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Cite this: DOI: 10.1039/d5qo01267h

A versatile and practical one-pot strategy for a greener, waste-minimized synthesis of aryloxy- and alkyloxy-substituted metallophthalocyanines *via* tandem S_NAr-cyclotetramerization

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Received 6th September 2025,
Accepted 19th December 2025

DOI: 10.1039/d5qo01267h

rsc.li/frontiers-organic

Phthalocyanines represent molecules of considerable scientific interest, yet their synthesis remains challenging, particularly under environmentally sustainable conditions. Due to the increasingly urgent need for developing sustainable and efficient synthetic methodologies, we report a general, practical, and potentially scalable one-pot procedure for the synthesis of aryloxy- and alkyloxy-substituted metallophthalocyanines. This method integrates a nucleophilic aromatic substitution on the phthalonitrile precursors with a subsequent metal-templated cyclotetramerization, all within a single reaction vessel, thus eliminating the need for intermediate isolation and minimizing solvent and reagent consumption. The protocol is compatible with a wide variety of phenols and alcohols, including sterically hindered or electron-withdrawing substituents, and can be performed using standard laboratory glassware and conventional heating, suggesting its practical suitability for scale-up. Selected phthalocyanines were obtained with up to nearly fourfold higher yields compared to literature-reported two-step procedures (*e.g.*, 27% *vs.* 7% for tetra(3,5-bis(trifluoromethyl)phenoxy)-zinc-phthalocyanine) and were characterized by UV-vis, IR, NMR spectroscopy, and mass spectrometry. Environmental efficiency, assessed through *E*-factor calculations, achieves over 90% reduction in waste generation relative to literature-reported two-step procedures, arising from the combined effect of the intrinsic advantages of the one-pot design with solvent recovery and simplified purification, thus demonstrating the benefits of our proposed strategy in terms of environmental sustainability, operational simplicity, waste reduction and broader applicability to green phthalocyanine synthesis.

Introduction

In the last few decades, increasing environmental and economic awareness has driven organic synthesis toward more sustainable practices in the preparation of organic materials, prioritizing efficiency, safety, and waste minimization.[1] As a result, green chemistry, whose principles focus on these key aspects, now plays a central role in modern synthetic design.[2] In this context, solvents and separating agents employed in the purification steps of a synthesis are major contributors to chemical waste, significantly affecting the overall environmental footprint of a chemical reaction. Pot-economical approaches, in which multiple synthetic transformations are carried out in a single reaction vessel without isolating and/or purifying the intermediates, have emerged as powerful solutions. Such strategies not only improve efficiency while minimizing solvent and reagent consumption, but also provide safer work conditions, by decreasing labour and reducing the chemical handling time, offering a more practical and sustainable methodology than conventional procedures.[3,4]

Phthalocyanines are organic dyes with considerable scientific interest and applicability, yet their synthesis remains notoriously challenging, particularly from a sustainable perspective. From a structural point of view, their extended 18-π conjugated electron system and a central cavity capable of hosting a wide variety of metal ions endow them with peculiar physical and chemical properties, such as high chemical, thermal, and light stability, intense coloration, and high inertness. Furthermore, functionalizing the peripheral positions of the phthalocyanine core with a plethora of different chemical groups enables fine tuning of such properties for different advanced applications,

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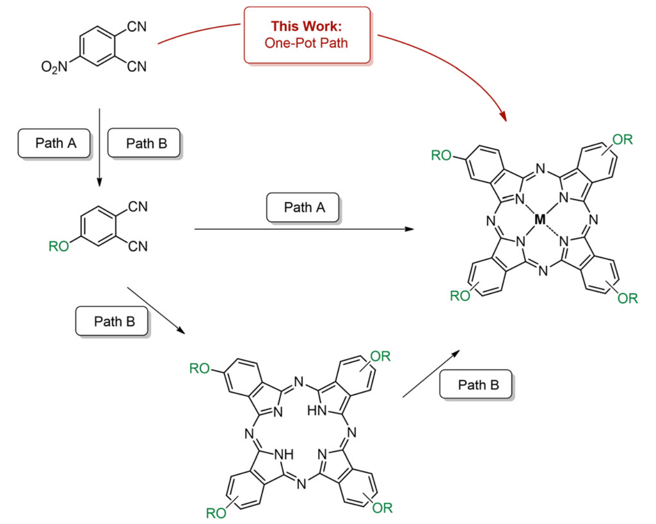
including catalysis,[5] sensing,[6,7] liquid crystals,[8] and medicinal chemistry.[9]

Among the various classes of phthalocyanine derivatives, aryloxy- and alkyloxy-substituted metallophthalocyanines have attracted particular attention due to their enhanced photophysical and electrochemical properties that make them suitable especially in photodynamic therapy (PDT) for cancer treatment,[10,11] chemical sensors,[12] non-linear optics (NLO),[13,14] photovoltaics,[15–17] and colour filters for liquid crystal displays.[18] Traditionally, their synthesis involves distinct, separate synthetic steps: a first nucleophilic aromatic substitution (S_NAr) on a fluoro-, chloro- or nitro-substituted phthalonitrile and the subsequent macrocyclization of the resulting compound.[19]

However, the generally harsh experimental conditions for phthalocyanine ring formation, such as high temperatures, anhydrous environment, and the use of solvents that can simultaneously facilitate metal-ion templating while remaining inert under the reaction conditions can render it a challenging task. In response to the emphasis on environmental sustainability, several alternative strategies have been explored, such as microwaves,[20–22] UV irradiation,[23,24] solvothermal routes,[25–27] and mechanochemical synthesis.[28] Although these approaches represent significant progress from a sustainability perspective, they often rely on specialized equipment that may not be readily available in standard synthetic laboratories, thereby limiting the applicability of these methods.

In light of this, the development of new methodologies that combine sustainability and operational simplicity for the synthesis of such relevant functional materials has become an area of growing interest.

As sketched in Scheme 1, in principle, the two main synthetic routes to metallophthalocyanines bearing different peripheral substituents are: (Path A) metal-templated cyclization of the already chemically functionalized precursors (phthalonitriles are some of the most widely utilized) and (Path B) metal insertion into the preformed, metal-free peripherally functionalized phthalocyanine.[29]



Scheme 1 Main synthetic pathways to synthesize peripherally substituted phthalocyanines with a metal in the central cavity.

