Journal of Porphyrins and Phthalocyanines
J. Porphyrins Phthalocyanines 2019; **23**: 1–9
DOI: 10.1142/S1088424619500755

Published at http://www.worldscinet.com/jpp/

Porphyrin synthesis using mechanochemistry: Sustainability assessment

Carla Gomes, Mariana Peixoto and Marta Pineiro*[◊]

CQC and Department of Chemistry, University of Coimbra, Rua Larga, 3004-535 Coimbra, Portugal

This paper is part of the 2019 Women in Porphyrin Science special issue.

Received 15 March 2019
Accepted 21 June 2019

ABSTRACT: Looking for sustainable synthetic methodologies, mechanochemistry as a new tool for one-step and two-step approaches for the synthesis of *meso*-substituted porphyrins was explored. The best results were obtained in a two-step procedure, under liquid-assisted grinding in the oxidation step using 2-methyltetrahydrofuran, an environmentally acceptable solvent, and MnO_2 as a heterogeneous oxidant. The sustainability was assessed using two sustainability metrics, E-factor and EcoScale, which allow comparison between procedures and methods.

KEYWORDS: porphyrin, synthesis, mechanochemistry, MnO_2, porphyrinogen, sustainability.

INTRODUCTION

Sustainability has been a recurring theme in society and in chemistry. The preservation of the environment and the quality of life of today's society is undoubtedly one of the great challenges of our society, in which chemistry plays a crucial role. Synthetic chemists have come a long way in the search for more sustainable processes, methods and techniques, seeking to implement the twelve principles that define the ideal of "Green Chemistry" [1]. Green Chemistry is focused on the design, development and implementation of chemical products and processes, aiming at reducing pollution at its source by minimizing or eliminating the hazards of chemical feedstock, reagents, solvents and products [2, 3]. It assesses the solvent used in processes, explores the potential use of catalysts, promotes the incorporation of renewable feedstock, attempts to minimize energy utilization and identifies materials that do not persist or bioaccumulate. Porphyrins, in the broadest sense of the word, are unquestionably compounds having unique properties which have led to their use in very diverse applications, from cancer diagnosis and therapy, to catalysis, to optical systems [4–16]. Moving from laboratory-scale to industrial production, for a wide range of applications, leads to production of large amounts of derivatives with different patterns of substitution in the development phase and a large amount of the same compound in the application phase. It has become necessary to look for more sustainable methods of porphyrin production, which has been carried out by the chemists involved in their synthesis. Since the work of Rothemund [17–19], synthesizing porphyrins in pyridine, going through the recognized meritorious classical methodologies of Adler and Longo [20, 21], Lindsey [22–26] or Rocha Gonsalves [27–29], much of the philosophy has changed, and new tools for Green Chemistry are used every day in organic chemistry labs.

Following the principles of Green Chemistry, several methods for the synthesis of porphyrins have been developed using alternative catalysts, reaction media and new tools such as microwave irradiation [30–33]. Microwave irradiation is very well established as a tool that allows decreasing the amount of solvent used and reducing the energy input, also decreasing the reaction times. The use of microwave to afford the

---

[◊] SPP full member in good standing

*Correspondence to: Marta Pineiro, Rua Larga, Department of Chemistry, University of Coimbra, 3049-535 Coimbra, Portugal, tel.: +351239857944, fax: +351239852080, email: mpineiro@qui.uc.pt.

energy input for the synthesis of porphyrins further allowed the development of new procedures such as the use of heterogeneous catalysts or new oxidants such as MnO_2 [34].

Mechanochemistry, an ancient way to promote reactions, has been widely used in the synthesis of polymers and in inorganic chemistry [35–38]. More recently, with the interest in reduction of the solvent in organic processes, mechanochemistry has been used in organic synthesis to promote reactions in the solid state [39–41], however, so far only one report on the synthesis of porphyrins under mechanical activation has been described [42].

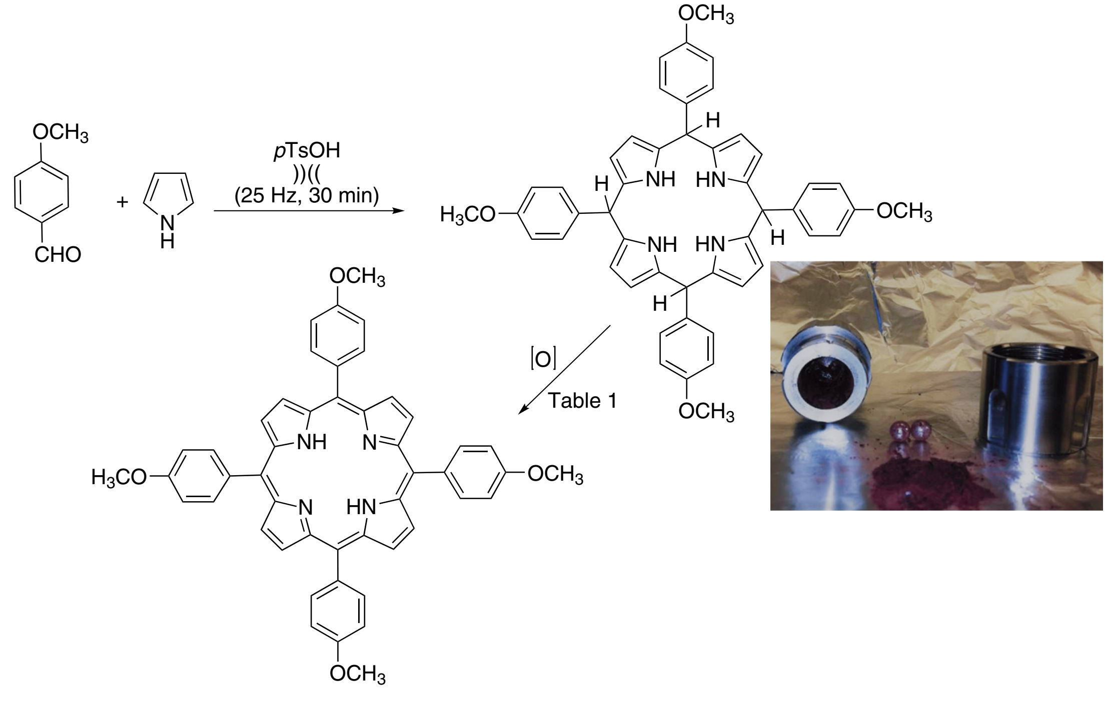
Following our previous work on the development of sustainable methodologies for the synthesis of porphyrins, herein we present the use of mechanochemistry for the synthesis of porphyrins in one or two steps and an analysis of sustainability or greenness using two metrics, E-factor and EcoScale, to allow comparison.

