NJC

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c5nj02888d

Extensive methodology screening of *meso*-tetrakys-(furan-2-yl)-porphyrin microwave-assisted synthesis†

Federica Bosca,[a] Silvia Tagliapietra,[a] Claudio Garino,[b] Giancarlo Cravotto*[a] and Alessandro Barge*[a]

Received (in Montpellier, France)
18th October 2015,
Accepted 12th January 2016

DOI: 10.1039/c5nj02888d

www.rsc.org/njc

Two novel microwave-assisted synthetic procedures for the preparation of *meso*-tetrakys-(furan-2-yl)-porphyrin are herein reported. A solvent-free method which uses solid supported reagents has been deeply investigated. However, yields were further improved when working in dioxane under heterogeneous catalysis. The reaction rate, yields and impurity profiles have been optimized as a function of all the main parameters: temperature, microwave power, concentration, time and metal ions. The Zn(II) porphyrin complex was obtained in acceptable yields after only 10 min of irradiation. Also included are preliminary studies on Diels–Alder reactions with furanyl derivatives which aim to achieve further porphyrin derivatization.

Introduction

Porphyrins take their name from the Greek word ''porphyra'' which means ''purple''. The peculiarity of these compounds is their intense purple colour which derives from their electronic absorption behaviour. Indeed, their UV-visible spectrum is characterized by a strong single band, from 400 to 460 nm (Soret or B band), in the high energy region and a series of bands, from 500 to 700 nm (Q bands), in the low energy region; metal ion complexation can increase porphyrin stability and modulate their optical properties.

Porphyrins are molecules of great interest because of their huge potential in a number of fields, including material chemistry,[1,2] catalysis,[3,4] nanotechnology,[5] supramolecular chemistry,[6,7] and fluorescent probes furthermore they can be used as agents for photo- and sono-dynamic therapy.[8–13] Porphyrins possess a wide range of biological and pharmacological activities, as they show antitumoral and antioxidant[14,15] properties, and can potentially be applied in the treatment of atherosclerosis, and neurodegenerative diseases and as anti-aging products.[16] Moreover, metalloporphyrins show good antifungal and antiparasitic potential and the presence of a metal ion can modify some physiological properties, such as cytotoxicity and antitumoral activity.

The synthesis of porphyrins that bear differently functionalized dangling arms is still an onerous, but exciting, task despite the number of studies reporting procedures.[17] The main difficulties stem from the intrinsic properties of porphyrins, such as their low solubility and photo-stability, and from the separation, purification and characterization of the final macrocyclic compound. Several methodologies have been studied over the years: the Lindsey method, a two-step one-pot room temperature approach to porphyrinogen macrocycle synthesis and further oxidation to the final porphyrin, was one of the first methods working under gentle conditions. Similar procedures have been developed, firstly by Rothemund and then by Alder–Longo,[17] but have resulted in low product yields. Two step procedures, based on condensation between two pyrrole units and one aryl aldehyde followed by condensation between two dipyrromethane units and two aryl aldehydes, have been separately studied by Lindsey and Dolphin[17] in the hope of increasing reaction yields and synthesizing asymmetric porphyrin derivatives. A completely different way was followed by Vieira *et al.*[18] who used a SiO_2 support to form the macrocyclic backbone. Of all the enabling technologies available in organic synthesis, microwaves (MWs) are the most effective energy source in solvent-free reactions with solid catalysts.[19] Henriques *et al.* have reported an eco-friendly procedure under MW which gives oxidized porphyrin.[20] In general, the preparation of symmetric *meso*-aryl-porphyrin, and in particular the synthesis of *meso*-tetrakis(furan-2-yl)porphyrin (Fig. 1), has shown several drawbacks and limitations. This fact prompted us to investigate alternative eco-friendly protocols under MW irradiation. Moreover, in an attempt to better understand the role of specific experimental variables, we have investigated the influence of several reaction parameters on the reaction behaviour. The parameters considered include reactant concentration, reaction time, reaction temperature,

[a] *Dipartimento di Scienza e Tecnologia del Farmaco, University of Turin, Via P. Giuria 9, 10125 – Torino, Italy. E-mail: giancarlo.cravotto@unito.it alessandro.barge@unito.it; Tel: +39 0116707684, +39 0116707080*

[b] *Dipartimento di Chimica, University of Turin, Via P. Giuria 7, 10125 – Torino, Italy*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5nj02888d

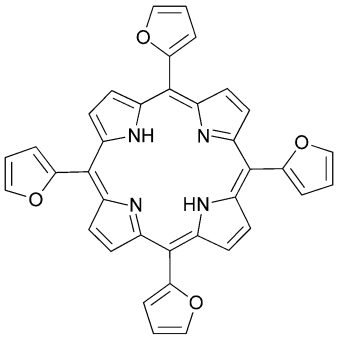


Fig. 1 Structure of *meso*-tetrakys-(furan-2-yl)-porphyrin.

the acid catalyst, the metal ion used and the homogeneous/heterogeneous reaction strategy.

Experimental

Materials and methods

All reagents and solvents were purchased from Sigma-Aldrich (Milan, Italy) and used without further purification. Pyrrole and furfural were distilled under vacuum prior to use. MW-assisted reactions were carried out in a multimode reactor SynthWave (Milestone Srl, Italy) equipped with a full monitoring system of temperature, pressure and power inputs. The CombiFlash RfTeledyne (ISCO) purification system was used to purify all crude reactions on silica gel. Analytical and Preparative HPLC-MS was performed using a Fraction Link autopurification system (Waters) equipped with a 2996 photo-diode array detector and a Micromass ZQ detector (ESCI hybrid ionization source). IR spectra were recorded on a FT-IR Spectrum BXII (Perkin Elmer) with KBr dispersion and diffuse reflectance apparatus DRIFT ACCY. NMR spectra were recorded on an Avance 300 spectrometer (Bruker) operating at 7 T, in deuterated THF. Chemical shifts were referenced according to solvent residual signals. MS spectra were obtained using electrospray ionization (ESI) or by atmospheric pressure chemical ionization (APCI), in positive ion mode, on a Micromass ZQ spectrometer (Waters). UV-Vis absorption and photoemission spectra were recorded in THF solution at ambient temperature. Absorption spectra were acquired on an Agilent Cary 60 UV-Vis spectrometer, while photoemission spectra were obtained on a Horiba Jobin Yvon FluoroLog 3 spectrofluorimeter (Horiba Ltd, Minami-Ku Kyoto, Japan), equipped with a 450 W xenon lamp and a Hamamatsu R928 photomultiplier. The spectral response was corrected for the spectral sensitivity of the photomultiplier and the fluorescence emission recording range was from 500 to 850 nm with slits at 3 nm.