In recent years, our research group has focused on the use of greener solvent alternatives to the conventional organic media for key solution-phase organic reactions,[30,31] including phthalocyanine synthesis,[32,33] with the aim of developing experimental protocols that are both efficient and respectful of human health and the environment. Building on this foundation, we present a straightforward, operationally simple and broadly applicable one-pot synthetic approach for the preparation of aryloxy- and alkyloxy-functionalized zinc phthalocyanines starting from phthalonitrile precursors.

The literature contains only a limited number of examples of one-pot phthalocyanine syntheses. These include the classical macrocycle-forming procedures, also known as the Wiler method, which employ phthalic anhydrides, phthalimides, or phthalic acid as precursors[34] as well as the formation of copper phthalocyanine-based polymers *via* copper-mediated crosslinking of phthalonitriles for catalytic applications.[35] In contrast, one-pot protocols that couple ring functionalization with macrocyclization are far less common. Nucleophilic aromatic substitution can, in principle, support such tandem processes, yet the few reported cases typically arise as unoptimized side reactions rather than deliberately designed synthetic strategies.[36] For example, phthalocyanine formation in high-boiling alcohols under strongly basic or metal-promoted conditions generates alkoxides *in situ*. These may then attack reactive sites on the phthalonitrile precursor, particularly those already containing alkoxy groups, leading to uncontrolled alkoxy displacement and, consequently, mixtures of inseparable products with variable substitution patterns.[37] Yet, to the best of our knowledge, no general, practical, and versatile protocol for accessing a broad range of related compounds of the same sub-family has been established to date.

Our method addresses this gap by successfully achieving the synthesis of diverse tetra- and octa-substituted aryloxy- and alkyloxy-zinc phthalocyanines, tolerating a broad range of nucleophilic partners bearing different functional groups and avoiding intermediate purification, with isolated yields of up to 49%. In cases where literature comparisons were available, our one-pot approach outperformed the existing two-step procedures, offering a practical alternative implementable in routine laboratory settings, relying solely on conventional heating and standard laboratory glassware. Moreover, the environmental sustainability and practicality of the developed protocol have been quantitatively assessed in terms of waste generation using green chemistry metrics such as the Environmental factor (*E*-factor). The calculated values, mostly below 180.0, were more than 90% lower than those reported for previously established two-step methods using conventional protocols, underscoring the environmental benefits of this approach. This analysis further demonstrates that the reduced environmental impact of the methodology stems from the synergistic contribution of the one-pot design together with the streamlined purification steps and the possibility of solvent recovery.

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Overall, this work contributes to the advancement of less environmentally impactful and practically accessible methodologies for the synthesis of functional zinc phthalocyanine derivatives, addressing a long-standing synthetic challenge and expanding the potential of their broader adoption in various fields of applications by the scientific community.

Results and discussion

Synthetic strategy, optimization, and product characterization

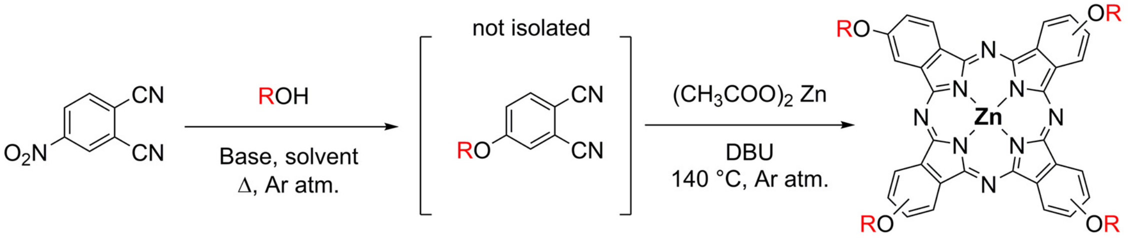
According to Scheme 2, our synthetic pathway involves the initial functionalization of a phthalonitrile derivative bearing a good leaving group, such as a nitro substituent, susceptible to nucleophilic aromatic substitution. After its replacement with different phenols/alcohols, under an inert atmosphere, the resulting intermediate is not isolated but instead directly used in the subsequent metal-templated cyclization step. In the same reaction vessel, and under inert conditions, a zinc salt and the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), commonly employed in phthalonitrile tetramerization, are thus introduced. The reaction mixture is then heated to 140–150 °C, to promote the macrocyclization process.

Optimization studies and broadening of reaction scope. Optimization of the reaction conditions began with the study of the synthesis of a model derivative, tetra-4-(3,5-dimethylphenoxy)-zinc-phthalocyanine (**1**), under a newly expanded set of experimental parameters.

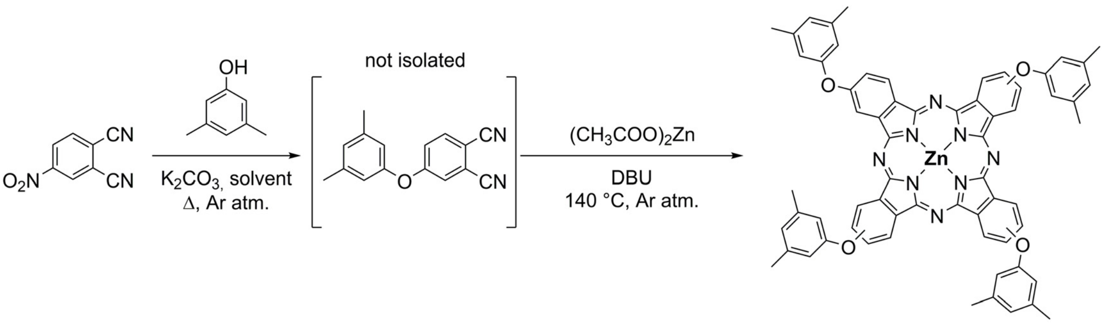
In this protocol, potassium carbonate was selected as the designated base for the nucleophilic aromatic substitution step, in which the phenol is deprotonated to generate the corresponding phenoxide, allowing displacement of the nitro group and formation of the phthalonitrile intermediate. Although other bases have been reported in related procedures,[38] potassium carbonate was chosen here for its advantageous combination of practicality, accessibility, and alignment with sustainability goals.[39–41] Its widespread use and solid performances in S_NAr chemistry therefore made it a suitable candidate for developing an efficient and more environmentally conscious one-pot synthesis.