RESULTS AND DISCUSSION

Synthesis

Porphyrins were synthesized in one-step or two-step procedures, *i.e.* separating or not the cyclization of pyrrole and aldehyde to form porphyrinogen from its oxidation to porphyrin. The studies were initiated using a two-step approach, which facilitates the individual analysis of cyclization and oxidation in order to maximize yield and sustainability. The porphyrinogen, 5,10,15,20-*tetrakis*-(4-methoxyphenyl)-5,10,15,20,22,24-hexahydroporphyrin, precursor of 5,10,15,20-*tetrakis*-(4-methoxyphenyl)porphyrin, chosen as model compound, was prepared under mechanochemical activation from the grinding of equimolar quantities of pyrrole and 4-methoxybenzaldehyde with *p*-toluenesulfonic acid (20 mol%) in a stainless-steel grinding jar with two stainless-steel balls for 30 min, adapting the conditions previously described [42], Scheme 1.

Oxidation of the porphyrinogen was performed using the classical conditions: 11 equivalents of DDQ in 50 mL of chloroform at room temperature for 2 h [42], obtaining of the desired porphyrin with 6% yield after column chromatography, (entry 1, Table 1). Manganese (IV) oxide is a green and cheap transition metal oxide with low toxicity [43] that has been successfully used as an effective heterogeneous oxidant of several organic compounds [44] including hydroporphyrins [34]. The oxidation of porphyrinogen under mechanical action using MnO_2 was tested using 10, 5 and 2.5 equivalents in solventless conditions. The best balance between porphyrin yield and simplicity of the purification process was obtained using 5 equivalents of MnO_2 yielding 3% of porphyrin (entries 2–4, Table 1). The use of other green oxidants such as iodine and hydrogen peroxide [45, 46] only afford traces of the desired product (entries 5 and 6, Table 1). It was previously observed than in liquid-assisted grinding (LAG) mechanochemical reactivity



Scheme 1. Two-step synthesis of 5,10,15,20-*tetrakis*-(4-methoxyphenyl)porphyrin, Photograph of the reaction product after grinding pyrrole, 4-methoxybenzaldehyde and *p*-toluenesulfonylhydrazine. Symbols:)) ((mechanical activation; [O] oxidation

Table 1. Oxidation of 5,10,15,20-*tetrakis*-(4-methoxyphenyl)porphyrinogen

Entry	Activation method	Solvent/Oxidant	Temp. (°C)	Time (min)	Yield (%)
1	Stirring, room temp.	$CHCl_3$ (50 mL)/DDQ (5 equiv.)	r.t.	120	6
2	Mechanical	MnO_2 (2.5 equiv.)	r.t	30	traces
3	Mechanical	MnO_2 (5 equiv.)	r.t	30	3
4	Mechanical	MnO_2 (10 equiv.)	r.t	30	4
5	Mechanical	I_2 (5 equiv.)	r.t	30	traces
6	Mechanical	H_2O_2 (5 equiv.)	r.t	30	traces
7	Mechanical	Ethyl acetate (0.2 mL)/MnO_2 (5 equiv.)	r.t	30	traces
8	Mechanical	H_2O (0.2 mL)/MnO_2 (5 equiv.)	r.t	30	3
9	Mechanical	2MeTHF (0.2 mL)/MnO_2 (5 equiv.)	r.t	30	10
10	Stirring	2MeTHF (5 mL)/MnO_2 (5 equiv.)	r.t.	120	19
11	MW	2MeTHF (2 mL)/MnO_2 (5 equiv.)	80	10	traces
12	MW	Propionic acid/$PhNO_2$	200	5	5

Table 2. One-step Synthesis of synthesis of 5,10,15,20-tetrakis-(4-methoxyphenyl)porphyrin

Entry	Activation method	Solvent/oxidant	Temperature (°C)	Time (min)	Yield (%)
1	MW	Water (0.2 mL)	200	10	14
2	MW	Propionic acid/$PhNO_2$ (5 mL)	120	10	20[a]
3	Mechanical	*p*-toluenesulfonic acid, MnO_2	r.t	75	3
4	Mechanical	*p*-toluenesulfonic acid, 2MeTHF/MnO_2	r.t	75	5
5	Mechanical	Propionic acid/$PhNO_2$ (0.2 mL)	r.t	75	traces