Procedure for the solid-support preparation of *meso*-tetrakys-(furan-2-yl)-porphyrin

Pyrrole (360 μL, 5.2 mmol) and furfural (431 μL, 5.2 mmol) were mixed and stirred at room temperature in a Pyrex test tube of 20 mm in diameter. After 15 min stirring, 620 mg of silica (or alumina; SiO_2/Al_2O_3 in 1 : 1, 1 : 2, 1 : 3 ratio; Al_2O_3 0.1% AcOH) was added to the mixture and the tube was placed in the MW oven cavity. The cavity was then hermetically sealed and the inner pressure increased to 50 bar by nitrogen. The reaction mixture was subsequently subjected to a temperature controlled MW irradiation (max power of 1000 W) for the required time, as described in the discussion section, at 170 °C.

After cooling to room temperature, the compact solid was ground in a mortar and subjected to a first rough separation. The finely grained solid was packed into the top of a flash chromatographic pre-column cartridge containing 4 g of silica gel and eluted using dichloromethane. The isolated fraction was directly oxidized because of the presence of porphyrinogen-like species (HPLC-MS analysis) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). To this purpose, the solvent was removed under vacuum, the residue weighted and re-dissolved in 30 mL of dichloromethane. DDQ (1.5 equivalents calculated considering a residue made up of only the porphyrinogen derivative) was added to the solution and heated to reflux for 4 h. Reaction progress was monitored by HPLC-MS. The mixture was then washed with water (3 × 20 mL), the organic layer was dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The final *meso*-porphyrin derivative was obtained by preparative HPLC-MS separation (more details are described in the ESI†). In all cases the isolated yield was lower than 1%.

General solution protocol for the preparation of *meso*-tetrakys-aryl-porphyrins

A solution of pyrrole and aryl-aldehyde in dioxane (12.5 mL, concentration of both reagents from 1 M to 0.1 M) was placed in a Pyrex test tube of 20 mm in diameter and stirred for 15 min at room temperature. Amberlyst 15 (2 mg), a strongly acidic resin, was added to the mixture and immediately subjected to a temperature controlled MW irradiation (max power of 1000 W), at 50 bar (air was not removed before increasing pressure with N_2), for variable reaction temperatures and times, as previously described. The catalyst was filtered off and washed with dichloromethane. The solvent was removed under reduced pressure and the residue was roughly purified by isocratic flash chromatography (silica, dichloromethane). The HPLC-MS analyses of the isolated fraction confirmed the presence of the final *meso*-porphyrin which was directly purified by preparative HPLC-MS.

HPLC separation methods

HPLC-MS analyses were carried out on a Waters SunFire (4.6 × 150, 5 μm) C18 column, using 0.1% trifluoroacetic acid (TFA) aqueous solution (A) and 0.1% TFA in methanol (B) as eluents. The flow rate was 1 mL min^{-1} and gradient timetables were as follows.

Method 1 (min, B%): 0, 50%; 7.50, 50%; 22.50, 100%; 32.50, 100%.

The product purity was calculated as the area ratio at 430 nm and MS TIC traces.

Method 2 (min, B%): 0, 65%; 15.00, 65%; 27.50, 100%; 42.50, 100%.

The product purity was calculated as the area ratio at 428 nm and MS TIC traces.

Method 3 (min, B%): 0, 50%; 7.50, 50%; 25.00, 100%; 35.00, 100%.

Preparative HPLC separations were carried out using a Phenomenex Gemini C18 (21.2 × 100, 5 μm, 110 Å) column, using water (A) and methanol (B) as eluents. The flow rate was 20 mL min^{-1} and gradient timetables were as follows.

Method 4 (min, B%): 0, 70%; 2.80, 70%; 4.30, 100%; 8.50, 100%.

Method 5 (min, B%): 0, 70%; 4.30, 100%; 7.50, 100%.

Method 6 (min, B%): 0, 80%; 7.00, 100%; 10.00, 100%.

meso-Tetrakys-(furan-2-yl)-porphyrin[21] (1)

meso-Tetrakys-(furan-2-yl)-porphyrin was obtained according to the solid-support procedure with yields lower than 1%. The solution protocol was also used and gave better results. A green solid was obtained, at yields up to 3.8%, after HPLC-MS purification (method 4).

HPLC-MS: (method 1) Rt = 14.71 min, purity 80%; ^{1}H NMR (300 MHz, THF-d_8, δ 1.73 ppm) δ 9.18 (s, 8H), 8.25 (br s, 4H), 7.39 (br s, 4H), 7.08 (br s, 4H), −2.55 (s, 2H); APCI-MS$^+$: m/z calcd for $C_{36}H_{22}N_4O_4$, 574.16; found 575.48 [M + H$^+$]; λ_{max} (THF) = 430 nm.

Zn(II)-*meso*-tetrakys-(furan-2-yl)-porphyrin (2)

The general solution protocol was followed and freshly distilled pyrrole (0.4 M in dioxane) and furfural (0.4 M in dioxane) were used, while $Zn(AcO)_2$ was added to give a final concentration of 0.13 M, at 140 °C for 10 min. Amberlyst 15 (2 mg), a strongly acidic resin, was added to the mixture. After purification (HPLC-MS method 5), the desired product was recovered as a violet-blue solid (yield 5.2%).

