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A facile and rapid iodine-catalyzed *meso*-tetraphenylporphyrin synthesis using microwave activation

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ABSTRACT

This Letter describes a rapid, easy and efficient one-pot procedure for tetraphenylporphyrin synthesis using iodine-catalysis and microwave activation. Commercial pyrrole, benzaldehyde and dichloromethane were being used as such, without prior distillation.

Since the pioneering synthesis by Fischer in the 1920s, research on porphyrins evolved dramatically. These tetrapyrrolic macrocyles are key biological compounds. Their photo-electro and biochemical properties opened a wide field of applications in, for example, electronic/electrooptical 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] Porphyrin macrocycle synthesis has attracted a lot of interest during one century. *meso*-Tetraarylporphyrins have been particularly concerned since they can be used in a large variety of model studies.

meso-Tetraphenylporphyrin can be synthesized by a one-step cyclocondensation of monopyrrole, with benzaldehyde, in the presence of a catalyst and an oxidant. Several catalyst-oxidant systems have been studied over 40 years, including notably Brönsted-acid catalysis with aerobic oxidation in the Adler–Longo procedure[6] and Lewis-acid catalysis with an organic oxidant (DDQ or *para*-chloranil) developed by Lindsey et al.[7] More recent methods introduced oxidizing co-solvents, clays, ionic liquids, hydrogen peroxide in acetic acid, mixtures of xylene and chloroacetic acid, transition metal salts or vapour phase synthesis without any solvent or catalyst.[8]

In parallel, molecular iodine has emerged as a really interesting, inexpensive, and readily available catalyst for carrying out numerous organic reactions.[9] Iodine catalysis has been recently used in the selective and efficient conjugate additions of pyrrole to nitroolefins or α,β-unsaturated ketones.[10] These two reactions take advantage of the mild Lewis-acidity of iodine, which first activates the carbonyl group. Mechanistic similarities between these reactions and porphyrinogen formation suggest that iodine could catalyze the condensation between pyrrole and aldehyde, leading to a new porphyrin synthesis method. On the other hand, the use of microwave activation resulted in a dramatic decrease of reaction times of various steps during porphyrin or metalloporphyrin syntheses.[11] This Letter reports the coupling of iodine-catalysis and microwave activation[12] allowing an efficient and rapid one-pot synthesis of tetraphenylporphyrin. *meso*-Tetrasubstituted porphyrins are particularly useful to generate mono-functionalized porphyrins like monoamino- or mononitroporphyrins.[13]

A preliminary study using pyrrole, benzaldehyde and iodine in dichloromethane has been conducted (Scheme 1) and at first, the influence of pyrrole and benzaldehyde (equimolar) concentrations has been studied (Table 1).

These results show that a catalytic amount of iodine (0.2 equiv) is sufficient to ensure the production of tetraphenylporphyrin (entries 1–3).[14] It was also observed that higher concentrations of reagents led to the formation of by-products which appeared as a black polymer (entries 4 and 5).

Reaction yields (27–30%) were found virtually independent of iodine amounts (in the 0.05–0.2 equiv range) when the reaction was conducted with high concentrations of reagents (10^{-1} mol/L) (Table 2, entries 1–3). Lower reagent concentration (10^{-2} mol/L, the actual concentration used for Lindsey's method) in the presence of 0.2 equiv I_2 gave 47% yield, although a longer activation time (20 min) was needed to complete the first reaction step (Table 2, entry 4). The same was true when smaller amounts of iodine

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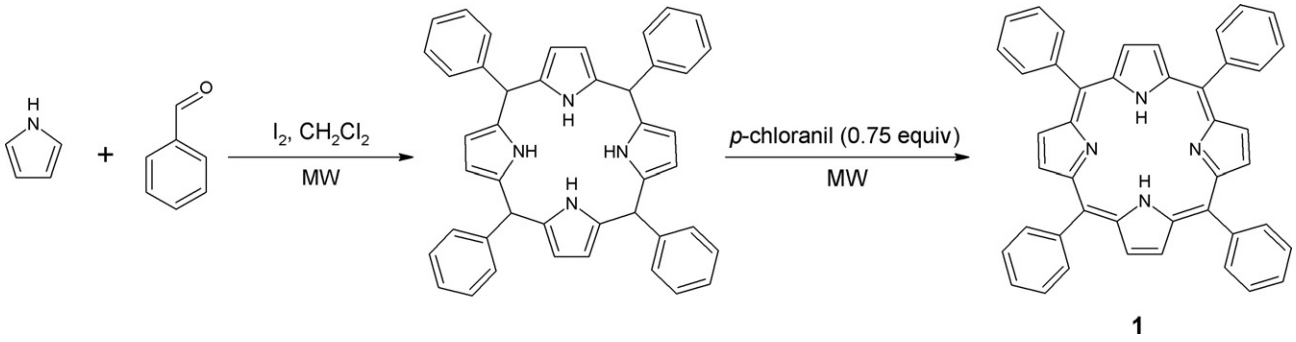