[a] Reference [57].

is induced or accelerated by near-stoichiometric or substoichiometric amounts of a liquid in comparison to solvent-free conditions [41, 47]. As the effect is highly dependent on the solvent, we have chosen green solvents with no specific danger regarding risk of explosion when subjected to friction or mechanical shock, such as water, 2-methyltetrahydrofuran (2MeTHF) and ethyl acetate, among the many possibilities [48, 49]. The addition of 0.2 mL ethyl acetate afforded only traces of the desired compound (entry 7, Table 1). The addition of the same amount of water yielded the porphyrin in similar yield as when using solventless conditions (entry 8, Table 1). However, the addition of 2MeTHF to the mechanochemical reaction improved the reaction yield to a remarkable 10% yield (entry 9, Table 1), while longer reaction times did not afford better yields.

By transferring the porphyrinogen prepared by mechanochemistry to a laboratory round glass vessel, adding 5 equivalents of MnO_2 and 25 mL of 2MeTHF and keeping the mixture under magnetic stirring at room temperature for 120 min, 19% yield was obtained (entry 10, Table 1). When performing the oxidation of the porphyrinogen under microwave irradiation using MnO_2 as oxidant, only traces of the desired product resulted (entry 11, Table 1). Furthermore, when the known mixture of propionic acid and nitrobenzene was used, only 5% yield of the desired porphyrin was obtained (entry 12, Table 1).

The synthesis of porphyrins in one-step under microwave irradiation at 200 °C for 10 min using pyrrole and aldehyde and just a small amount of water has proven to be a very sustainable method for the synthesis of porphyrins and therefore a mark to compare other methods [31]. The synthesis under microwave irradiation with water gave 5,10,15,20-*tetrakis*-(4-methoxyphenyl)porphyrin with 14% yield after purification by precipitation and recrystallization (entry 1, Table 2). The synthesis of 5,10,15,20-*tetrakis*-(4-methoxyphenyl)porphyrin under microwave irradiation was performed following the methodology we previously described, where propionic acid and nitrobenzene were used as solvent and oxidant, yielding 20% of porphyrin after purification by column chromatography (entry 2, Table 2).

The synthesis of the reference compound under mechanical activation was performed using MnO_2 as oxidant, mixing pyrrole, 4-methoxybenzaldehyde, *p*-toluenesulfonic acid and MnO_2 in a stainless-steel grinding jar along with two stainless-steel balls, for 75 min. Samples were taken at 30 and 45 min, and the

Table 3. Values for each of the parameters evaluated in EcoScale

		EcoScale Penalty Points					
Entry	Activation method/Solvent/ Oxidant	1. Yield	2. Price	3. Safety	4. Technical setup	5. Temp./Time	6. Workup and Isolation
Two-step procedures							
1	Stirring/$CHCl_3$/DDQ	47	23	21	2	1	10
2	Mechanical/MnO_2	48.5	18	13	2	0	1
3	Mechanical/H_2O/MnO_2	48.5	18	13	2	0	1
4	Mechanical/2MeTHF/MnO_2	45	21	17	2	0	1
5	Stirring/2MeTHF/MnO_2	40.5	23	17	2	1	1
6	MW/Propionic acid/$PhNO_2$	47.5	21	22	2	2	10
One-step procedures							
7	MW/ Propionic acid/$PhNO_2$	40	16	17	2	2	10
8	MW/Water	43	8	7	2	2	1
9	Mechanical/2MeTHF/MnO_2	47.5	23	17	2	0	1

formation of the porphyrin was controlled by UV-vis spectroscopy. After filtration over celite and column chromatography, a 3% yield was obtained (entry 3, Table 2). In an independent experiment, by adding 0.2 mL of 2MeTHF to the initial mixture, 5% yield of porphyrin was obtained (entry 4, Table 2). Comparing this result with the oxidation in two-steps with MnO_2, which yielded 10%, this could be explained by the negative influence of the solvent in the cyclization step. The use of a propionic acid/nitrobenzene mixture as acid catalyst and oxidant under mechanochemistry conditions did not afford the desired product (entry 5, Table 2).

Sustainability assessment

The development of metrics for comparing the greenness and sustainability of competing methodologies is still a field in development [50, 51]. To compare the methods in this study, we chose two metrics. One was the E-factor, one of the original mass-based metrics focused on the elimination of waste, *i.e.* the efficiency of source utilization [52]. Mass-based metrics gave a rapid and clear assessment of the efficiency of the reaction, but failed in the consideration of the nature of raw materials and waste energy efficiency, and economical aspects. Therefore, a metric with a more global analysis was also used, the EcoScale, developed by Van Aken and co-workers [53]. This was one of the first metrics developed which includes all the environmental factors and also economic issues and therefore considers not only greenness but also sustainability.