HPLC-MS: (method 2) Rt = 31.22 min, purity 83%; IR (KBr) 3122, 2801, 1676, 1200, 1144, 797, 724 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ 7.26 ppm) δ 8.60 (s, 8H), 8.37 (s, 4H), 7.82 (d, J = 2.94 Hz, 4H), 7.20 (s, 4H); APCI-MS$^+$: m/z calcd for $C_{36}H_{2o}N_4O_4Zn$, 636.08; found 637.60 [M + H$^+$]; λ_{max} (from HPLC-MS analysis, MeOH–TFA, H_2O–TFA) = 428, 564, 610 nm.

meso-Tetrakys-(phenyl)-porphyrin[22] (3)

The general solution protocol was followed and freshly distilled pyrrole (0.1 M in dioxane) and benzaldehyde (0.1 M in dioxane) were used at 170 °C for 20 min. Amberlyst 15 (2 mg), a strongly acidic resin, was added to the mixture. After purification, the desired product was recovered as a brownish solid (yield 5%).

^{1}H NMR (300 MHz, $CDCl_3$, δ 7.26 ppm) δ 8.61 (s, 4H), 8.57 (s, 8H), 7.98 (m, 16H); APCI-MS$^+$: m/z calcd for $C_{44}H_{30}N_4$, 614.25; found 615.40 [M + H$^+$]; λ_{max} (from HPLC-MS analysis, MeOH–TFA, H_2O–TFA) = 433 nm.

meso-Tetrakys-(4-nitrophenyl)-porphyrin[23] (4)

The general solution protocol was followed using freshly distilled pyrrole (0.1 M in dioxane) and 4-nitrobenzaldehyde (0.1 M in dioxane), at 170 °C for 20 min. Amberlyst 15 (2 mg), a strongly acidic resin, was added to the mixture. After purification, the desired product was recovered as a solid (yield 2%).

^{1}H NMR (300 MHz, $CDCl_3$, δ 7.26 ppm) δ 8.93 (d, J = 8.31 Hz, 8H), 8.79 (d, J = 8.31 Hz, 8H) 8.63 (s, 8H); APCI-MS$^+$: m/z calcd for $C_{44}H_{26}N_8O_8$, 794.19; found 795.26 [M + H$^+$]; λ_{max} (from HPLC-MS analysis, MeOH–TFA, H_2O–TFA) = 418 nm.

meso-Tetrakys-(4-methoxyphenyl)-porphyrin[24] (5)

The general solution protocol was followed using freshly distilled pyrrole (0.1 M in dioxane) and 4-methoxybenzaldehyde (0.1 M in dioxane), at 170 °C for 20 min. Amberlyst 15 (2 mg), a strongly acidic resin, was added to the mixture. After purification, the desired product was recovered as a solid (yield 3%).

^{1}H NMR (300 MHz, THF-d_8, δ 1.73 ppm) δ 8.84 (s, 8H), 8.11 (m, 8H) 7.34 (m, 8H), 1.29 (s, 12H); APCI-MS$^+$: m/z calcd for $C_{48}H_{38}N_4O_4$, 734.29; found 735.39 [M + H$^+$]; λ_{max} (from HPLC-MS analysis, MeOH–TFA, H_2O–TFA) = 447 nm.

General procedure for the Diels–Alder reaction

Zn(II)-*meso*-tetrakys-(furan-2-yl)-porphyrin (7 mg, 0.011 mmol) and ethyl crotonate (11 μL, 0.088 mmol) were dissolved in THF (4 mL) and anhydrous $ZnCl_2$ (3 mg) was added as the catalyst. The mixture was heated to reflux for 2 days. The reaction was monitored by HPLC-MS which was set up to detect the mono-Diels–Alder derivative (**6**) and the disappearance of the starting materials. The solvent was removed and the desired product was isolated by preparative HPLC-MS (method 6) in a 30% yield.

HPLC-MS: (method 3) Rt = 27.39 min; ^{1}H NMR (300 MHz, $CDCl_3$, δ 7.26 ppm) δ 7.52–7.33 (m, 8H), 7.12–703 (br-m, 3H) 7.03–6.87 (br-m, 6H), 6.08 (m, 2H), 5.38 (m, 1H), 4.25 (m, 2H), 3.85 (br-m, 2H), 2.81 (m, 3H), 2.02 (t, J = 4.30 Hz, 3H); HRMS (APCI$^+$): m/z calcd for $C_{42}H_{30}N_4O_6Zn$, 750.1457; found 751.1540 [M + H]$^+$; λ_{max} (from HPLC-MS analysis, MeOH–TFA, H_2O–TFA) = 426 nm.

Results and discussion

Structure design

Specific porphyrin applications require their conjugation or grafting to a variety of substrates, such as nanoparticles, dendrimers, polymers, fullerene, graphene or carbon nanotubes, as well as a variety of small molecules. Porphyrin structural modification, *via* the insertion of one or more specific dangling arms, is therefore an important task. The synthetic target often involves the protection and deprotection of many functional groups in order to display the selected functionality. The introduction of a reactive group which is orthogonal to the most common functional groups on the porphyrin surface may make the conjugation of a further dangling arm easier and furan may be a useful reactive group in Diels–Alder reactions[25] or as a precursor to an aldehyde carbonyl. For these reasons, we have considered a porphyrin bearing four exposed furanyl moieties on its surface (Fig. 1). This structure could be applied in the synthesis of more complicated porphyrins or used for its hydrophobicity and luminescence behaviour in a number of application fields. So far, the reported syntheses of this particular porphyrin

did not give satisfactory yields (1–2.1%),[21,22,26] and higher yields (10%) could be achieved with a time consuming (5 min + overnight stirring) and multi-step procedure.[21] Moreover, none of the published procedures report the purity of the isolated porphyrin. This study explores the preparation of symmetrical *meso*-tetrakys-(furan-2-yl)-porphyrin by the acid catalysed condensation of four furfural and four pyrrole derivatives. Two different routes have been investigated. They are both in the heterogeneous phase, one over a solid support and the other in solution (Scheme 1). In the former, the solid support also plays the role of an acid catalyst, while in the solution protocol the catalyst is an acidic polymeric resin. From both protocols, the desired porphyrin was obtained after only 10 min of MW irradiation under pressure. Fast HPLC purification (8.5 min long) gave *meso*-tetrakys-(furan-2-yl)-porphyrin with a purity of 80%.