The reaction scheme is sketched in Scheme 3. The two methyl groups on the aromatic ring of the phenol are expected to have, indeed, little influence on the reaction's progress, being weak electron-donating groups positioned at the *meta* position to the hydroxyl group. Their location avoids steric hindrance near the reactive site, thereby allowing us to investigate and refine the synthetic conditions while minimizing the number of variables involved. Table 1 summarizes the reaction variables that have been scrutinized, which include the reaction medium, the molar ratio between the reagents used, the concentration of 4-nitrophthalonitrile in the reaction solvent, the amount of DBU added for the cyclotetramerization step, and the isolated yield obtained.

Solvent selection was the first parameter to be evaluated during reaction optimization. The ideal solvent needed to be chemically inert under the reaction conditions, thermally stable at reaction temperatures, and capable of supporting both reaction steps without interfering with the reaction com-



Scheme 2 Synthetic route for the one-pot synthesis of tetra-substituted aryloxy/alkyloxy zinc phthalocyanines.



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Scheme 3 Synthetic route for the synthesis of tetra-4-(3,5-dimethylphenoxy)-zinc-phthalocyanine (**1**).

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Table 1 Experimental conditions for the synthesis of **1**

Solvent	Phthalonitrile/phenol molar ratio	Phthalonitrile concentration (mmol mL^{-1})	DBU in the 2^{nd} step (eq.)	Yield (%)
DMPU	1 : 1.1	0.72	0.07	19
DMSO	1 : 1.1	0.72	0.035	15
DMF	1 : 1.02	0.72	0.0	29
DMF	1 : 1.02	0.72[a]	1.0[b]	23
DMF	1 : 1.02	1.44	1.0	35
DMF	**1 : 1.02**	**0.72**	**1.0**	**48**

[a] The concentration of the aryloxyphthalonitrile intermediate (calculated assuming complete S_NAr, as indicated by TLC) decreases to 0.58 mmol mL^{-1} after DMAE addition. [b] 1.0 mL of DMAE was added as a cosolvent during the cyclization step.

ponents. Generally, *N*,*N*-dimethylformamide (DMF) stands out as the most effective for the purpose.[42]

In an effort to further align the process with principles of green chemistry, two polar aprotic and less environmentally impactful solvents, dimethyl sulfoxide (DMSO) and *N*,*N*′-dimethylpropyleneurea (DMPU), were also investigated, as they are well suited to facilitate both nucleophilic aromatic substitution and the subsequent phthalonitrile tetramerization, while adopting a more sustainable perspective. However, under the tested conditions, neither solvent achieved satisfactory performance. DMF, on the other hand, uniquely enabled both steps to proceed efficiently under one-pot conditions. In this context, its lower intrinsic greenness is counterbalanced by higher efficacy, while the one-pot approach inherently reduces solvent use and waste generation, delivering a net process-level sustainability gain in line with current solvent-replacement guidance for S_NAr-type chemistry.[43]

Then, further optimization steps were implemented. We addressed the ratio of reagents, particularly the amount of phenol relative to the phthalonitrile precursor. While many established protocols rely on a slight excess of phenol to ensure complete substitution, in our case, this approach required reconsideration. Under the basic conditions employed for the macrocyclization step, any residual phenol is likely to be present as a phenate anion, a nucleophilic species that might interfere with the metal-templated cyclotetramerization. Therefore, careful control of the phenol-to-phthalonitrile ratio was considered essential to minimize potential side reactions and ensure clean progression of the one-pot process. The best result in terms of yield of the final product was achieved with a 1 : 1.02 molar ratio, respectively, confirming the advantage of limiting phenol excess under the conditions of the subsequent macrocyclization step.

As for the second step, the addition of DBU was generally found to improve phthalocyanine yields. Catalytic amounts, which are frequently employed in the literature for phthalonitrile tetramerization, proved insufficient, with an equimolar amount required instead. This evidence suggests on the one hand that potassium carbonate can promote phthalocyanine ring formation to some extent, but its basicity alone is not sufficient to achieve satisfactory yields under the selected conditions, and on the other hand that the complexity of the reaction environment, due to the presence of various by-products from the nucleophilic substitution reaction, may interfere with the catalytic activity of DBU, thus requiring higher amounts. Conversely, the addition of *N*,*N*-dimethylaminoethanol (DMAE), a polar protic solvent frequently used for the tetramerization of phthalonitriles, as a co-solvent did not prove beneficial, likely due to unfavorable dilution effects within the reaction mixture.

In addition, increasing the concentration of 4-nitrophthalonitrile in solution did not enhance the reaction outcome; rather, a twofold increase led to a decrease in yield from 48% to 35%. In all cases, the cyclization step was carried out at 140 °C, in line with most solution-based syntheses reported in the literature using DMAE, which has a boiling point of 135–138 °C.

After achieving and optimizing the best set of reaction conditions, a series of different phenols bearing both electron-withdrawing and electron-donating groups have been investigated as nucleophiles to afford various aryloxy zinc phthalocyanines (Fig. 1). The temperature variable for the S_NAr required special consideration: while this synthetic step could in some cases be accomplished at room temperature, its rate and overall efficiency were strongly dependent on the substitution pattern of the phenol. Reaction conditions were therefore optimized case by case, accounting for specific electronic and steric effects. In addition to expanding the scope of our approach, efforts were made to refine the purification process in order to obtain the target phthalocyanines in a more sustainable manner. For this purpose, solvent washings and, when applicable, Soxhlet extraction of residual by-products were explored, as both techniques allow for efficient solvent recycling. In the case of more challenging purification, particularly those affected by the high solubility of the final products, a filtration on a short silica pad was employed and proved to be effective in isolating target products from reaction impurities, greatly reducing the amounts of both the stationary phase and solvents that are commonly used in the conventional column chromatography approach, while also enabling recovery and reuse of a significant fraction of the employed eluent mixtures. As a first example, we prepared compound **2** using 4-nitrophthalonitrile and 4-methylphenol (*p*-cresol) as the phe-

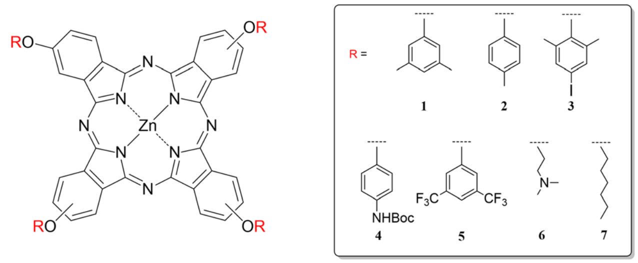

Fig. 1 Chemical structure of phthalocyanine derivatives. Phthalocyanine core (black) and different modifications R (red) denote substituents at the periphery of the macrocycle ring.