Calculation of the E-factor was determined using Equation 1. Calculation of the EcoScale was achieved by subtracting, from the 100 initial points the six parameters in Table 3 represented in Fig. 1. The values of both metrics are collected in Table 4 and represented in Fig. 2.

$$\text{E-factor} = g \text{ of Waste} / g \text{ of Product} = ((g \text{ of Reactants} + g \text{ of Solvents} + g \text{ of Oxidant}) - g \text{ of Product}) / g \text{ of Product} \quad (1)$$

The E-factor for the two-step procedures includes the reactants needed for the first-step, the porphyrinogen synthesis, *i.e.* 2.5 mmol of pyrrole and *p*-methoxybenzaldehyde and 0.5 mmol of *p*-toluenesulfonic acid, which gave a constant value of 0.60 g. Therefore, the differences obtained in the final value are due to the different oxidation procedures. The rational use of the solvent has an important influence on the E-factor. In fact, the use of large quantities of solvents led to very high E-factor values, on the order of thousands and hundreds (entries 1 and 6, Table. 4) while lower values were obtained when reducing the quantity of solvent, both under conventional stirring conditions and under mechanical activation (entries 2–5, Table 4). The lowest value was obtained for the liquid-assisted mechanochemical oxidation with MnO_2 (entry 4, Table 4) where the increase of waste using

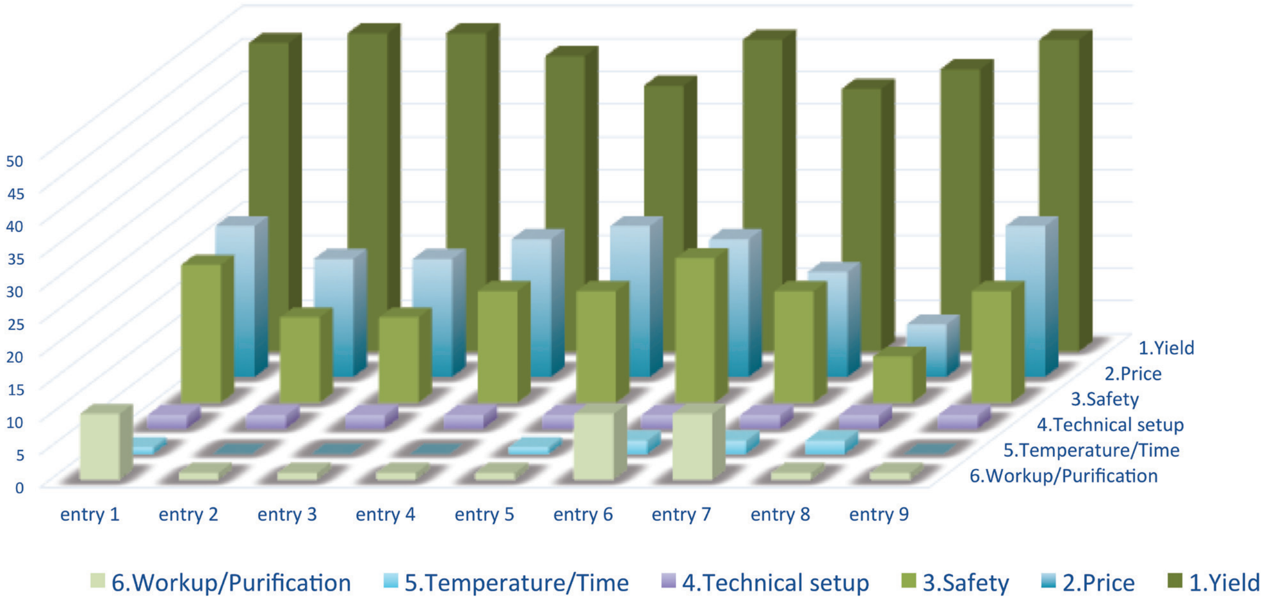


Fig. 1. Penalty points of each of the six parameters evaluated in EcoScale for one- and two-step synthesis of porphyrins

Table 4. E-factor and EcoScale values obtained for the one- and two-step procedures

Entry		Activation method/Solvent/Oxidant	Yield (%)	E-factor	EcoScale
1	Two-step procedures Oxidation conditions	Stirring/$CHCl_3$/DDQ	6	2800	-4
2		Mechanical/MnO_2	3	62	17.5
3		Mechanical/H_2O/MnO_2	3	77	17.5
4		Mechanical/2MeTHF/MnO_2	10	22	14
5		Stirring/2MeTHF/MnO_2	19	58	15.5
6		MW/Propionic acid/$PhNO_2$	5	121	-4.5
7	One-step Procedures	MW/Propionic acid/$PhNO_2$	20	19	13
8		MW/Water	14	8	37
9		Mechanical/ 2MeTHF/MnO_2	5	32	9.5

minimal amounts of solvent is balanced by the increase in the reaction yield.

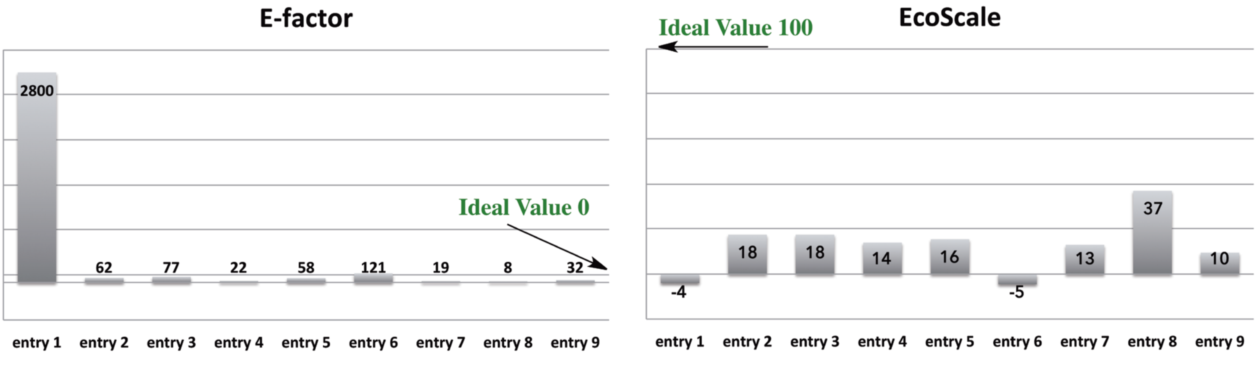
Analyzing the EcoScale parameters, it is obvious that the biggest contribution to the loss of points is the low yield. The use of MnO_2 and greener solvents instead of hazardous solvents and oxidants such as DDQ, $CHCl_3$ or nitrobenzene led to fewer penalty points in safety. The use of reaction conditions that allow the isolation of the porphyrin by filtration, avoiding column chromatography, gave fewer penalty points in the workup and purification parameter. The above described factors led to higher EcoScale values when MnO_2 was used as oxidant (entries 2–5, Table 4).