Furthermore, preliminary investigations on the photophysical properties of *meso*-tetrakys-(furan-2-yl)-porphyrin and Zn(II)-*meso*-tetrakys-(furan-2-yl)-porphyrin were carried out.

Solid-support synthesis

Six different solid supports, silica gel,[20] neutral alumina, a mixture of the two (SiO_2/Al_2O_3 = 1 : 1; 1 : 2; 1 : 3) and acetic acid (0.1% w/w) on alumina, have been investigated. All reactions were carried out under the same conditions: MW irradiation, 30 min, 170 °C, support/pyrrole/aldehyde ratio = 119/1/1 (w/mol/mol). *meso*-Tetrakys-(furan-2-yl)-porphyrin was obtained after the oxidation of the crude material with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Porphyrinogen, partially oxidized porphyrinogen and porphyrin were detected by HPLC-MS analysis in all reactions before the last oxidative step. The ratio between porphyrin and the sum of reduced species depends on the support used; it was 0.6 with silica gel and decreased to 0.3 in the case of alumina. When silica and alumina were mixed, the ratio was markedly lower than with neat alumina (namely 0.1 for the two higher SiO_2/Al_2O_3 ratio and 0.2 for SiO_2/Al_2O_3 = 1 : 3, Fig. 2). The ratio reaches the value of 0.9 in acetic acid adulterated alumina. If the various supports have an effect on the distribution of porphyrin like species, it does not affect the reaction yield. Indeed, preparative HPLC-MS purification of the final compound always gave an overall yield of about 1% after DDQ oxidation. This behaviour (Fig. 2) may be explained by the acidity of the support and its morphology after heating. Silica gel is more acidic than neutral alumina, but it shows a more vitreous morphology after heating than alumina which has a spongy appearance. Both the acidity and sponginess are lost when the two substances are combined. Optimal conditions are reached enhancing the soft and springy nature of the support by acidity. This is the case of acetic acid tainted alumina. Silica gel is unfavourable to oxygen diffusion into the mass, whereas neutral alumina is less acidic but can boast of the morphology that facilitates oxygen diffusion and thus porphyrin formation.

Another interesting aspect to study, beside the formation of porphyrin/porphyrinogen like species, is the impurity profile. The impurity amount and distribution were evaluated by HPLC analysis at 254 nm. This wavelength does not correspond to the maximum absorption value for porphyrin, but it is a good compromise to monitor the signals of porphyrin-like species and impurities alike (Fig. 3).

HPLC profiles were conveniently divided into three regions (see Fig. S9 in the ESI†) in order to rationalize the HPLC data and extract some general information on impurities. The area with a retention time higher than porphyrin like species (Rt2), the area which includes porphyrin-like species and the area with lower retention times than porphyrin (Rt1). The number of impurity peaks and the distribution profile are different when the solid support composition changes from silica to alumina. The Rt2 impurity peak area decreases when the amount of alumina in the solid support is increased, whereas the opposite is observed for Rt1 impurities. Interestingly, the chromatographic profile is characterized by a very clear Rt2 region when acid doped alumina is used.

The impurities could reasonably be ascribed to different kinds of variably sized linear condensation products on the basis of these experimental data. This impurity distribution may be related to the different types of interactions that exist between the reagents/products, the solid supports and oxygen.

Finally, the reaction time was also investigated and we can conclude that 20 min is the optimal value to minimize the amount of both starting materials and side-products in the final reaction mixture.

In summary, we can assert that, under these reaction conditions (MW irradiation, 20 min, 170 °C, support/pyrrol/aldehyde ratio = 119/1/1 g/mol/mol) the best solid support, in terms of porphyrin/porphyrinogen like ratio and impurity quantity, is 0.1% acetic acid treated alumina.

