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Iodine-catalyzed one-pot synthesis of unsymmetrical *meso*-substituted porphyrins

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ABSTRACT

The wide range use of 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin is well established, but its synthesis requires two steps and is not very practical. This article describes an iodine-catalyzed one-pot synthesis of this unsymmetrical porphyrin that uses commercial reagents and reactants as such, without prior distillation. Unsymmetrical mono functionalized porphyrins with various functional groups have also been obtained to validate this method. The influence of electronic effects of functional groups (donor or acceptor) has also been studied.

1. Introduction

Porphyrins are key biological compounds. Their photo-electro and biochemical properties opened a wide field of applications in, e.g., electronic/electro-optical and nonlinear optics,[1] selective catalysis,[2] or material chemistry.[3] One of these applications is the well-known use of porphyrins as photosensitizers in photodynamic therapy,[4] which accounts for the importance of these dyes in bioconjugation chemistry.[5]

Since the 'Fischer era',[6] organic chemists have built a huge 'catalogue' of porphyrins. This amazing diversity results from the use of a number of imaginative synthetic routes but, very often, overall reaction yields are matters of concern. For example, the synthesis of unsymmetrical porphyrins presents a real challenge especially when practicable yields are needed. The well-known Little's mixed aldehyde method[7] leads to mono functionalized *meso*-substituted porphyrins in low yields (4–7%). Although reactants are mixed in stoichiometric amounts, the symmetrical *meso*-tetraarylporphyrin is obtained as the main product.

Recently, a particular attention has been given to the mono functionalized 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin which paves the way to valuable intermediates in the synthesis of substituted porphyrins, thanks to the vicarious nucleophilic substitution (VNS)[8] of hydrogen in *ortho* position of the nitro group and/or the reduction of the latter to amino group.[9] However, obtaining this porphyrin is not an easy task. Indeed, several publications mention a two-step synthesis, which begins with the preparation of *meso*-tetraphenylporphyrin, followed by a selective nitration[10] at the *para* position of one of the phenyl groups. These two steps, conducted in restrictive conditions, require intermediate product purification, and lead to the final product with 20–30% global yield.

On the other hand, molecular iodine has emerged as a really interesting, inexpensive, and readily available catalyst for carrying out numerous organic reactions.[11] Iodine catalysis has been recently used in selective and efficient conjugate additions of pyrrole to nitroolefins or α,β-unsaturated ketones.[12] These two reactions take advantage of the mild Lewis-acidity of molecular iodine, which first activates the carbonyl group. Mechanistic similarities between these reactions and porphyrinogen formation suggest that iodine could catalyze the condensation of pyrrole with aldehyde. Recent work in this field[13] confirms this hypothesis, and thus allows avoidance of the traditional BF_3/Et_2O or propionic acid systems. This paper reports an iodine-catalyzed, one-pot synthesis of 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin, a method that, contrary to the Little's protocol, does not require prior reactant or solvent distillation.

2. Results and discussion

The synthesis of *meso*-tetraphenylporphyrin (Scheme 1) was performed as a preliminary test of iodine catalysis. Various concentrations of reactants and catalyst were assayed. Dichloromethane, pyrrole, and benzaldehyde were used without prior distillation.

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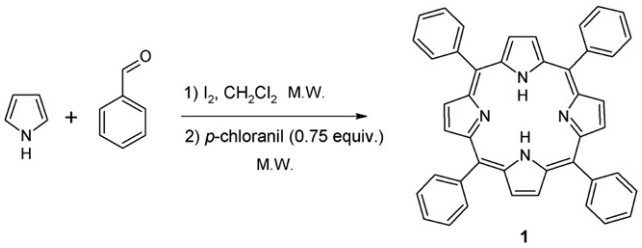
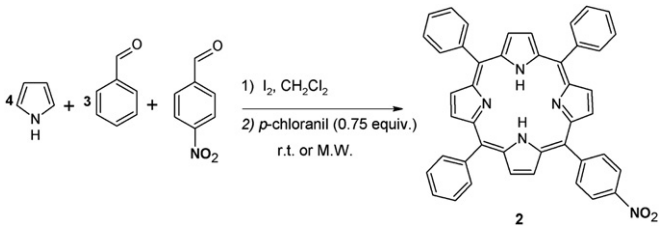


Scheme 1. One-pot synthesis of *meso*-tetraphenylporphyrin **1**.