Comparing the one-step method (entry 9, Table 4) with the two-step method, using MnO_2 and 2MeTHF (entry 4, Table 4), where the same quantities of pyrrole, aldehyde, acid catalyst, solvent and oxidant were used, the E-factor increased from 22 to 32 and the EcoScale decreased from 14 to 9.5 as a consequence of the decrease in the reaction yield. Therefore, the use of mechanical activation does not bring any improvements in sustainability.

In any case, under mechanical activation the E-factor values are higher, while EcoScale values lower than those obtained in the microwave methods using water as solvent (entry 8, Table 4), which once again gave the best sustainability values, an EcoScale value of 37 and E-factor of 8, the closest values to 100 (ideal value of EcoScale) and to 0 (ideal value of E-factor).

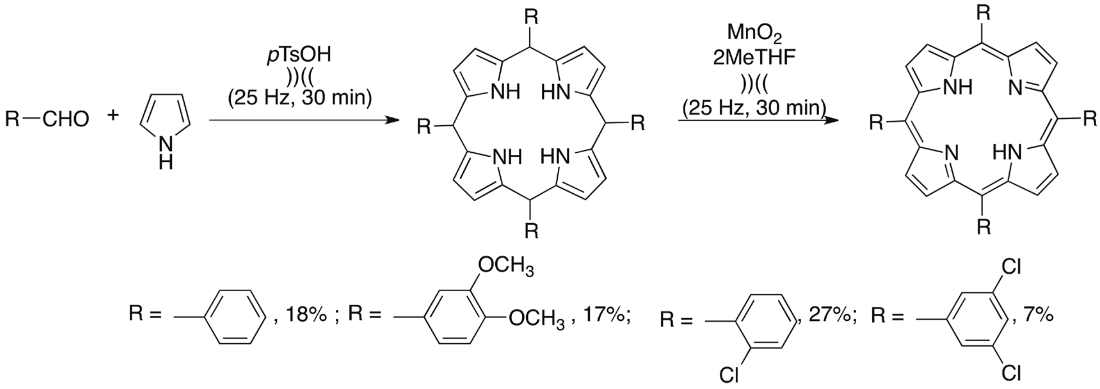
Scope of two-step liquid-assisted mechanochemical procedure

Considering the use of mechanical activation, the more adequate procedure from the view point of sustainability is



(a) (b)

Fig. 2. Panel (a) E-factor and Panel (b) EcoScale values for one- and two-step methods for the synthesis of porphyrins at Table 4



Scheme 2. Scope of the two-step mechanical synthesis of porphyrins

the two-step liquid-assisted mechanochemical procedure, where the oxidation is performed with MnO$_2$ in the presence of 2MeTHF. Using these reaction conditions, 5,10,15,20-*tetrakis*-(3,4-dimethoxyphenyl)porphyrin, 5,10,15,20-tetraphenylporphyrin, 5,10,15,20-*tetrakis*-(2-chlorophenyl)porphyrin and 5,10,15,20-*tetrakis*-(3,5-dichlorophenyl)porphyrin were obtained with 17, 18, 27 and 7% yield, respectively, indicating the applicability of mechanochemistry to the synthesis of porphyrins, Scheme 2.

EXPERIMENTAL

General

Benzaldehyde (Riedel deHaën, 99.0+%), *p*-anisaldehyde (Acros Organics, 99.0+%), 3,4-dimethoxybenzaldehyde (Sigma–Aldrich, 99.0%), 3,4-dihydroxybenzaldehyde (Sigma–Aldrich, 97.0%), 3,5-dichlorobenzaldehyde (Alfa Aesar, 97.0%), 2-chlorobenzaldehyde (Sigma–Aldrich, 99.0%), *p*-tolu-enesulfonic acid monohydrate (Sigma–Aldrich, 98.5%), activated manganese (IV) oxide (Alfa Aesar, 90.0%), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Sigma–Aldrich, 98%) and SiO$_2$ 60A 30–70 micron (Fluorochem) were used as received. Pyrrole (Fluorochem, 99%) was used as received or, when necessary, distilled under vacuum for purification prior to use.

All commercially-acquired solvents were purified according to literature procedures prior to use [54], with the following exceptions: 2-methyltetrahydrofuran anhydrous (Sigma–Aldrich, ≥ 99.0%), deuterated chloroform (Sigma–Aldrich, 99.9% D, 0.03% v/v TMS (Trimethylsilane); Euriso-Top, 99.8% D, 0.03% v/v TMS), propionic acid (Acros Organics, 99.0%) and nitrobenzene (Acros Organics, 99.0%); these were used as purchased.

