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# Exploring the limitations of the MacDonald ‘3 + 1’ condensation in the preparation of porphyrins with fused electron-withdrawing heterocyclic rings: Synthesis of a bis(thiadiazolo)benzoporphyrin and a related benzocarbaporphyrin

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ABSTRACT

A pyrrole ethyl ester with a fused bis(thiadiazolo)benzo unit was prepared by reacting 4-nitrobenzo[1,2-*c*:3,4-*c*′]bis(1,2,5)thiadiazole with ethyl isocyanoacetate in the presence of a non-nucleophilic base. Cleavage of the ester moiety, followed by reaction with a chloromethylpyrrole in refluxing pyridine, afforded a tripyrrane and subsequent acid-catalyzed condensation with pyrrole or indene dialdehydes gave porphyrinoids incorporating fused electron-deficient heterocyclic units.

## Introduction

Porphyrins and related systems with extended chromophores due to the presence of fused aromatic subunits have been widely investigated [1–4]. These modified porphyrinoids may exhibit strongly red shifted electronic absorptions, although the effects due to ring fusion show considerable variations [4]. The UV–vis spectra of porphyrins with a single fused benzene [5], phenanthrene [6], quinoline [7], pyrene [8a], fluoranthene [8b] or corannulene [9] ring have modest bathochromic shifts but fusion to other polycyclic aromatic units such as acenaphthylene give much larger effects [10]. One approach to porphyrins with fused aromatic rings makes use of a modification of the Barton-Zard pyrrole condensation [11–13]. Nitroaromatic compounds **1** with a degree of nitroalkene character react with isocyanoacetate esters **2** in the presence of a non-nucleophilic base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give ring-fused pyrroles **3** that can be utilized in the synthesis of porphyrinoid derivatives (Scheme 1) [14]. Porphyrin-like systems with strong absorptions in the red or far red have potential value in the development of chemical sensors [15] or as photosensitizers in photodynamic therapy (PDT) [16]. Furthermore, the introduction of fused heterocyclic subunits may facilitate complexation to metal ions at the macrocyclic periphery [17]. In an attempt to introduce fused 9,10-phenanthroline units, 5-nitrophenantholine (**4a**) was reacted with **2** in the presence of DBU to give phenanthrolinopyrroles **5** (Scheme 2) [18,19]. Nitro-neocuproine **4b** reacted similarly to form the related pyrrole esters **6** [19]. Reaction of **5a-c** with acetoxymethylpyrroles afforded dipyrrolic intermediates that could be deprotected to form **7** [18,19]. It had been intended that this intermediate could be reacted with a dipyrrylmethane dialdehyde **8** in a MacDonald ‘2 + 2’ condensation [20] to afford the targeted phenanthrolinoporphyrin **9**, but numerous attempts to conduct this reaction failed to give any porphyrin product [18]. It was speculated that the electron-deficient phenanthroline unit deactivated the fused pyrrole component of **7** and thereby inhibited electrophilic substitution reactions required for macrocycle formation. In order to overcome these difficulties, an alternative ‘3 + 1’ approach was developed (Scheme 3) [18,21]. Treatment of **5a** or **6a** with KOH in ethylene glycol at 200 °C gave α-unsubstituted phenanthrolinopyrroles **10** and these reacted with two equivalents of acetoxymethylpyrroles **11** under mildly acidic conditions to afford tripyrranes **12** [18,19]. Subsequent cleavage of the terminal *tert*-butyl ester protective groups with trifluoroacetic acid (TFA), followed by condensation with pyrrole dialdehyde **13** and oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), afforded a series of phenanthrolinoporphyrins **14** [18,19]. The carbon–carbon bond forming reactions, which are essentially electrophilic aromatic