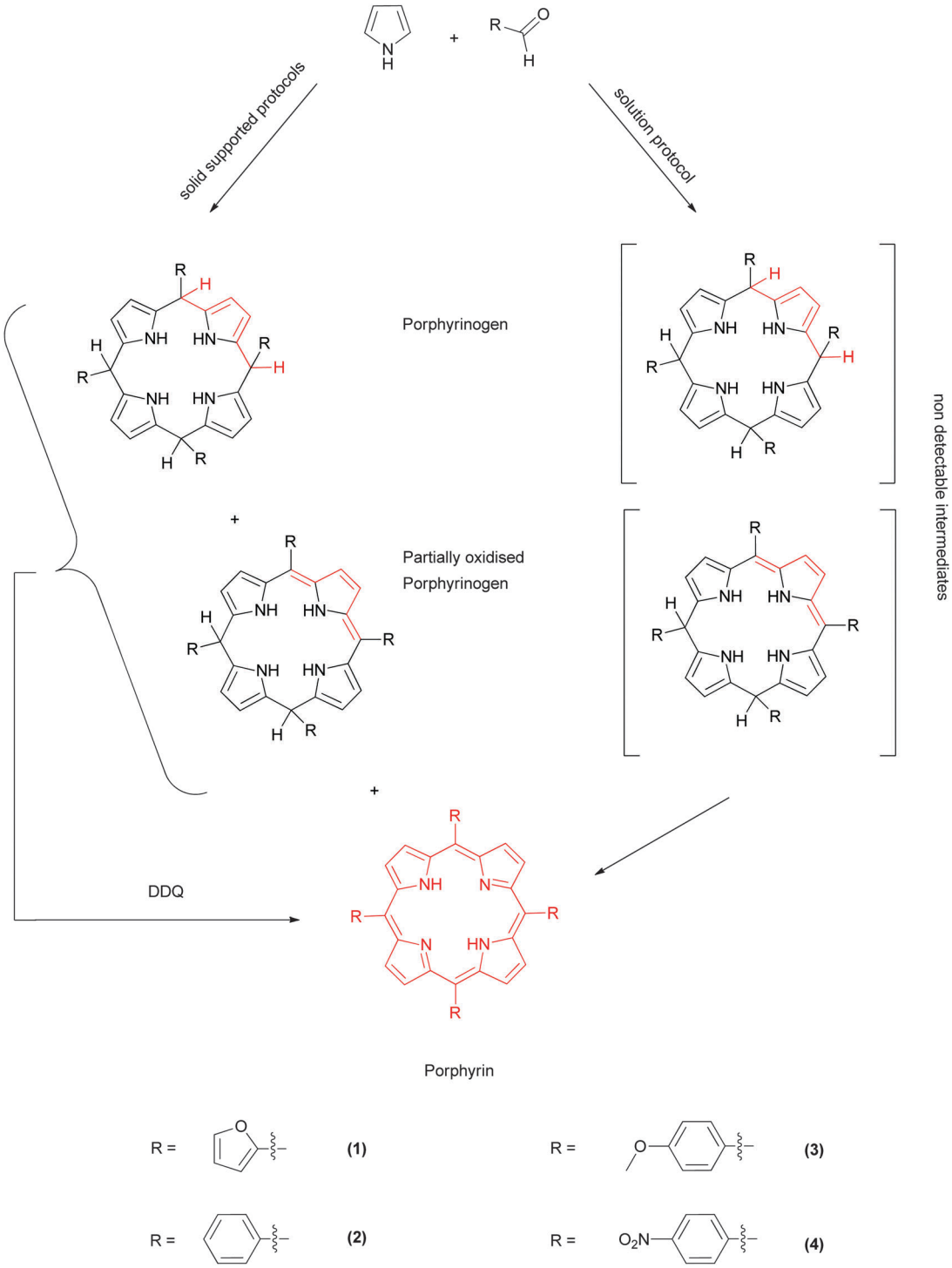
In-solution synthesis

Solid support reaction optimization did not give gratifying results in terms of yield. Therefore we decided to try a new approach which combines some aspects of solid-support synthesis with others from solution synthesis. We took the heterogeneous acid catalyst and MW irradiation from supported syntheses and all the advantages of a homogeneous reaction medium from solution synthesis.

Surprisingly, the in-solution synthesis carried out directly gave *meso*-tetrakys-(furan-2-yl)-porphyrin in higher yield values. This major improvement in aldehyde-pyrrole condensation reduces the required synthetic steps, as the intermediate species is immediately oxidised. This phenomenon may be due to in-solution oxygen diffusion which is enhanced by the high pressure conditions set for all the experiments performed.

Catalyst

All in-solution reactions were carried out using Amberlyst 15,[27] a strongly acidic cation exchanger resin, as the solid acid catalyst. The resin was activated by washing with HCl 2 M and dried before each use. Preliminary catalyst amount screening showed that the reaction yield and the impurity profile did not change with the catalyst amount, so we decided to use a fixed amount of 2 mg.



Scheme 1 Two different protocols for *meso*-aryl-porphyrin synthesis.

Temperature

Initially, solid-support conditions were directly transferred to the solution protocol. The temperature was set to 170 °C, the reaction time to 20 min and the reagent concentration was fixed at 1 M. The boiling point of dioxane is lower than the reaction temperature, hence a pressurized MW reactor was selected to carry out solution reactions and the pressure (nitrogen atmosphere) was set to 50 bar. The HPLC-MS analysis of the crude product showed the absence of all porphyrinogen like species, because residual oxygen present is sufficient for the oxidizing process. Furthermore, the peak area for the 254 nm trace in the Rt2 region is close to zero. The overall yields were again lower than 1% after the final purification by preparative HPLC-MS. No improvement was observed, either in

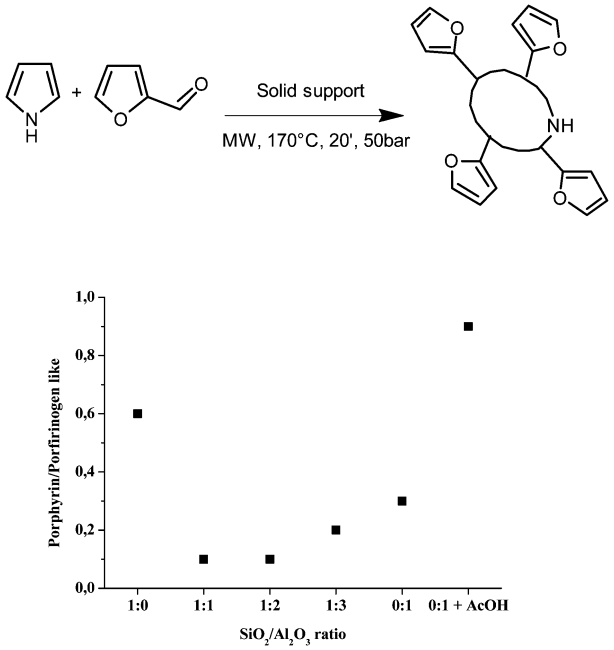


Fig. 2 Porphyrin/porphyrinogen like species ratio *vs.* solid support composition.