Microwave-assisted reactions were performed in a CEM Discover S-Class single-mode microwave reactor featuring continuous temperature, pressure and microwave power monitoring.

Automated sample grinding was carried out using a Retsch Mixer Mill MM400 in a stainless-steel grinding jar (10 mL volume) along with two stainless steel balls (7 mm diameter, 1.38 g). TLC-monitoring of the reactions was performed using SiO$_2$ 60 F254-coated aluminum plates (Merck). ^{1}H NMR spectra were registered at room temperature on a Bruker Avance III spectrometer operating at 400 MHz. TMS (Trimethylsilane) was the internal standard used. Chemical shifts (δ) and coupling constants (J) are indicated in ppm and Hz, respectively.

UV-vis absorption spectra were obtained on a Shimadzu UV-2100 spectrometer.

Synthesis

Preparation of porphyrinogen under conventional procedure. In a 500 mL round-bottom flask, 250 mL of dichloromethane and 4-methoxybenzaldehyde (2.5 mmol) were added and the solution was bubbled with nitrogen and magnetically stirred at room temperature for 15 min. Then, pyrrole was added (2.5 mmol, 0.17 mL) under nitrogen atmosphere and the solution stirred magnetically for a few minutes before the addition of boron trifluoride diethyl etherate (0.2 mmol, 31 μL). The reaction was kept, with stirring, at room temperature under nitrogen atmosphere for 4 h.

Preparation of porphyrinogen under mechanical activation. Pyrrole (2.5 mmol, 0.17 mL) and 4-methoxybenzaldehyde (2.5 mmol) were combined with *p*-toluenesulfonic acid (0.5 mmol, 95.1 mg) in a stainless-steel grinding jar (10 mL volume) along with two stainless-steel balls (7 mm diameter). The mixture was ground in a Retsch MM400 mill at a frequency of 25 Hz for 30 min, yielding a pink solid.

Procedure for the oxidation of the porphyrinogen under microwave irradiation with propionic acid/nitrobenzene. The porphyrinogen and propionic acid/nitrobenzene (7:3 v/v, 2 mL) were thoroughly mixed in an appropriate 10 mL thick-walled glass vial. The glass vial was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 200 °C for 5 min, under microwave irradiation, with an initial power setting of 250 W.

Procedure for the oxidation of the porphyrinogen under microwave irradiation with MnO_2. The porphyrinogen and 5 equivalents of MnO_2 in 2 mL of 2-methyltetrahydrofuran (2MeTHF) were thoroughly mixed in an appropriate 10 mL thick-walled glass vial. The glass vial was tightly sealed with a Teflon cap and the reaction mixture was stirred and heated at 80 °C for 10 min, under microwave irradiation, with an initial power setting of 250 W.

General procedure for the oxidation of the porphyrinogen under conventional stirring conditions. The porphyrinogen and 5 equivalents of MnO_2 in 25 mL of 2MeTHF were thoroughly mixed in a 50 mL round-bottom flask, and stirred magnetically at room temperature for 2 h. Alternatively, the porphyrinogen and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (11.19 mmol, 2.54 g) in 50 mL of chloroform were thoroughly mixed in a 100 mL round-bottom flask and stirred magnetically at room temperature for 2 h.

General procedure for the oxidation of the porphyrinogen under mechanical activation. A mixture of the porphyrinogen and 5 equivalents of MnO_2 with 0.2 mL of the appropriate solvent, 2MeTHF, water or ethyl acetate, was placed in a stainless-steel grinding jar (10 mL volume) along with two stainless-steel balls (7 mm diameter). The mixture was ground in a Retsch MM400 mill at a frequency of 25 Hz for 30 min.

Preparation of porphyrin under mechanical activation. Pyrrole (2.5 mmol, 0.17 mL) and 4-methoxybenzaldehyde (2.5 mmol) were combined with *p*-toluenesulfonic acid (0.5 mmol, 95.1 mg) and the appropriate oxidant, and placed in the stainless-steel grinding jar (10 mL volume) with two stainless-steel balls (7 mm diameter). The mixture was ground in a Retsch MM400 mill at a frequency of 25 Hz for 75 min.

Porphyrin yields

Porphyrin yields were determined by UV-vis spectroscopy using calibration curves from pure porphyrins in 2MeTHF. Aliquots of the reaction mixture (2 mg) were dissolved in 3 mL of 2MeTHF and diluted until the maximum of the Soret band was observable in the interval of the corresponding calibration curves. The yield of the porphyrin was determined by the intensity of the Soret band measured from the apex to the base of the red edge of the band to avoid the contribution of polypyrromethanes [26]. The Soret band absorption coefficients in 2MeTHF for 5,10,15,20-*tetrakis*-(4-methoxyphenyl)porphyrin, 5,10,15,20-tetraphenylporphyrin, 5,10,15,20-*tetrakis*-(3,4-dimethoxyphenyl)porphyrin, 5,10,15,20-*tetrakis*-(2-chlorophenyl)porphyrin and 5,10,15,20-*tetrakis*-(3,5-dichlorophenyl)porphyrin were $3.1 \times 10^5\ M^{-1} \cdot cm^{-1}$; $1.1 \times 10^5\ M^{-1} \cdot cm^{-1}$; $2.4 \times 10^5\ M^{-1} \cdot cm^{-1}$; $1.0 \times 10^5\ M^{-1} \cdot cm^{-1}$ and $2.1 \times 10^5\ M^{-1} \cdot cm^{-1}$, respectively.