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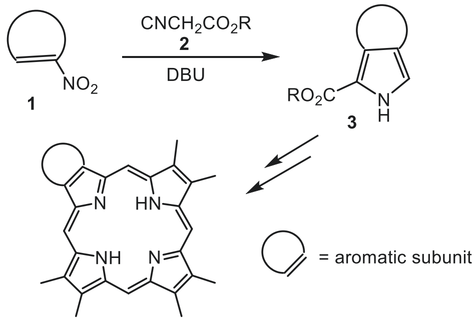
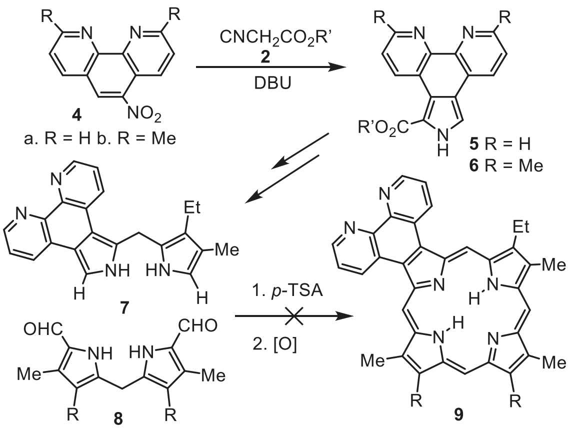
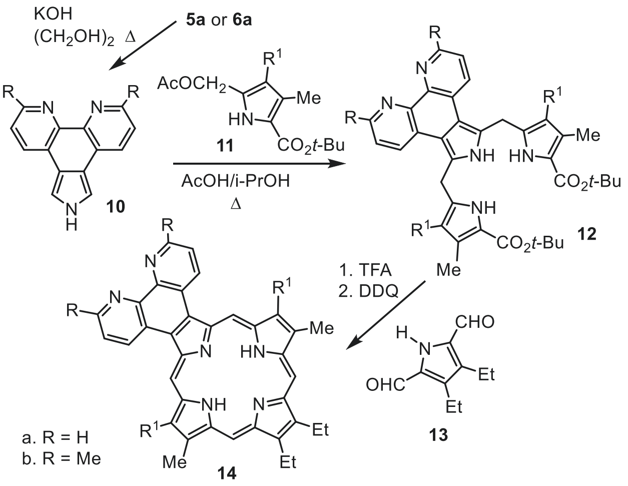


**Scheme 1.** Synthesis of annelated porphyrins from nitroaromatic compounds.



**Scheme 2.** Attempted '2 + 2' synthesis of phenanthrolinoporphyrins.



**Scheme 3.** '3 + 1' Synthesis of phenanthrolinoporphyrins.

substitutions, occur on pyrrolic units that are well removed from the electron-withdrawing phenanthroline and macrocycle formation is no longer inhibited. Indeed, in some cases exceptional high yields (>80%) were achieved [18,19]. Phenanthrolinoporphyrins have been shown to form ruthenium(II) complexes [17] and have the potential to act as molecular alligator clips [22].

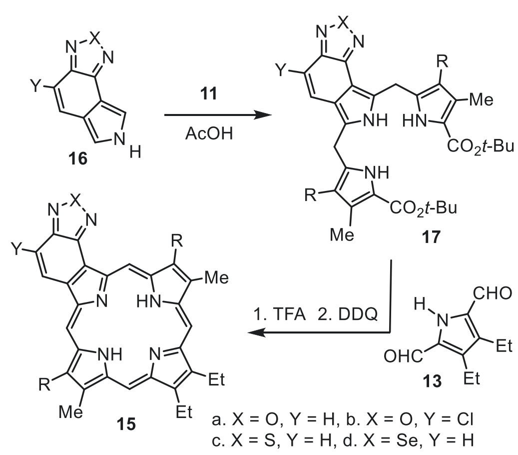
These studies were extended to a series of heterodiazolobenzoporphyrins **15** that exhibit unusual spectroscopic properties [23,24]. Oxa-, thia- and selena-diazolobenzopyrroles **16a-d** were reacted with acetoxymethylpyrroles **11** in the presence of acetic acid to give tripyrranes **17** and subsequent acid-catalyzed condensation with **13** generated modified porphyrins **15** (Scheme 4). Metalation with nickel(II), copper(II) or zinc acetate afforded metalloporphyrins with unusually intense absorption bands between 600 and 627 nm, values that approach the desired region for applications in PDT. Although the synthetic strategy was successful, it was dependent upon the heterodiazolopyrroles retaining sufficient reactivity to enable the formation of tripyrrane intermediates. The formation of oxadiazolobenzo-fused tripyrranes **17a** and **17b** proved to be particularly difficult and the intermediates could only be obtained at higher temperatures in refluxing toluene or xylenes [24].