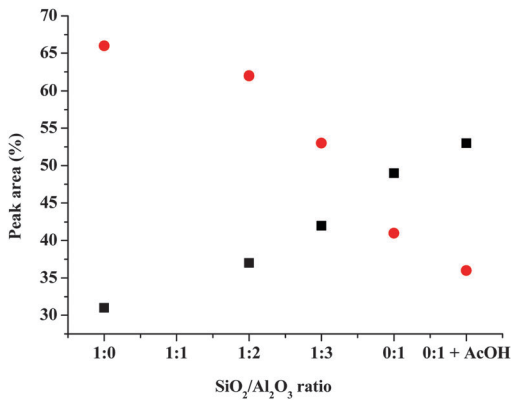


Fig. 3 Impurity peak area (% calculated at 254 nm) in the Rt1 region (black square) and the Rt2 region (red circle) *vs.* solid support composition.

terms of yield or impurity profile, when the reaction temperature was reduced to 140 °C and all the other conditions were maintained constant.

Concentration

It is well known that cyclization reactions take advantage of high dilution conditions. Hence, this *meso*-tetrakys-(furan-2-yl)-porphyrin synthesis was studied at four different reactant concentrations (from 1 to 0.1 M) at 170 °C and 140 °C. As depicted in Fig. 4, the reaction yield, calculated as the isolated product (by preparative HPLC-MS), increases when reactant concentrations decrease, giving a maximum value of 4% at 0.1 M and 170 °C. Further dilutions do not improve the reaction yield, since the extremely low amount of reagent contained in the low volume tubes employed does not allow for the yield to be correctly evaluated.

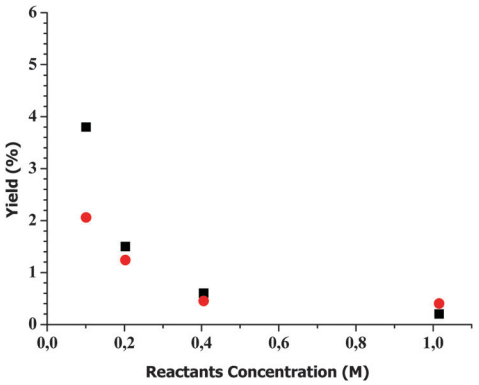


Fig. 4 Porphyrin yield *vs.* reactant concentration. MW enhanced reactions carried out in dioxane, 50 bar (N_2), 20 min, 140 °C (red circle) and 170 °C (black square).

Yield behaviour was very similar at the two different temperatures. Yield does not depend on temperature (between 140 and 170 °C) at higher concentrations, but an improvement is observed in reactions carried out at 170 °C at the lower concentration.

Time

Our attention moved to reaction time at a single temperature value (140 °C). Four different reaction times (10, 20, 40, and 60 min) were considered for two different reactant concentrations (0.1 and 0.2 M). The yield increases incrementing the reaction time from 10 to 40 min, with the same trend for both concentration values. After this maximum, the curve decreases rapidly to very low yields (Fig. 5). Simultaneously, the impurity amount increases after 40 min as observed in HPLC-MS profiles.

Metal template synthesis

A further improvement in the synthetic protocol was achieved by exploiting the template ability of the Zn(II) ion. The cyclocondensation of four aldehydes and four pyrroles is a favourable process in the presence of zinc acetate.

In contrast to previously observed results (Fig. 4), the cyclization reaction, in the presence of Zn(II) ions, is less favourable at

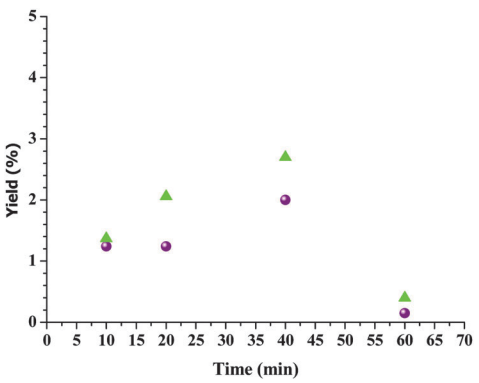


Fig. 5 Porphyrin yield *vs.* reaction time (min). MW enhanced reactions carried out in dioxane, 50 bar (N_2), 140 °C, 0.1 M (green triangle) and 0.2 M (purple sphere).

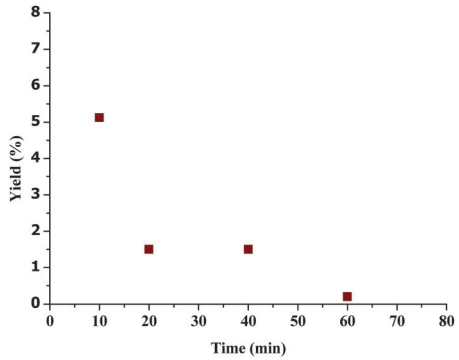


Fig. 6 Zn-porphyrin yield *vs.* reaction time (min). MW enhanced reactions carried out in dioxane in the presence of $Zn(AcO)_2$ (0.13 M), 50 bar (N_2), 140 °C, reactant concentration 0.4 M.

170 °C than at 140 °C. The trend depicted in Fig. 6 shows a faster reaction rate with a maximum yield of 5% after only 10 min. The role of Zn(II) is not only related to the synthetic procedure (higher yield, shorter time, and one step reaction), but also to the stability of these delicate and frail compounds which is improved by the formation of the metal complex.

Analogous results, in terms of kinetics, were observed with different metals (Cu(II), Fe(III), and Mn(II)) but markedly lower reaction yields were obtained.

Preliminary investigation on the photo-physical properties of *meso*-tetrakys-(furan-2-yl)-porphyrin and Zn(II)-*meso*-tetrakys-(furan-2-yl)-porphyrin

As previously reported by Santosh and Ravikanth,[28] replacing the six-membered aryl groups with the five-membered furyl groups at the *meso*-positions considerably alters porphyrin electronic properties. The absorption spectrum of *meso*-tetrakys-(furan-2-yl)-porphyrin, recorded in toluene, shows three clear Q-bands (526, 571, 605 (shoulder), and 670 nm) and one Soret band (433 nm). Thus, the number of Q-bands is reduced from four to three and the Soret and Q-bands are red shifted and broadened as compared to tetrakys-arylporphyrins. In a similar way, the emission spectrum of *meso*-tetrakys-(furan-2-yl)-porphyrin displays one band (697 nm) that is red shifted with regard to the two emission bands of *meso*-tetrakys-arylporphyrins.