Porphyrin purification was achieved by washing with ethanol and filtration over celite. When necessary, the reaction mixture was dissolved in 2MeTHF, neutralized with triethylamine and then porphyrin purified by flash column chromatography using 2MeTHF/ethyl acetate (10:1 v/v) as eluent.

The ^{1}H-NMR of the obtained compounds are in good agreement with the those previously described.

5,10,15,20-Tetrakis-(4-methoxyphenyl)porphyrin. ^{1}H-NMR (400 Mz, $CDCl_3$), δ (ppm) = δ (ppm) = -2.8 (2H, s), 4.05 (12H, s), 7.28 (8H, d, J = 8.8 Hz), 8.12 (8H, d, J = 8.8 Hz), 8.85 (8H, s) [4].

5,10,15,20-Tetraphenylporphyrin. ^{1}H-NMR (400 Mz, $CDCl_3$), δ (ppm) = -2.82 (2H, s), 7.68 (12H, m), 8.17 (8H, m), 8.80 (8H, s) [29].

5,10,15,20-Tetrakis-(3,4-dimethoxyphenyl)porphyrin. ^{1}H-NMR (400 Mz, $CDCl_3$), δ (ppm) = -2.75 (2H, s), 3.98 (3H, s), 4.17 (3H, s), 7.26 (4H, d, J = 4.5 Hz), 7.74 (4H, d, J = 4.5 Hz), 7.78 (4H, s), 8.90 (8H, s) [29].

5,10,15,20-Tetrakis-(4-chlorophenyl)porphyrin. ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm) = -2.66 (2H, s), 7.62–7.90 (8H, m), 8.12–8.30 (8H, m), 8.70 (8H, s) [55].

5,10,15,20-Tetrakis-(3,5-dichlorophenyl)porphyrin. ^{1}H-NMR (400 Mz, $CDCl_3$), δ (ppm) = -2.80 (2H, s), 7.84 (4H, t, J = 2 Hz), 8.11 (8H, d, J = 2 Hz), 8.89 (8H, s) [56].

CONCLUSION

The use of mechanochemistry for the one-step and two-step synthesis of porphyrins allowed us to obtain *meso*-tetrasubstituted porphyrins in good yields and short reaction times. Using greener solvent and oxidant alternatives such as 2-methyltetrahydrofuran and manganese (IV) oxide it was possible to achieve sustainability scores, from E-factor and EcoScale calculations, of the same order of magnitude obtained using overheated water under microwave irradiation, which is a serious improvement when compared with the approach used in classical methodologies.

Acknowledgments

The authors acknowledge FCT (Fundação para a Ciência e a Tecnologia, I.P.) project UID/QUI/00313/2019 for funding. This work was performed under the project "SunStorage — Harvesting and storage of solar energy," with reference POCI-01-0145-FEDER-016387, funded by the European Regional Development Fund (ERDF), through COMPETE 2020 — Operational Programme for Competitiveness and Internationalization (OPCI), and by national funds, through FCT — Fundação para a Ciência e a Tecnologia I.P. Carla S. Gomes thanks FCT and PhD program CATSUS for PhD grant FCT- PD/BD/135531/2018.

REFERENCES

1. Anastas PT and Warner JC. *Green Chemistry: Theory and Practice*, University Press: Oxford, 1998.
2. EPA; https://www.epa.gov/greenchemistry/basics-green-chemistry 2019.
3. ACS; https://www.acs.org/content/acs/en/greenchemistry/what-is-green-chemistry.html 2019.
4. Kadish KM, Smith KM and Guilard R., Eds. *The Porphyrin Handbook*: *Applications*: *Past, Present and Future*; Academic Press, 1999; Vol. 6.
5. Imran M, Ramzan M, Qureshi AK, Khan MA and Tariq M. *Biosensors* 2018; **8**: 95.
6. Huang H, Song W, Rieffel J and Lovell JF. *Frontiers in Physics* 2015; **3**: 23.
7. Cook LP, Brewer G and Wong-Ng W. *Crystals* 2017; **7**: 223.
8. Alves E, Faustino MAF, Neves MGPMS, Cunha A, Nadais H and Almeida A. *J. Photochem. Photobiol. C* 2015; **22**: 34–57.
9. Kadish KM, Smith KM and Guilard R., Eds. Handbook of Porphyrin Science: With Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine — Volume 4: Phototherapy, Radioimmunotherapy and Imaging; World Scientific, 2010; Vol. 4.
10. Kadish KM, Smith KM and Guilard R., Eds. Handbook of Porphyrin Science: With Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine — Volume 10: Catalysis and Bio–Inspired Systems; World Scientific, 2010.
11. Kadish KM, Smith KM and Guilard R., Eds. Handbook of Porphyrin Science: With Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine — Volume 12: Applications; World Scientific, 2011.
12. Kadish KM, Smith KM and Guilard R., Eds. Handbook of Porphyrin Science: With Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine — Volume 18: Applications and Materials; World Scientific, 2012.
13. Kadish KM, Smith KM and Guilard R., Eds. Handbook of Porphyrin Science: With Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine — Volume 33: Applications — part II; World Scientific, 2014.
14. Kadish KM, Smith KM and Guilard R., Eds. Handbook of Porphyrin Science: With Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine — Volume 39: Towards Diagnostics and Treatment of Cancer; World Scientific, 2016.
15. Biesaga M, Pyrzyriska K and Trojanowicz M. *Talanta* 2000; **51**: 209–224.
16. Li L-L and Diau EW-G. *Chem. Soc. Rev.* 2013; **42**: 291–304.
17. Rothemund P. *J. Am. Chem. Soc.* 1935; **57**: 2010–2011.
18. Rothemund P. *J. Am. Chem. Soc.* 1939; **61**: 2912–2915.
19. Rothemund P and Menotti AR. *J. Am. Chem. Soc.* 1941; **63**: 267–270.
20. Adler AD, Longo FR, Finarelli JD, Goldmacher J, Assour J and Karsakoff L. *J. Org. Chem.* 1967; **32**: 476.
21. Adler AD, Longo FR and Kampas F. *Inorg. Chem.* 1979; **32**: 2443–2445.
22. Lee C-H and Lindsey JS. *Tetrahedron* 1994; **50**: 11427–11440.
23. Lindsey JS, Hsu HC and Schreiman IC. *Tetrahedron Lett.* 1986; **27**: 4969–4970.
24. Lindsey JS, MacCrum KA, Tyhonas JS and Chuang Y-Y. *J. Org. Chem.* 1994; **59**: 579–587.
25. Lindsey JS, Schreiman IC, Hsu HC, Kearney PC and Marguerettaz AM. *J. Org. Chem.* 1987; **52**: 827–833.
26. Lindsey JS and Wagner RW. *J. Org. Chem.* 1989; **54**: 828–836.
27. Rocha Gonsalves AMdA and Pereira MM. *J. Heterocyclic Chem.* 1985; **22**: 931–933.
28. Rocha Gonsalves AMdA, Varejão JMTB and Pereira MM. *J. Heterocyclic Chem.* 1991; **28**: 635–640.
29. Johnstone RAW, Nunes MLPG, Pereira MM, Rocha Gonsalves AMdA and Serra AC. *Heterocycles* 1996; **43**: 1423–1437.