## Results and discussion

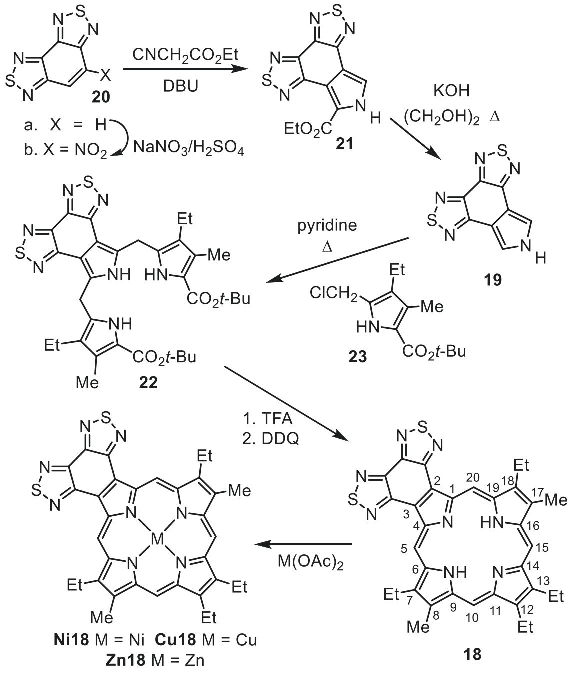
Given the unusual spectroscopic properties observed for porphyrins **15a-d**, access to related systems would be of some interest. With this in mind, we targeted the synthesis of bis(thiadiazolo) benzoporphyrin **18** where the heterocyclic component of the fused aromatic unit has been extended (Scheme 5). Porphyrin **18** also has a plane of symmetry, which simplifies spectroscopic interpretation, and the external heterocycle could potentially coordinate to transition metal cations. However, pyrrolic precursor **19** is even more electron-deficient and this feature is likely to further impede the formation of tripyrrane intermediates.

Benzo[1,2-*c*:3,4-*c*']bis(1,2,5)thiadiazole (**20**) [25] was reacted with $NaNO_3$-$H_2SO_4$ at 95–102 °C to give the corresponding nitro compound **20b**. Base-catalyzed condensation of **20b** with ethyl isocyanoacetate in THF afforded bis(thiadiazolo)pyrrole ethyl ester **21** in 84% yield, and subsequent treatment with KOH in ethylene glycol containing a small amount of hydrazine gave the parent heterocycle **19** in quantitative yields. Structures **19** and **21** are the first examples of bis(thiadiazolo)pyrroles. Although these heterocycles are rather insoluble, the proton NMR spectrum for **19** could be obtained in DMSO $d_6$ and showed the CH resonance at 7.8 ppm, a value that is consistent with an aromatic system. The EIMS for **21** gave a molecular ion at $m/z$ 305 and a base peak at $m/z$ 259, showing that the primary fragmentation involves loss of ethanol (Scheme 6).

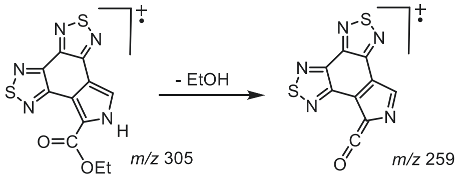
As had been anticipated, the formation of tripyrrane **22** from electron-deficient tetracycle **19** proved to be problematic. Usually, tripyrrane formation involves reaction of an α-unsubstituted pyrrole such as **11** with two equivalents of an acetoxymethylpyrrole under acidic conditions. However, no more than a trace of tripyrrane product was formed under any of the conditions examined. The presence of catalytic acid is required to facilitate elimination of acetic acid from **11** but this may also further deactivate the pyrrole unit in **19**. Scheme 7 illustrates the increased withdrawal of



**Scheme 4.** Synthesis of heterodiazolobenzoporphyrins.



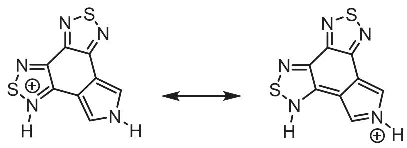
**Scheme 5.** Synthesis of a bis(thiadiazolo)benzoporphyrin.