Upon metalloporphyrin formation,[29] the Q bands in the visible region collapse into essentially two bands (565 and 615 nm) due to the higher D_{4h} symmetry, while the Soret band is not affected (see ESI,† Fig. S5). Upon Soret band excitation, Zn(II)-*meso*-tetrakys-(furan-2-yl)-porphyrin displays one emission band at 655 nm that is blue shifted as compared to the emission band of the free base.

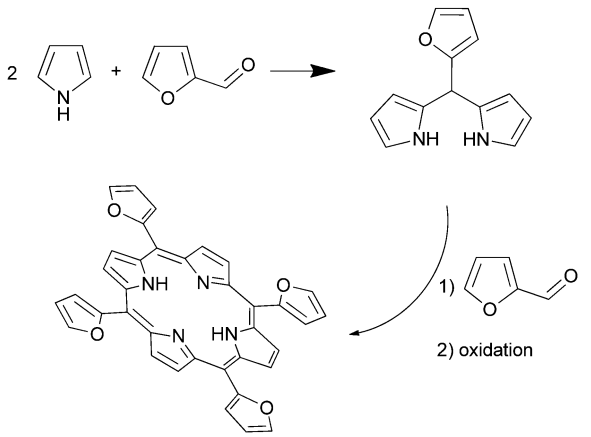
Preliminary study of different *meso* substitutions

In order to fully exploit the peculiarity of the solution procedure (170 °C, 50 bar, 40 min, 0.1 M), three other aldehydes were considered; benzaldehyde, *p*-nitro-benzaldehyde and *p*-methoxy-benzaldehyde. Similarly to the previous procedures, HPLC-MS profiles do not show the presence of porphyrinogen like species, but only the desired final porphyrins. The impurity distribution and concentration are similar to those observed for *meso*-tetrakys-(furan-2-yl)-porphyrin, but the isolated yields are slightly lower. With these three aldehydes, the purification of cyclocondensation products was more difficult, affecting negatively the overall yield.

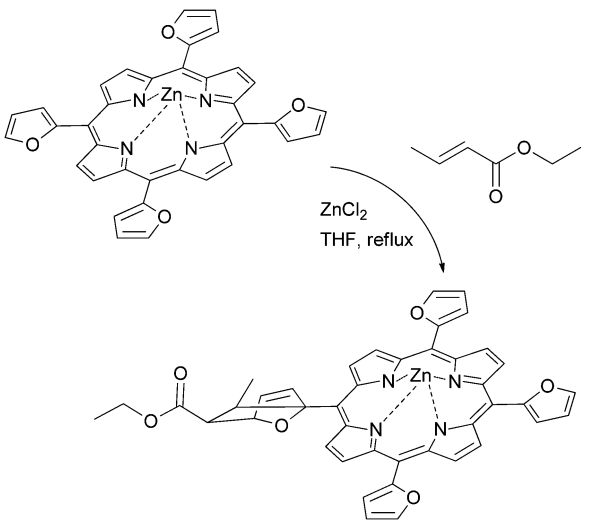
Preliminary study of a two step procedure (MacDonald 2 + 2 method[24])

As described in the literature, the MacDonald 2 + 2 method is used to synthesize *meso* substituted porphyrins, and especially for obtaining asymmetric derivatives. This method consists of a first step which generates the dipyrromethane intermediate, a further condensation with an aldehyde to give the *meso*-substituted porphyrinogen and the final oxidation to *meso*-porphyrin (Scheme 2).

In theory, the procedure described in this paper could also be employed to obtain the dipyrromethane intermediate, if the ratio between pyrrole and aryl aldehyde is set at 2 : 1. This first preliminary study leads us to conclude that the intermediate is converted to porphyrinogen and then immediately to porphyrin. This last oxidation step involves ring aromatization and so moves the reaction to *meso*-tetra-aryl-porphyrin formation.



Scheme 2 Schematic representation of the MacDonald 2 + 2 procedure.



Scheme 3 Schematic representation of porphyrin derivatization using the Diels–Alder reaction.

Indeed, dipyrromethane was not present in the chromatogram and only the final compound was detected in remarkable amounts.

New application paths of *meso*-tetrakys-(furan-2-yl)-porphyrin

A Diels–Alder reaction between ethyl crotonate and Zn(II)-*meso*-tetrakys-(furan-2-yl)-porphyrin was investigated as a means to evaluate the possibility of further functionalizing *meso*-tetrakys-(furan-2-yl)-porphyrin (Scheme 3). The Zn(II) porphyrin complex was chosen because of its higher stability as compared to the free metal. Following the reaction by HPLC-MS analysis, it was possible to observe the disappearance of the starting material and the sole formation of the mono derivate of the Diels–Alder cycloaddition with a yield of about 34% (by HPLC-MS).

Although this reaction still requires optimisation, a wide portfolio of multifunctional porphyrin derivatives is in the offing.

Conclusions

Two novel MW-assisted synthetic protocols for the preparation of *meso*-tetrakys-(furan-2-yl)-porphyrin have been investigated. The solvent-free method was carried out using solid supported reagents to give moderate yields and required an oxidation step. Better results were achieved in dioxane under heterogeneous catalysis.

The few published synthetic procedures entail time-consuming multi-steps and laborious purifications, moreover they only refer to the reaction yield omitting product purity. The advantages of the reported procedure are the short reaction time (10–20 min), the one step conversion (no further porphyrinogen oxidation is required) and the efficient, fast and relatively easy purification of crude porphyrin. The presence of $Zn(AcO)_2$ in the reaction mixture increases the reaction rate giving the corresponding metallo-porphyrin. Furanyl moieties on the porphyrin surface were functionalized by the Diels–Alder reaction.