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nolic component. In this case as well, the methyl substituent on the aromatic ring was not expected to significantly influence the course of the reaction, either by promoting or hindering the key steps.

To verify the consistency and robustness of the synthetic protocol, a small set of reaction conditions (reaction medium, reagents molar ratio, S_NAr temperature, DBU amount) was also screened for this substrate, with the results in terms of isolated yields summarized in Table 2. Also in this case, the use of a slight excess of phenol relative to 4-nitrophthalonitrile, together with equimolar amounts of DBU in the second step, was necessary to achieve the highest yields. Interestingly, adding a catalytic amount of the base 15 minutes after the temperature increase required for the second step of the one-pot protocol resulted in lower yields than adding the same amount immediately when DMPU was chosen as the solvent. This may be explained by the occurrence of one or more side processes that are triggered rapidly upon heating, potentially depleting the phthalonitrile reactant through oxidation or polymerization involving the cyano groups. DMPU generally performed better as a solvent in comparison with its performance in the synthesis of **1**, affording phthalocyanine **2** in up to 30% yield. However, the best results were obtained by reacting 4-nitrophthalonitrile and *p*-cresol at 60 °C in DMF, affording the target molecule in 43% yield and confirming the efficacy of our optimized reaction conditions.

With a deeper understanding of the synthetic method, the procedure was subsequently extended to a broader set of derivatives featuring more complex substitution patterns and increased electronic and steric demands. The main results for the syntheses of compounds **3–9** are reported in Table 3.

Table 2 Experimental conditions for the synthesis of **2**

Solvent	Phthalonitrile/ phenol molar ratio	S_NAr T (°C)	Amount of DBU in the second step (eq.)	Yield (%)
DMPU	1 : 1.1	60	0.07	27
DMPU	1 : 1.1	40	0.07	30
DMPU	1 : 1.1	60	0.0[a]	18
DMF	1 : 1.1	60	0.07	28
DMF	**1 : 1.02**	**60**	**1.0**	**43**

[a] DBU (0.07 eq.) was added 15 minutes after reaching the tetramerization temperature.

Table 3 General conditions for the synthesis of phthalocyanines **3–9**

Compound	Phthalonitrile/phenol molar ratio	S_NAr T (°C)	Yield (%)
3	1 : 1.02	65	37
4	1 : 1.02	75	n.d.[a]
5	1 : 1.02	75	27
6	1 : 1.02	75	49
7	1 : 1.02	60	22
8	1 : 3.1	100	30
9	1 : 3.1	100	31

Reactions were carried out in DMF, using 3.0 eq. of K_2CO_3 as the base for the S_NAr step, and 1.0 eq. of DBU in the cyclotetramerization step. [a] The results for this compound are further discussed within the text.

The synthesis of **3** was explored using 2,6-dimethyl-4-iodophenol as the nucleophilic component, a substrate that combines steric congestion with electronically neutral yet synthetically valuable functionality. Indeed, the methyl substituents at the 2 and 6 positions introduce steric hindrance around the hydroxyl group, which can reduce the accessibility of the corresponding phenate anion to the electrophilic center on the phthalonitrile during the S_NAr step. The iodine atom at the 4-position does not substantially influence the reactivity in this context, although it provides a useful handle for potential post-functionalization. To further evaluate the behaviour of this hindered substrate under the tandem conditions, an aliquot of the crude reaction mixture was analyzed by ^{1}H NMR after completion of the first step. The phthalonitrile intermediate was identified as the major species, together with minor unidentified side products (Fig. 2). These did not interfere with the subsequent macrocyclization, and the final zinc phthalocyanine **3** was isolated in 37% yield after the standard workup and purification. This result confirms that even sterically demanding phenols can be effectively incorporated through our one-pot protocol.

The versatility of this approach has been also tested towards phenolic substrates bearing amino substituents. This type of functional group is well known in organic synthesis for its potential as a crucial derivative for further functionalization. In this case, we used 4-aminophenol as the phenolic component after primarily protecting the amino moiety with a *tert*-butyloxycarbonyl (BOC) protection group. This was important to prevent side reactions that might occur with the amino group during phthalocyanine ring formation. The outcome of the reaction did not allow us to clearly confirm the formation of the target compound **4**, as the purified product proved highly insoluble in most organic solvents, except for *N*-coordinating bases such as pyridine, making it impossible to obtain a clear mass spectrum to confirm its molecular mass. In some instances, interpretation was further complicated by residual solvent peaks overlapping with expected signals. IR spectroscopy shows features that could be consistent with partial thermal cleavage of the BOC group during phthalonitrile tetramerization.

