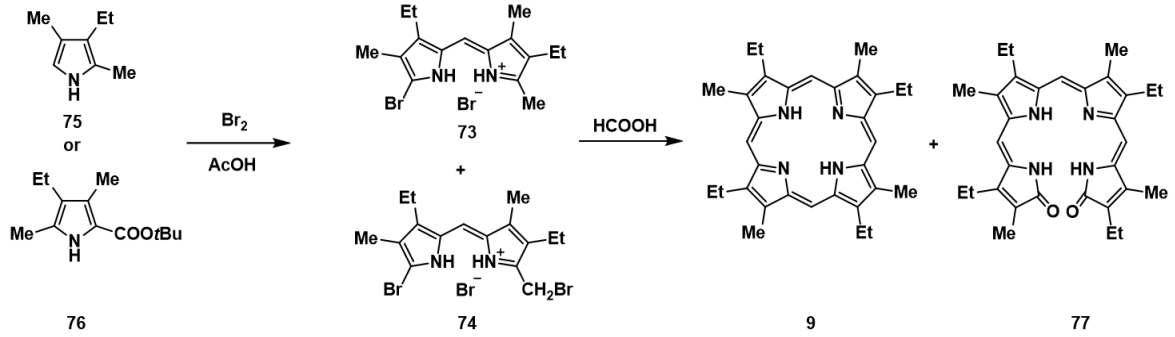
71 72

As mentioned above, individual etioporphyrins cannot be obtained by condensation of monopyrrole precursors, therefore they have to be obtained by condensation of dipyrrolylmethenes or biladienes that cannot undergo isomerization under condensation reaction conditions. However, the starting compounds for the synthesis of these precursors are monopyrroles, obtained with sufficiently high yields using the Knorr or Barton-Zard reaction[5,34] with further transformations of side substituents in the α-positions of the pyrrole cycle.[5]

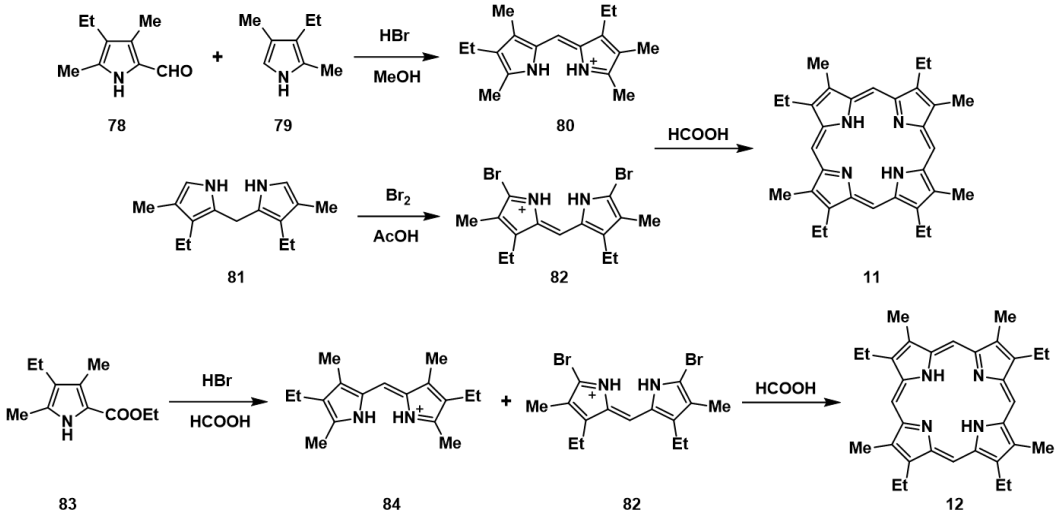
The most used dipyrrole intermediates for synthesis of porphyrins are dipyrrolylmethenes and dipyrrolylmethanes ([2+2] method). Since dipyrrolylmethanes are sensitive to acidic reagents, most of the early methods developed by Fisher[62] used dipyrrolylmethenes, which are not capable of rearrangement in an acidic environment, as standard building blocks. The presence of only two different substituents in the etioporphyrin cycle greatly simplifies the methods of their synthesis along the [2+2] route. Typically, dipyrrolylmethenes with bromine and methyl (bromomethyl) substituents in the 5,5'-positions of dipyrrolylmethenes are used for the synthesis of porphyrins.