Scheme 2. Synthesis of 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin.

Iodine as an acid promoter in catalytic amount was the key of this reaction, because it avoided inconvenient conditions, such as the use of propionic acid. At the same time, we investigated the influence of several microwave activation conditions. Results summarized in Table 1 show that iodine as catalyst afforded the final product (except for entry 2); a high concentration of pyrrole and benzaldehyde ($>10^{-1}$ mol/L) did not lead to any product (entry 2), and finally an excessive power of activation ($\geq$400 W) favored a significant polymerization of pyrrole instead of the expected tetraphenylporphyrin (entry 5).

Table 1
Most significant results for this method

Entry	I_2 (equiv)	Reagent concentration (mol L^{-1})	Activation conditions	Activation time first; second (min)	Yield (%)
1	0.2	5.10^{-2}	30 °C to 100 W	10; 1	43
2	0.2	2.10^{-1}	30 °C to 100 W	30; —	0
3	0.05	10^{-1}	30 °C to 100 W	8; 1	28
4	0.1	10^{-2}	30 °C to 100 W	20; 1	47
5	0.2	10^{-1}	40 °C to 400 W	1/12; 1/6	18

The use of excess iodine, expected to directly oxidize porphyrinogen, resulted in the vanishing of the benzaldehyde spot, although a black polymer was produced instead of the desired final compound. Optimum conditions (entry 4, Table 1) present several interesting advantages in comparison to other synthesis methods (Table 2): it is very easy to implement, it uses undistilled reagents and solvent and gives the final product within a short reaction time with good yields (47%).

This method was then used to obtain unsymmetrical porphyrins especially 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (Scheme 2).

We first compared the synthesis of **2** with the classical Little pathway and with the mononitration of *meso*-tetraphenylporphyrin (which requires prior synthesis of tetraphenylporphyrin **1**). Results summarized in Table 3 show that addition of molecular iodine at room temperature instead of another acid system led to the final product with a sensible yield (12%). Furthermore, taking into account a previous work,[12] activation by microwave irradiation resulted in a significant yield increase (22%). These two results confirm that iodine as Lewis acid catalyzes the synthesis of 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin in good yield after purification, and show the possible effect of microwave on the selectivity of this reaction (Table 3).

Table 3
Comparison of global yields

Entry	Global Yield (%)
Little synthesis (1 step)[a]	~7%
Mononitration (2 steps)	~46–56%
I_2 at rt (1 step)[a]	12%
I_2 with M.W. (1 step)[a,b]	**22**%

[a] Conditions: pyrrole (1 equiv), benzaldehyde (0.75 equiv),4-nitrobenzaldehyde (0.25 equiv).
[b] Activation: 100 W, 30 °C, 15 min.

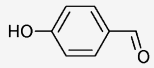
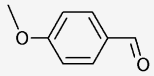
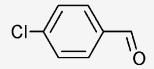
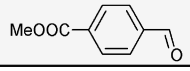
In order to confirm this interesting result, we applied this method to the synthesis of a variety of mono functionalized porphyrins, –OH **3**, –OMe **4**, –COOMe **5**, and –Cl **6**. The presence of these substituents allows the conjugation of porphyrins with a wide range of molecules: hydroxyl group permits a Williamson alkylation, carboxylic acid can be obtained by hydrolysis of methoxycarbonyl group, and chlorine can take part in aromatic nucleophilic substitution.[17] In similar conditions of reaction, all these porphyrins have been obtained in suitable yields, ranging from 8 to 27% (Table 4).