In particular, the broad absorption band around 3250 cm^{-1} may be attributable to overlapping N–H stretching modes from both carbamate and primary amine functionalities. Additionally, there is only a weak shoulder at 1721 cm^{-1}, a region typically associated with strong absorptions from BOC-derived carbonyl groups. Nevertheless, no definitive conclusion regarding the chemical structure of **4** can be drawn at this stage, as the formation of intermolecular aggregates, possibly promoted by hydrogen bonding between the phthalocyanine protecting groups, may also contribute to the reduced solubility and the poor interpretability of the spectra. However, the UV-Vis spectrum recorded in pyridine confirmed the presence of the Q and Soret bands characteristic of the phthalocyanine core. Given the potential for further derivatization or

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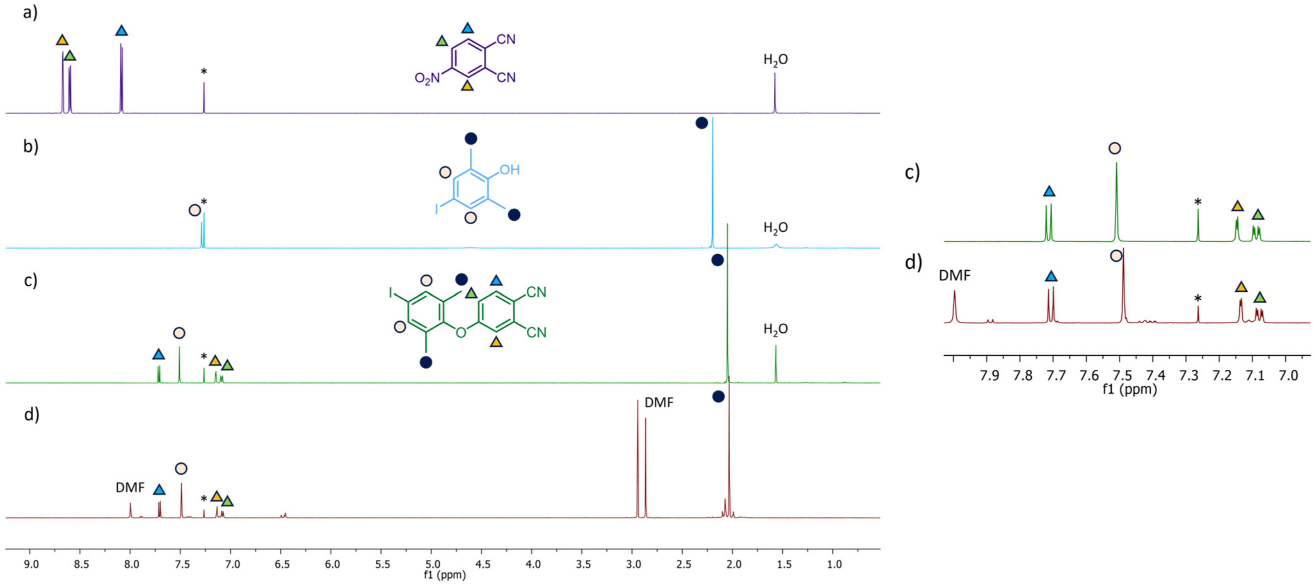

Fig. 2 Left panel: Stacked ^{1}H NMR spectra showing (a) 4-nitrophthalonitrile, (b) 2,6-dimethyl-4-iodophenol, (c) the isolated 4-(4-iodo-2,6-dimethylphenoxy)phthalonitrile intermediate and (d) the crude reaction mixture after completion of the first step of the tandem sequence leading to phthalocyanine **3** ($CDCl_3$, 600 MHz). Right panel: Magnification of the aromatic regions of spectra (c) and (d). The symbol * corresponds to the $CDCl_3$ residual peak.

quaternization of the free amine group, additional studies are warranted to further investigate and optimize this transformation within the context of pot-economical synthetic strategies.

The synthesis of **5** also required additional consideration due to the electronic nature of the substituents present on the phenolic component. In this case, the starting phenol is substituted with two trifluoromethyl groups positioned at positions 3 and 5 of the aromatic ring. These substituents are well known for their strong electron-withdrawing character, which is expected to reduce the nucleophilicity of the oxygen atom, thereby increasing the activation energy required for the S_NAr reaction with 4-nitrophthalonitrile. In practice, this prediction was confirmed by the necessity to increase the reaction temperature to 75 °C in order to achieve successful conversion of 4-nitrophthalonitrile into 4-(3,5-bis(trifluoromethyl)phenoxy)phthalonitrile. Despite the increased difficulty of the S_NAr step under these electronically demanding conditions, the subsequent cyclotetramerization proceeded smoothly, ultimately affording the desired phthalocyanine derivative **5** in 27% isolated yield.

Eager to further gauge the scope of such a strategy, we challenged our method by using alcohols rather than phenols as nucleophiles in the aromatic nucleophilic substitution, targeting the synthesis ofalkyloxy-substituted metallophthalocyanines.

Although the alkoxide ion is a strong nucleophile, the use of aliphatic alcohols in S_NAr often requires stronger bases and more forcing conditions due to their lower acidity compared to phenols. Nevertheless, under optimized conditions, their inherent nucleophilicity may still enable the substitution to proceed efficiently, potentially even under mild conditions. To verify these hypotheses, we synthesized a known compound reported in the literature, tetra-(2-dimethylaminoethoxy)-zinc-phthalocyanine (**6**), given its relevance as a precursor of the corresponding cationic species, which have been widely investigated as telomerase inhibitors[44] and singlet oxygen generators for photodynamic therapy applications.[45] Any attempt to perform the reaction at room temperature with alkyl alcohols failed, likely due to the inability of K_2CO_3 to completely deprotonate them. This behavior mirrors prior S_NAr precedents where higher basicity/temperature or longer reaction times are needed for aliphatic alcohols *versus* phenols.[46] As a result, the reaction time proved to be remarkably long, requiring temperatures up to 65 °C. Nonetheless, phthalocyanine **6** was successfully obtained in 49% yield, a value that falls within the broad range reported in the literature and is generally considered satisfactory given the variability of the existing procedures. In contrast, phthalocyanine **7**, obtained from the reaction of 4-nitrophthalonitrile with hexan-1-ol, was isolated in moderate yield, suggesting that further optimization of the reaction and workup conditions may be required for derivatives bearing longer alkyl chains. Overall, three practical design rules emerged from our findings: limit phenol excess to avoid phenolate interference in cyclotetramerization, use ~1.0 eq. of DBU under one-pot conditions to offset competing side processes and increase S_NAr temperature for strongly deactivated phenols or aliphatic alcohols.