Thus, etioporphyrin I **9** is obtained by self-condensation of a mixture of 5-bromo-5'-methyldipyrrolylmethene **73** and (or) 5-bromo-5'-bromomethyldipyrrolylmethene **74** in anhydrous formic acid at boiling or in a melt of maleic anhydride,[64] a mixture of dipyrrolylmethenes **73**, **74**,[61-67,69] in turn it is synthesized by condensation of 2,4-di-methyl-3-ethylpyrrole (cryptopyrrole) **75**[61,63,64] or 2-*tert*-butyloxycarbonyl-3,5-dimethyl-4-ethylpyrrole **76**[62,63,65,66,69] with bromine in acetic acid (Scheme 14). During the condensation reaction of dipyrrolylmethenes in 90% formic acid, verdine **77** is formed in significant quantities.[63]

To obtain etioporphyrins II **10**, III **11** and IV **12**, condensation of a pair of dipyrrolylmethenes is required, which does not allow the formation of isomeric structures, for example, pairs 5,5'-dimethylpyrrolylmethene **80** and 5.5'-dibromodipyrrolylmethene **82** (Scheme 15). To obtain a single product, at least one of the dipyrrolylmethenes **80** or **82** must be symmetrical with respect to the *meso*-carbon atom. Table 3 shows the yields of randomized etioporphyrins.



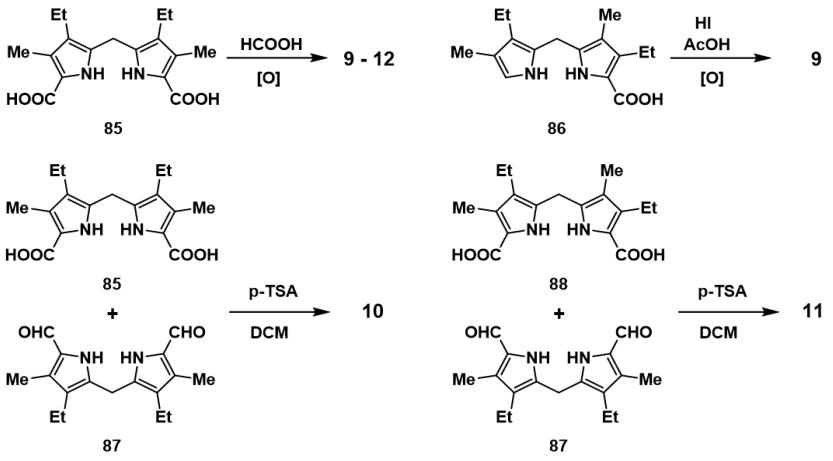
Scheme 14.



Scheme 15.

Table 3. Conditions of synthesis and yield of randomer etioporphyrins **9**-**12**.

Porphyrin	Scheme	Initial compounds	Conditions	Yield (%)	Ref.
Etioporphyrin I **9**	14	**75** → **73** + **74**	HCOOH, reflux	21	[61]
	14	**74**	HCOOH, reflux	16	[63]
	14	**74**	HCOOH, reflux	15	[69]
	14	**73**	HCOOH, reflux	52	[63]
	14	**73**	HCOOH, reflux	52	[69]
	14	**73** + **74**	Maleic anhydride, 190 ºC	44	[64]
	14	**76** → **73** + **74**	HCOOH, reflux	21-30	[65]
	14	**76** → **73** + **74**	HCOOH, reflux	21	[66]
	15	**86**	HI, AcOH, air	44	[70]
Etioporphyrin II **10**	16	**85** + **87**	$CHCl_3$, $HC(OEt)_3$, TFA, reflux	19	[61]
	16	**81** + **87**	$CHCl_3$, $HC(OEt)_3$, TFA, reflux	66	[67,68]
	16	**85** + **87**	CH_2Cl_2, *p*-TSA	29	[72]
	17	**91**	1. $CuCl_2$, DMF	60	[73]
	17	**91**	1. $CuCl_2$, DMF; 2. H_2SO_4, TFA	31	[66]
Etioporphyrin III **11**	15	**80** + **82**	HCOOH, reflux	36	[61]
	16	**87** + **88**	CH_2Cl_2, *p*-TSA	42	[72]
	18	**95**	$CHCl_3$, $HC(OEt)_3$, TFA, reflux	53	[66]
	20	**101**	DMSO, pyridine	83	[71]
	21	**102**	TBD, 200 ºC	62	[77]
Etioporphyrin IV **12**	15	**82** + **84**	HCOOH, reflux	39	[61]
	19	**87** + **88**	$CHCl_3$, $HC(OEt)_3$, TFA, reflux	32	[66]



Scheme 16.