In conclusion, these promising results and the fast synthesis of *meso*-tetrakys-(furan-2-yl)-porphyrins may pave the way for their decoration and grafting onto nanomaterials.

Acknowledgements

This research was supported by MIUR (fondi ricerca locale 2013) and Associazione Italiana per la Ricerca sul Cancro (MFAG 2012 and MFAG-13048).

Notes and references

1 Y. Xu, Z. Liu, X. Zhang, Y. Wang, J. Tian, Y. Huang, Y. Ma, X. Zhang and Y. Chen, *Adv. Mater.*, 2009, **21**(12), 1275.
2 C. D. Natale, D. Monti and R. Paolesse, *Mater. Today*, 2010, **13**(7-8), 46.
3 B. Meunier, *Chem. Rev.*, 1992, **92**(6), 1411.
4 B. Gao, Y. Chen and Q. Lei, *J. Inclusion Phenom. Macrocyclic Chem.*, 2012, **74**(1–4), 455.
5 (*a*) D. Kim and A. Osuka, *Acc. Chem. Res.*, 2004, **37**, 735; (*b*) P. D. W. Boyd and C. A. Reed, *Acc. Chem. Res.*, 2005, **38**, 235; (*c*) T. S. Balaban, *Acc. Chem. Res.*, 2005, **38**, 612.
6 M. Wathier and M. W. Grinstaff, *J. Am. Chem. Soc.*, 2008, **130**(30), 9648.
7 C. M. Drain, A. Varotto and I. Radivojevic, *Chem. Rev.*, 2009, **109**(5), 1630.
8 H. Chen, X. Zhou, Y. Gao, B. Zheng, F. Tang and J. Huang, *Drug Discovery Today*, 2014, **19**(4), 502.
9 İ. Rosenthal, J. Z. Sostaric and P. Riesz, *Ultrason. Sonochem.*, 2004, **11**, 349.
10 E. S. Nyman and P. H. Hynninen, *J. Photochem. Photobiol., B*, 2004, **73**, 1.
11 S. Hilderbrand and R. Weissleder, *Curr. Opin. Chem. Biol.*, 2010, **14**, 71.
12 W. W. L. Chin, W. K. O. Lau, R. Bhuvaneswari, P. W. S. Heng and M. Olivo, *Cancer Lett.*, 2007, **245**, 127.
13 K. Berg, P. K. Selbo, A. Weyergang, A. Dietze, L. Pransmickaite and A. Bonsted, *J. Microsc.*, 2005, **218**, 133.
14 N. A. Antonova, V. P. Osipova, M. N. Kolyada, N. O. Movchan, E. R. Milaeva and Y. T. Pimenov, *Macroheterocycles*, 2010, **3**(2–3), 139.
15 M. Yuasa, K. Oyaizu, H. Murata, Y. Sahara, T. Hatsugai and A. Ogata, *J. Oleo Sci.*, 2007, **56**(2), 87.
16 K. J. Barnham, C. L. Masters and A. I. Bush, *Nat. Rev. Drug Discovery*, 2004, **3**, 205.
17 (*a*) J. S. Lindsey, Synthesis of *meso*-Substituted Porphyrins, in *The Porphyrin Handbook*, ed. K. M. Kanish, K. M. Smith and R. Guilard, Academic Press, San Diego, 2000, ch. 2, p. 45; (*b*) D. Holten, D. F. Bocian and J. S. Lindsey, *Acc. Chem. Res.*, 2002, **35**, 57; (*c*) A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour and L. Korsakoff, *J. Org. Chem.*, 1967, **32**(2), 476.
18 L. F. Vieira Ferreira, D. P. Ferreira, A. S. Oliveira, R. Boscencu, R. Socoteanu, M. Ilie, C. Constantin and M. Neagu, *Dyes Pigm.*, 2012, **95**, 296.
19 D. Garella, A. Barge, D. Upadhyaya, Z. Rodríguez, G. Palmisano and G. Cravotto, *Synth. Commun.*, 2010, **40**, 120.
20 (*a*) C. A. Henriques, S. M. A. Pinto, G. L. B. Aquino, M. Pineiro, M. J. F. Calvete and M. M. Pereira, *ChemSusChem*, 2014, **7**, 2821; (*b*) M. Pineiro, *Curr. Org. Chem.*, 2014, **11**, 89.
21 R. P. Bonar-Law, *J. Org. Chem.*, 1996, **61**, 3623.
22 J. S. Lindsey, I. C. Schreiman, H. C. Hsu, P. C. Kearney and A. M. Marguerettaz, *J. Org. Chem.*, 1987, **52**, 827.
23 M. Seredyuk, E. Gumienna-Kontecka, A. Brzuszkiewicz, T. S. Iskenderov and V. A. Kalibabchuk, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2014, **70**, o1147.
24 G. P. Arsenault, E. Bullock and S. F. MacDonald, *J. Chem. Soc.*, 1960, **82**, 4384.
25 (*a*) *The Diels–Alder Reaction: selected protical methods*, ed. F. Fringuelli and A. Taticchi, J Wiley & Sons, West Sussex, England, 2002; (*b*) C. O. Kappe, S. S. Murphrees and A. Padwa, *Tetrahedron*, 1997, **53**(42), 14179.
26 A. Treibs and N. Aberle, *Liebigs Ann. Chem.*, 1968, **718**, 183–207.
27 R. Pal, T. Sarkar and S. Khasnobis, *ARKIVOC*, 2012, 570.
28 (*a*) G. Santosh and M. Ravikanth, *Tetrahedron*, 2007, **63**, 7833; (*b*) A. Ghosh, S. M. Mobin, R. Fröhlich, R. J. Butcher, D. K. Maity and M. Ravikanth, *Inorg. Chem.*, 2010, **49**, 8287.
29 C.-K. Tai, W.-H. Chuang and B.-C. Wang, *J. Lumin.*, 2013, **142**, 8.