After the successful synthesis of various tetra-substituted phthalocyanine derivatives, the scope of the study was extended to include the preparation of octa-substituted analogues. For this purpose, 4,5-dichlorophthalonitrile was selected as the starting material and reacted with two different phenolic nucleophiles, as illustrated in Scheme 4. A critical challenge in adapting the one-pot protocol to this system lay in the precise monitoring and control of the nucleophilic aromatic substitution step. While the initial substitution of one

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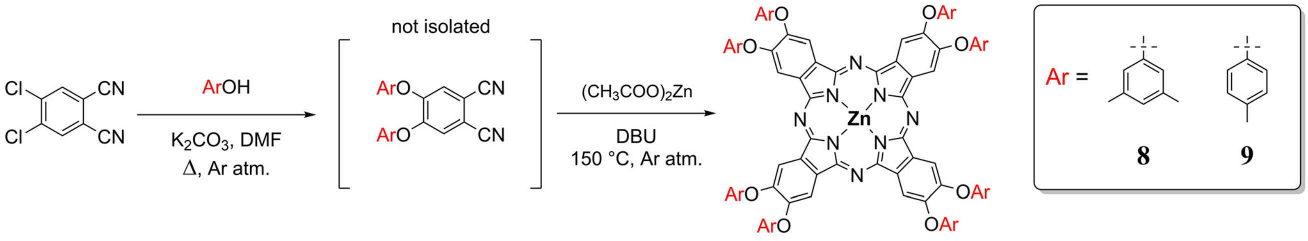

Scheme 4 Synthetic route for the synthesis of phthalocyanines **8** and **9**.

chlorine atom generally occurred without difficulty, the introduction of the second substituent proved considerably more challenging. This can be attributed to the combined effects of steric hindrance and electronic deactivation following the first substitution, which markedly reduce the reactivity of the second chloride leaving group. Several attempts under previously optimized conditions led to mixtures containing partially chlorinated intermediates, indicating that disubstitution was incomplete. To address this issue, the experimental parameters were systematically adjusted by substantially increasing the reagent ratios and reaction temperature to drive the reaction to completion, as detailed in Table 3. The subsequent cyclotetramerization proceeded smoothly, affording the target octa-substituted zinc phthalocyanines **8** and **9** in 30% and 31% yields, respectively.

Spectroscopic characterization of the synthesized molecules

The structures of the target phthalocyanines were confirmed by a combination of NMR, UV-Vis, FT-IR, and mass spectrometry analysis, with all data provided in the SI. Among these techniques, ^{1}H NMR spectroscopy proved particularly informative in highlighting the structural complexity arising from tetrasubstitution and the related presence of regioisomers. Indeed, the spectra of tetra-substituted compounds (**1**, **2**, **3**, **5**, **6**, and **7**) generally display a high degree of complexity, which arises from two main factors: the lack of symmetry introduced by tetrasubstitution and the statistical formation of four possible regioisomers in variable proportions. These features result in signal broadening, splitting, and overlapping in several spectral regions.

To better illustrate this aspect, we present a comparative analysis of the ^{1}H NMR spectra, recorded in THF-d_8, of a tetra-substituted phthalocyanine (compound **2**) and its octa-substituted analogue (compound **9**), both functionalized with 4-methylphenoxy groups. The aromatic region is particularly diagnostic: as shown in Fig. 3, compound **2** displays a dense and highly structured set of multiplets, originating from both the macrocyclic protons and the aromatic protons of the peripheral 4-methylphenoxy groups. In contrast, the octa-substituted compound **9**, characterized by a higher degree of symmetry and the absence of regioisomerism, shows only two sharp signals. Furthermore, the four aromatic protons of the 4-methylphenoxy moiety, which typically display a well-defined AA′XX′ splitting characteristic of a *para*-substituted

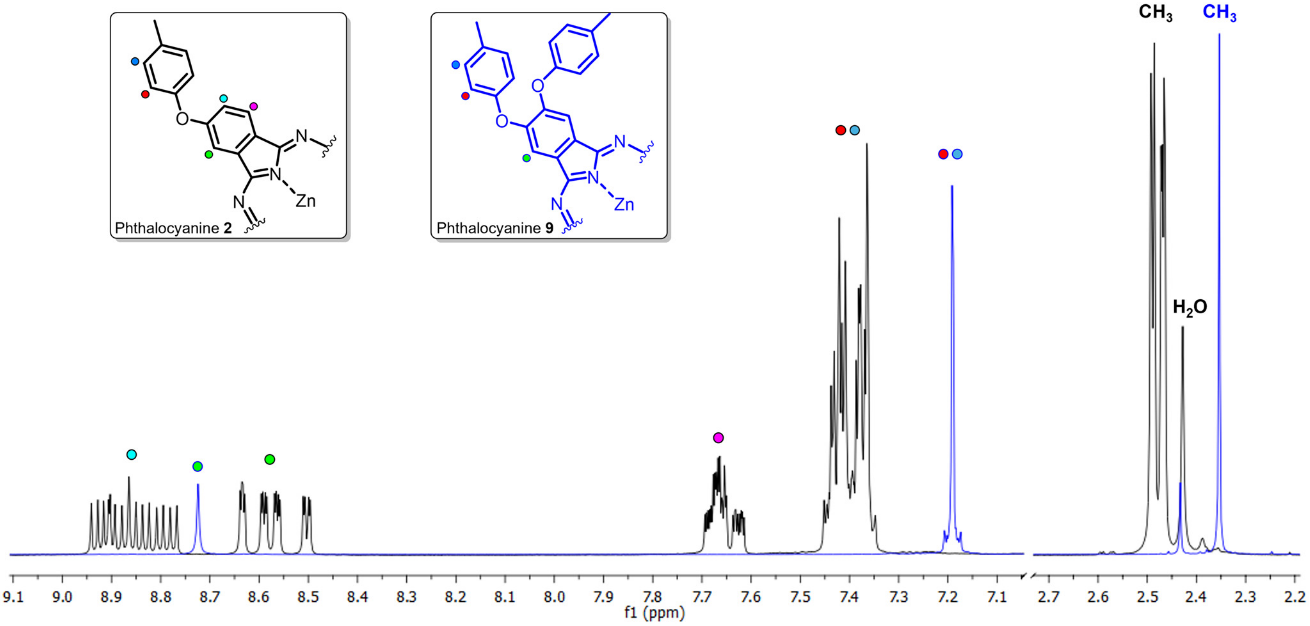

Fig. 3 Comparison between ^{1}H NMR spectra of phthalocyanines **2** and **9** recorded in THF-d_8.