30. Pineiro M. *Curr. Org. Syn.* 2014; **11**: 89–109.
31. Henriques CA, Pinto SMA, Aquino GLB, Pineiro M, Calvete MJF and Pereira MM. *ChemSusChem* 2014; **7**: 2821–2824.
32. Pinto SMA, Henriques CA, Tomé VA, Vinagreiro CS, Calvete MJF, Dabroswski JM, Pineiro M, Arnaut LG and Pereira MM. *J. Porphyrins Phthalocyanines* 2016; **20**: 45–60.
33. Vignaud Y, Granet R and Krausz P. *J. Porphyrins Phthalocyanines* 2016; **10**: 937–941.
34. Nascimento BFO, Rocha Gonsalves AMdA and Pineiro M. *Inorg. Chem. Commun.* 2010; **13**: 395–398.
35. Kajdas C. *Mat. Sci. Appl.* 2015; **6**: 60–67.
36. Huot J and Balema V. In *Material Matters*, 2010; **5**: 112–115.
37. Kaupp G. *Cryst. Eng. Comm.* 2009; **11**: 388–403.
38. Badding JV. *Annu. Rev. Mater. Sci.* 1998; **28**: 631–658.
39. Štrukil V. *Synlett* 2018; **29**: 1281–1288.
40. Do J-L and Friščić T. *ACS Cent. Sci.* 2017; **3**: 13–19.
41. Margetić D and Štrukil V. *Mechanochemical Organic Synthesis*; 1st ed.; Elsevier: Amsterdam, Netherlands, 2016.
42. Shy H, Mackin P, Orvieto AS, Gharbharan D, Peterson GR, Bampos N and Hamilton TD. *Faraday Discuss* 2014; **170**: 59–69.
43. Egorova KS and Ananikov VP. *Organometallics* 2017; **36**: 4071–4090.
44. Remucal CK and Ginder-Vogel M. *Environ. Sci. Processes Impacts* 2014; **16**: 1247–1266.
45. Reddy PN, Reddy VBS and Padmaja P. *Curr. Org. Syn.* 2018; **15**: 815–838.
46. Yusubova MS and Zhdankin VV. *Res. Effic. Tech.* 2015; **1**: 49–67.
47. Bowmaker GA. *Chem. Commun.* 2013; **49**: 334–348.
48. Isoni V, Wong LL, Khoo HH, Halim I and Sharratt P. *Green Chem.* 2016: 6564–6571.
49. Byrne FP, Jin S, Paggiola G, Petchey THM, Clark JH, Farmer TJ, Hunt AJ, McElroy CR and Sherwood J. *Sustain. Chem. Process.* 2016; **4**:**7**: 1–24.
50. Andraos J. *ACS Sustainable Chem. Eng.* 2018; **6**: 3206–3214.
51. Sheldon RA. *ACS Sustainable Chem. Eng.* 2018; **6**: 32–48.
52. Sheldon RA. *Green Chem.* 2017; **19**: 18–43.
53. Van Aken K, Strekowski L and Patiny L. *Beilstein J. Org. Chem.* 2006; **2**: 3.
54. Perrin DD and Armarego WLF. *Purification of Laboratory Chemicals*; 3rd ed.; Pergamon Press: U. K., 1988.
55. Chauhan SMS, Sahoo BB and Srinivas KA. *Synthetic Comm.* 2001; **31**: 33–37.
56. Tamiaki H, Matsumoto N, Unno S, Shinoda S and Tsukube H. *Inorg. Chim. Acta* 2000; **300–302**: 243–249.
57. Nascimento BFO, Pineiro M, Rocha Gonsalves AMdA, Silva MR, Beja AM and Paixão JA. *J. Porphyrins Phthalocyanines* 2007; **11**: 77–84.