Scheme 1. Microwave-assisted *meso*-tetraphenylporphyrin synthesis.

Table 1
Effect of pyrrole and benzaldehyde concentrations[a]

Entry	Reagent concentration (mol/L)	Activation time (min) first/second	**1** Isolated yield (%)
1	10^{-2}	20; 1	41
2	5×10^{-2}	10; 1	43
3	10^{-1}	5; 1	26
4	2×10^{-1}	30; —	0
5	3×10^{-1}	30; —	0

[a] Conditions: I_2 (0.2 equiv), activation (100 W; 30 °C). Reaction times allowing virtual completion (checked by TLC: disappearance of the benzaldehyde spot).

Table 2
Effects of I_2 concentration and MW activation[a]

Entry	I_2 (equiv)	Reagent concentration (mol/L)	Activation conditions	Activation time (min) first/second	Isolated yield (%)
1	0.2	10^{-1}	30 °C–100 W	5; 1	27
2	0.1	10^{-1}	30 °C–100 W	5; 1	30
3	0.05	10^{-1}	30 °C–100 W	8; 1	28
4	0.1	10^{-2}	30 °C–100 W	20; 1	47
5	0.2	10^{-1}	35 °C–300 W	1; 1	35
6	0.1	10^{-1}	35 °C–300 W	1; 1	32
7	0.025	10^{-1}	35 °C–300 W	2; 1	33
8	0.2	10^{-1}	40 °C–400 W	1/12; 1/6	18

[a] Conditions: pyrrole and benzaldehyde (1 mmol). Reaction times allowing virtual completion (checked by TLC: disappearance of the benzaldehyde spot).

(less than 0.1 equiv) were tested (Table 2, entry 3 compared to entries 1 and 2, and entry 7 compared to entries 5 and 6).

Different conditions of temperature and power of activation were also tested (Table 2). Data reported in this table show that high reagent concentration (10^{-1} mol/L), led to an optimal result (35%) after only 1 min of activation at 35 °C and with a 300 W power. On the other hand, increased power (400 W, reaction completion in 15 s checked by TLC) resulted in a yield drop, certainly due to high polymerization.

The use of excess iodine, expected to directly oxidize porphyrinogen, resulted in the vanishing of the benzaldehyde spot; however, a black polymer was produced instead of the desired final compound.

This method presents several interesting advantages: reasonably good yields (35–47%), the use of undistilled reagents and solvent, a short reaction time and the use of high reagent concentration- by comparison with Lindsey's method. An extension of this method towards the synthesis of unsymmetrical porphyrins is currently under study.

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14. General procedure (e.g., Table 2, entry 5): Benzaldehyde (101 μL, 1 mmol), iodine (51 mg, 0.2 equiv) then pyrrole (70 μL, 1 mmol) were added successively to 10 mL CH_2Cl_2, without particular precautions. After the first activation (300 W, 35 °C, 1 min), TLC showed total conversion of benzaldehyde. *para*-Chloranil (0.75 equiv, 184 mg) was then added and a second activation was performed (300 W, 35 °C, 1 min). The mixture was evaporated on florisil

and purified by flash chromatography using CH_2Cl_2/petroleum ether (50:50) as eluent. Pure product was obtained as a purple solid (54 mg, 35%). All physicochemical properties coincided with literature data. ^1H NMR (400 MHz, $CDCl_3$): 8.84 (8H, s, Pyrrole–H), 8.20–8.23 (8H, m, Ho–Ph), 7.72–7.79 (12H, m, Hm–Ph and Hp–Ph), −2.77 (2H, pyrrole NH); ^{13}C NMR (100 MHz, $CDCl_3$): 142.2, 134.6, 131.1, 127.7, 126.7, 120.1, 118.7.