Dipyrrolylmethene **84** can be easily obtained by boiling 2-carbethoxy-3,5-dimethyl-4-ethylpyrrole **83** in formic acid in the presence of hydrobromic acid[43] or by formylation of 2,4-dimethyl-3-ethylpyrrole **64** with phosphorus chloroxide and DMF according to Wilsmeier[43] and its subsequent condensation with pyrrole **75** in the presence of hydrobromic acid.[11] Dipyrrolylmethenes **80** or **84** were obtained by a similar method to the latter, of which, by condensation with dipyrrolylmethene **82** (obtained by bromination and oxidation of dipyrrolylmethane **80**), etioporphyrins **11** and **12** were synthesized.[61]

Many successful syntheses of porphyrins by Fischer using dipyrrolylmethenes[60] have slowed down the development of porphyrin syntheses with the use of dipyrrolylmethanes as intermediates. Some justification for this is that dipyrrolylmethanes are too unstable to acidic reagents (at least those used by Fischer) to be used in the synthesis of porphyrins. It has been shown that upon condensation of dipyrromethane-5,5'-dicarboxylic acids, type **85**, in boiling formic acid forms a mixture of randomized porphyrins,[60] and not pure etioporphyrins II **10** (Scheme 16).

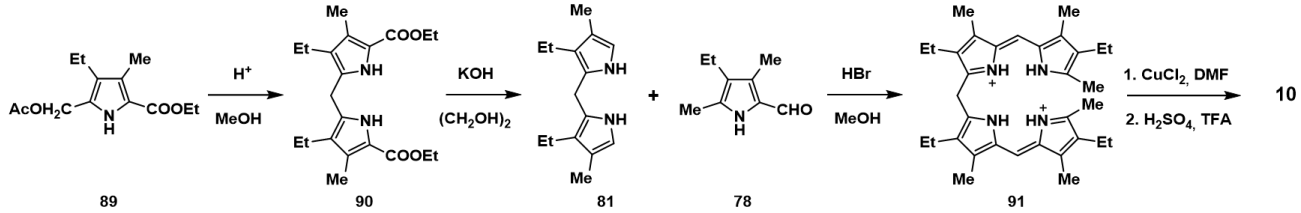
Methods for the synthesis of porphyrins from dipyrrolylmethanes are undoubtedly represented by McDonald's discovery,[74] that 5,5'-diformyldipyrrolylmethanes, for example **86**, can condense with 5,5'-disubstituted dipyrrolylmethane **80** or its 5,5'-dicarboxylic acid **84**, in the presence of an acid catalyst (hydrochloric acid in McDonald's initial publications), giving pure porphyrin with yields often exceeding 60%. *p*-Toluene sulfonic acid (*p*-TSA) or trifluoroacetic acid (TFA), as shown in [75,76], are more convenient alternatives to hydrochloric acid as a catalyst.

Self-condensation of 5-formyldipyrrolimethane **85** leads to etioporphyrin I **9** in acetic acid in the presence of hydrogen iodide during oxidation with air oxygen with a yield of 44%.[70] Upon condensation of dipyrrolylmethane **84** with orthomuric ether in chloroform in the presence of TFA and subsequent oxidation with chloranyl, etioporphyrin II **10** is formed with an yield of 56%.[67] The use of dicarboxylic acid of dipyrrolylmethane **85** reduces the yield of **10** to 19%.[61] Thus, the formyldipyrrolylmethanes used in the syntheses make it possible to obtain