Interestingly, these results show a possible influence of electronic effects of each substituent on the reactivity of the carbonyl group. As a matter of fact, electro acceptor groups, such as $-NO_2$ or –COOMe tend to increase reaction yields (22% and 27%) whereas, electro donor groups like –OH or –OMe have the opposite effect (8% and 11%). This could be interpreted as an increase of the carbonyl group reactivity induced by electro acceptors via an increase of the partial positive charge of the carbonyl carbon. This result was confirmed by a reaction realized with *para*-tolualdehyde, in which the electro donor effect is low compared to hydroxyl or methoxy groups. 5-(4-Methylphenyl)-10,15,20-triphenylporphyrin **7** was obtained with a reference yield of 14%, similar to the 15% yield

Table 2
Synthesis of TPP, comparison with well-known methods

	Rothemund[14]	Adler[15]	Lindsey[16]	I_2/M.W.
Solvent	Pyridine	(I) Propionic Acid (II) Acetic Acid	Dichloromethane Chloroform	Dichloromethane
Temperature	220 °C	(I) 141 °C (II) 120 °C	25 °C	30 °C
Catalyst	—	Solvolysis	TFA BF_3, Et_2O BF_3, Et_2O/EtOH	I_2
Oxidant	—	O_2	DDQ or *p*-chloranil	*p*-Chloranil
Reactants concentration	3.6 mol L^{-1}	0.3–1 mol L^{-1}	0.001–0.1 mol L^{-1}	0.1 mol L^{-1}
Reaction time	48 h	0.5–1 h	1 h	21 min
Synthesis	1 step	1 step	2 steps	One-pot
Purification	Recrystallization	Filtration	Chromatography	Filtration
Yield	<10%	~20%	Up to 45%	**47**%

Table 4
Yield comparison between literature and I_2/M.W. methods

Compounds	Aldehydes	Ref. 18 (%)	This study (%)
3		7	8
4		7.4	11
5		15	15
6		5	27

obtained with the synthesis of 5-(4-chlorophenyl)-10,15,20-triphenylporphyrin; the latter attests for the competition between the two possible effects of the chlorine group, which is at the same time electro donor and acceptor.

3. Conclusions

A series of mono functionalized porphyrins have been synthesized by a variation of the Little mixed aldehyde method in which propionic acid was replaced by catalytic amounts of molecular iodine. The use of undistilled solvents and reactants are major advantages of this method because it spares time and avoids inconvenient conditions. Furthermore, this method allows the use of high reactant concentration compared to the classical Lindsey method. Activation by microwave irradiation has been used to provide final product in short times and with sometimes a good selectivity (–NO_2 and –COOMe). 5-(4-Nitrophenyl)-10,15,20-triphenylporphyrin is an interesting product, able to provide valuable intermediates through the production of amino porphyrin by reduction of NO_2, or Vicarious Nucleophilic Substitution (VNS). This method has been validated by synthesis of other mono functionalized porphyrins of interest, with yields ranging from 8 to and 27%, always higher than reference yields provided by the Little's method.

4. Experimental section

4.1. General methods

All the solvents and chemicals were commercially available and, unless otherwise stated, were used as received. Benzaldehyde (99%), pyrrole (98%), and *p*-anisaldehyde (98%) were purchased from Aldrich, and tolualdehyde (98%) was purchased from Alfa Aesar. Reactions were monitored by thin-layer chromatography (TLC) on precoated 0.2 mm silica gel 60 F_{254} (Merck) plates and visualized with an ultraviolet light source at 254 nm. Microwave irradiations were performed by the means of an Ethos 1600 MicroSynth reactor from Milestone. Temperature was measured with a fiber optic thermometer (ATC-FO)/Ethos. ^{1}H NMR spectra were recorded at 400.13 MHz with a Brüker DPX spectrometer. Chemical shifts (δ) are expressed in parts per million with Me_4Si as an internal standard (δ=0). Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br, broad), coupling constants (Hz) and assignment.

4.2. General procedure for porphyrin synthesis

Substituted aldehydes (0.25 mmol), benzaldehyde (76 μL, 0.75 mmol), molecular iodine (25 mg, 0.1 equiv), then pyrrole (70 μL, 1 mmol) were added successively to 10 mL CH_2Cl_2, without particular precautions. After the first activation (100 W, 30 °C), TLC showed the total conversion of benzaldehyde. *para*-Chloranil (0.75 equiv, 184 mg) was then added and a second activation was performed (100 W, 30 °C). The reaction mixture was evaporated on florisil and purified by flash chromatography (eluent gradient: EP/$CHCl_3$, 8/2–1/9).

4.3. Spectroscopic data

All physicochemical properties coincided with literature data.[10,13,18]

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