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phenyl ring, exhibit a more complex pattern than expected. This increased complexity also extends into the aliphatic region: in compound **2**, the methyl protons of the 4-methylphenoxy units appear as multiple singlets, corresponding to the different environments in the statistical mixture of regioisomers. In contrast, compound **9** shows a single sharp singlet for the same methyl groups, consistent with a symmetric and chemically uniform substitution pattern. Similarly, the ^{13}C spectra of the tetra-substituted compounds display a dense set of signals in the aromatic region, with each peak appearing as a cluster of closely spaced signals due to the presence of regioisomers. In contrast, the octa-substituted derivatives exhibit a more defined and simplified pattern, consistent with higher molecular symmetry. This structural heterogeneity, as expected, is not reflected in the MALDI-TOF mass spectra, given that all regioisomers share the same molecular mass. UV-Vis spectra were recorded in THF for all compounds, except for phthalocyanine **4** which required pyridine to ensure adequate solubility, and are reported in the SI (page S28). In all cases, the spectra displayed the characteristic features of phthalocyanine derivatives: an intense Q-band with maxima between 675 and 685 nm, typically accompanied by vibronic shoulder peaks, and a less intense Soret band centered around 350 nm. The limited variation in the Q-band position across the series can be attributed to multiple factors. First, THF is a coordinating solvent capable of suppressing molecular aggregation, thereby minimizing aggregation-induced spectral shifts.

Second, it is well established that substituents at the β-positions of the macrocycle exert weaker electronic effects compared to those at the α-positions, resulting in a comparatively minor impact on optical absorption.

Consistent with these considerations, the variation in spectral features remained limited despite the diversity in substituent shape and electronic nature, suggesting that the influence of the aryloxy or alkyloxy oxygen atom may dominate the overall electronic behaviour.

Yield and *E*-factor evaluation of one-pot synthesized phthalocyanines

Table 4 shows the results obtained with our one-pot procedure in terms of yields and *E*-factor values. Where possible, *i.e.*, when the product has already been described in the literature, a comparison is made between our synthetic procedure and the conventional two-step protocols. Notably, several derivatives reported here have no precedents in the literature, underscoring the originality and synthetic versatility of our approach.

From a synthetic perspective, the yields obtained with our one-pot synthesis are generally higher than those achieved for stepwise procedures. In particular, the 27% yield obtained for phthalocyanine **5** represents a substantial improvement over the previously reported value of 7% for the same compound, which holds potential for application in PDT,[48] corresponding to a 385% increase. In the few instances where the one-pot protocol led to lower yields, the method remains advantageous due to its procedural simplicity and reduced environmental impact. In the case of compound **7**, although it has been previously reported, the literature provides only the yield of the tetramerization step from 4-hexyloxyphthalonitrile (49%), without sufficient detail on the preceding nucleophilic substitution. As a result, the overall two-step yield cannot be reconstructed and no meaningful comparison can be made with our one-pot synthesis, which afforded the compound in 22% yield. A comprehensive evaluation of the environmental sustainability of our procedure in terms of waste generation was conducted by calculating the *E*-factor value for the synthesis of each phthalocyanine derivative, as detailed in the SI and summarized in Table 4.

As shown, the *E*-factor values for our one-pot synthesis are generally moderate, mostly below 180.0, and in some cases notably lower than those associated with the current state-of-the-art phthalocyanine syntheses.[51] It should also be emphasized that most literature *E*-factor values refer only to the tetra-

Table 4 Yields and *E*-factor values of the aryloxy and alkyloxy zinc phthalocyanines synthesized with our one-pot procedure compared to the two-step reported data

	This work			Literature			
		E-Factor			*E*-Factor		
Compound	Yield (%)	No solvent recovery	80% solvent recovery	Total yield for two-step procedures (%)	No solvent recovery	80% solvent recovery	Ref.
1	48	257.7	86.9	—	—		—
2	43	326.2	111.3	38	1441.7	496.3	47
3	37	556.6	176.7	—	—		—
5	27	192.1	83.9	7	1236.7	591.6	48
6	49	47.4	34.0	13	10 566.8	5320.2	44
				55	3087.0	1039.9	49
7	22	443.0	179.8	n.d.[a]	n.d.		50
8	30	797.4	294.3	—	—		—
9	31	751.1	289.5	—	—		—

[a] Only the tetramerization yield (49%) is reported in the literature; the preceding step is not described in sufficient detail to calculate a total yield.

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merization step, whereas our calculation accounts for the entire one-pot process.

In cases where a direct comparison was possible, *i.e.* for derivatives **2**, **5**, and **6**, our *E*-factors were at least one order of magnitude lower than those calculated for the corresponding two-step protocol.

In addition, to enable a more rigorous, complete, and fair comparison between methodologies, additional *E*-factor values were calculated by considering an 80% solvent recovery both for our one-pot approach and the literature syntheses. The comparison clearly shows that solvent recycling exerts a large impact on reducing waste production for both traditional and one-pot methodologies. Nonetheless, even in the absence of recycling, the one-pot approach consistently displays lower *E*-factor values than the conventional two-step syntheses, even when the latter include a hypothetical solvent recovery. This demonstrates that the design of the synthetic protocol itself contributes substantially to waste reduction. When solvent recovery is applied, the superiority of the one-pot method becomes even more pronounced, reaching the lowest *E*-factor among all investigated scenarios.

Overall, these results underscore the efficiency of the proposed one-pot methodology not only from a synthetic standpoint but also in terms of economic and environmental impact. The process demonstrates a clear advantage in aligning with the principles of green chemistry, offering a practical and more sustainable alternative for the synthesis of functionalized zinc phthalocyanines.