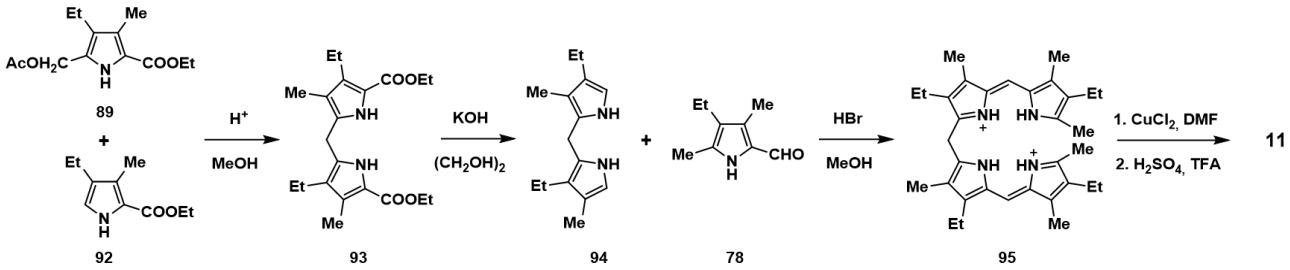
porphyrins according to the same rules as for dipyrrolylmethenes, however, under much milder conditions, allowing the use of dipyrrolylmethanes with labile substituents in syntheses.

An important method for the synthesis of etioporphyrins is the biladiene methods, which, after detailed development of the closure of the porphyrin cycle using 1,19-dimethyl- and 1-bromo-19-methylbiladiene derivatives,[66,71] make it possible to obtain randomized etioporphyrins with high yields (Schemes 17-21, Table 3).

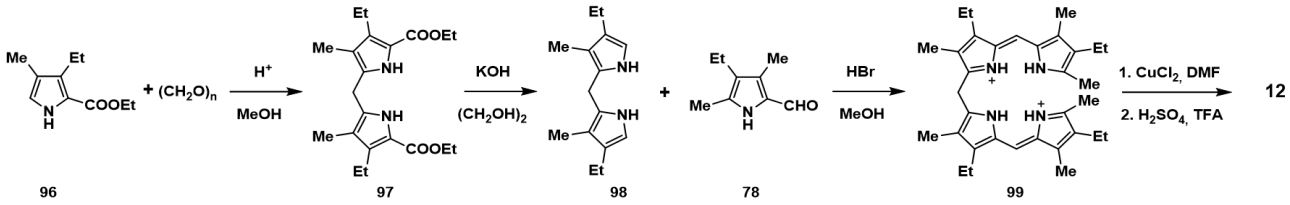
And finally, a rather original method for the synthesis of etioporphyrin III **11** with a high yield consists in the degradation of natural protoporphyrin IX **102** under the action of 1,5,7-triazobicyclo[4.4.0]dec-5-ena (TBD).[77]



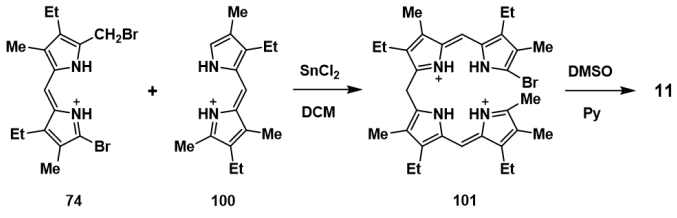
Scheme 17.



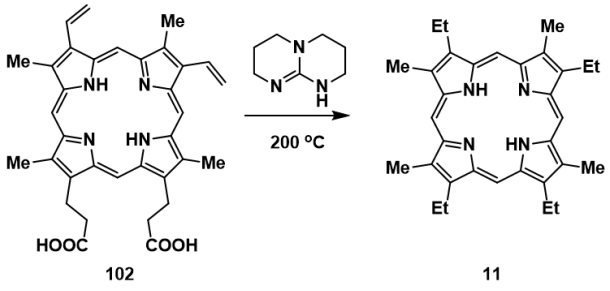
Scheme 18.



Scheme 19.



Scheme 20.



Scheme 21.

Conclusion

Methods known in the literature for the synthesis of β-octasubstituted porphyrins through the condensation of monopyrroles are presented. The syntheses of pyrroles from non-pyrrole precursors via the Knorr and Barton-Zard routes, as well as their subsequent modification into derivatives that can undergo condensation with pyrroles to form porphyrin rings, are described.

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