Experimental section

Materials and instruments

All reagents and solvents were purchased from Merck Life Science, TCI Chemicals, and Carlo Erba Reagents and used without further purification. *N*,*N*-Dimethylformamide was used freshly distilled. Reactions were monitored by thin-layer chromatography (TLC) employing a polyester layer coated with 250 mm F254 silica gel. Chromatographic filtrations, when needed, were performed using silica gel 60A 35–70. ^{1}H NMR spectra were recorded on a Bruker AVANCE 600 NMR spectrometer operating at a proton frequency of 600.13 MHz; chemical shifts (δ) are given in ppm relative to TMS. Infrared spectra were recorded on a Shimadzu FT-IR prestige-21 spectrometer using an attenuated total reflectance (ATR) unit. UV-Vis spectra were recorded on a PerkinElmer Lambda 950 UV-Vis/NIR spectrophotometer. MALDI-TOF spectra were recorded at the Toscana Life Science facility on a MALDI-TOF/TOF Ultraflex III (Bruker).

Synthetic procedures

All the one-pot reactions were performed in a two-necked round-bottom flask equipped with a reflux condenser and a magnetic stirrer. All the glassware used was oven-dried at 110 °C for at least 24 hours prior to use. Regarding tetra-substituted phthalocyanines, they are typically obtained as a mixture of four regioisomers, having point group symmetries $D_{2h}:C_s:C_{2v}:C_{4h}$, depending on their substitution pattern. In most cases, regioisomeric separation is not pursued, as their electronic properties are only marginally affected by the positional isomerism of the peripheral substituents. As a result, the mixture is often used directly in applications where these minor differences do not significantly impact performance or functionality. Given that the primary objective of this study was to develop and optimize a novel synthetic procedure, no efforts were made to isolate individual regioisomers.

Recovery procedures for methanol and eluent mixtures are described in the SI.

Synthesis of *tert*-butyl(4-hydroxyphenyl)carbamate (4a). The synthesis was carried out according to the procedure reported in the literature.[52] Briefly, in a one-neck round-bottom flask, 4-aminophenol (0.5 g, 1 eq.) was stirred in 8 mL of glycerol, and then Boc_2O (1 eq.) was added. The reaction mixture was stirred at room temperature until complete disappearance of 4-aminophenol was observed *via* TLC monitoring. The resulting reaction mixture was extracted with a mixture of petroleum ether/ethyl acetate (9 : 1), and the combined organic layer was dried over anhydrous magnesium sulphate and concentrated under reduced pressure. Purification of the raw product by crystallization with hexane gave the target product in 86% yield as a white solid.

General one-pot procedure for the synthesis of tetra-substituted zinc phthalocyanines 1–7. Phenol/alcohol (1.02 eq.) and anhydrous K_2CO_3 (3 eq.) were stirred in 4 mL of DMF at room temperature for 30 minutes. Then, 4-nitrophthalonitrile (1 eq., 0.5 g) was added in one portion and the reaction mixture was stirred at the chosen temperature until the complete disappearance of 4-nitrophthalonitrile, as confirmed by TLC. Zinc acetate dihydrate (0.27 eq.), pre-dried in an oven at 110 °C for at least 6 hours, and DBU (1 eq.) were then added and the reaction mixture was stirred at 140 °C under an argon atmosphere until completion of the reaction. After quenching with 1 M HCl, the resulting precipitate was filtered, washed with water and methanol, and dried under vacuum.

General one-pot procedure for the synthesis of octa-substituted zinc phthalocyanines 8 and 9. Phenol (3.1 eq.) and K_2CO_3 (3 eq.) were stirred in 4 mL of DMF at room temperature for 30 minutes. Then, 4,5-dichlorophthalonitrile (1 eq., 0.2 g) was added and the reaction mixture was stirred at 100 °C until its complete disappearance, as confirmed by TLC. Zinc acetate dihydrate (0.27 eq.), pre-dried in an oven at 110 °C for at least 6 hours, and DBU (1 eq.) were then added and the reaction mixture was stirred at 150 °C under an argon atmosphere until completion of the reaction. After quenching with 1 M HCl, the resulting precipitate was filtered, washed with water and methanol, and dried under vacuum.

Details of the purification procedures for the crude reaction mixtures of each phthalocyanine, along with their spectroscopic and analytical data, are provided in the SI.

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Conclusions

In summary, we have developed a versatile and sustainable one-pot synthetic approach for the preparation of functionalized zinc phthalocyanines, enabling the direct conversion of nitro- and chloro-substituted phthalonitriles into tetra- and octa-substituted aryloxy- and alkyloxy-phthalocyanines. Nine different phthalocyanines were synthesized with isolated yields ranging from 22% to 49%, demonstrating both the generality and the reliability of the protocol. Notably, compound **5** was obtained in 27% yield, representing a marked improvement over previously reported values. In most cases, purification was achieved without the use of conventional column chromatography, emphasizing the operational simplicity of the method. Furthermore, comparative *E*-factor analysis with literature protocols revealed a substantial reduction in waste generation, resulting from the combined effect of the one-pot design, simplified purification and solvent recovery, thereby reinforcing the process's green credentials. In summary, by eliminating intermediate isolation, reducing reaction times, and relying on readily available equipment and solvents, this methodology provides a practical, potentially scalable, and greener route for phthalocyanine synthesis, with potential applications in fields where sustainable access to functional organic materials is desired, such as photodynamic therapy, chemical sensing and optoelectronics.

Author contributions

F. P.: investigation, data curation, methodology, writing – original draft, writing – review & editing; V. R.: investigation, data curation, formal analysis, visualization, writing – review & editing; L. M.: investigation, data curation, writing – review & editing; G. Z.: conceptualization, funding acquisition, supervision, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: tabulated spectroscopic and analytical data for all synthesized phthalocyanines, together with the corresponding ^{1}H and ^{13}C NMR, FT-IR, UV-Vis (solution-phase), and MALDI-TOF spectra, and detailed *E*-factor calculations for the compounds prepared in this work, along with comparative values from literature protocols. See DOI: **https://doi.org/10.1039/d5qo01267h**.

Acknowledgements

F. P. gratefully acknowledges financial support from the Rome Technopole Innovation Ecosystem (NextGenerationEU, PNRR; CUP B83C22002890005), administered by the Italian Ministry of University and Research (MUR). G. Z. and V. R. gratefully acknowledge financial support from MUR under Grant PRIN2022 REPLACE (2022C4YNP8).

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