**Scheme 6.** EIMS fragmentation of fused-ring pyrrole **21**.

electron density from the pyrrole moiety due to monoprotonation of this system. In an attempt to overcome these problems, nonacidic conditions for tripyrrane formation were investigated. Chloromethylpyrrole **23**[24] was dissolved in pyridine and then reacted with **19** under refluxing conditions. Initially, a pyridinium derivative is generated and subsequent elimination of pyridine would then give the cationic intermediate required for carbon–carbon bond formation. This procedure afforded modest yields of tripyrrane **22**. Purification on silica, eluting with 1% triethylamine-dichloromethane, gave crude **22** in 24% yield. Proton NMR spectroscopy indicated that the compound was 80–90% pure but further attempts to purify the product led to decomposition. When refluxing 4-picoline was used instead of pyridine, poorer yields were obtained, and addition of 4-dimethylaminopyridine also failed to give beneficial results. Nevertheless, the procedure provided sufficient material to explore the synthesis of bis(thiadiazolo)benzoporphyrin **18**.

Tripyrrane **22** was treated with TFA for 5 min and then condensed with pyrrole dialdehyde **13** in dichloromethane. Following oxidation with DDQ, purification by column chromatography and recrystallization, **18** was isolated in 35% yield. The proton NMR spectrum for **18** in TFA-$CDCl_3$ showed the *meso*-protons at 12.10 (5,20-H) and 10.65 ppm (10,15-H), while the internal NH protons appeared near −3 ppm. In addition, the methyl substituents gave a 6H singlet at 3.71 ppm, while the methylene units of the ethyl groups gave rise to two 4H quartets at 4.15 and 4.30 ppm. These results confirm that the macrocycle retains a strong diamagnetic ring current. The carbon-13 NMR spectrum showed the *meso*-carbons at typical values of 99.4 and 102.7 ppm. The UV–vis spectrum of **18** in chloroform gave a strong Soret band at 436 nm and two moderately strong absorptions at 574 and 602 nm (Fig. 1). Two weaker Q bands were also noted at 530 and 642 nm. The spectrum shows that the porphyrin chromophore has been substantially modified by the presence of the fused heterocyclic unit, but no useful long wavelength absorptions are observed. Addition of TFA led to the formation of cationic species and an absorption appeared at 621–623 nm (Fig. 1). Although the proton NMR spectrum indicated that both of the internal imine nitrogens had been protonated, it was not clear whether the bis(thiadiazolo)benzo unit had also been protonated.



**Scheme 7.** Protonation of **19** further deactivates the pyrrole unit towards electrophilic substitution.

Reaction of **18** with nickel(II), copper(II) or zinc acetate in refluxing DMF gave the related metalloporphyrins **Ni18**, **Cu18** and **Zn18** (Scheme 5). All three complexes were highly insoluble but could be characterized by high resolution mass spectrometry. In addition, UV–vis spectra for the series were also obtained (Fig. 2). **Ni18** gave a Soret band at 430 nm and an additional strong absorption at 608 nm. These bands appeared at 434 and 615 nm for **Cu18** and 444 and 623 nm for the zinc complex, showing a trend towards longer wavelengths with increasing atomic number. The solubility of **Zn18** was improved by addition of pyrrolidine but this also led to increased intensities for the absorption bands and bathochromic shifts to give the major absorptions at 457 and 632 nm.

Carbaporphyrins [26], porphyrin-like structures with carbons replacing one or more of the nitrogens with the macrocycle, can also be prepared by the '3 + 1' methodology. Reaction of tripyrrane **22** with indene dialdehyde **24** in the presence of TFA, followed by oxidation with DDQ, gave porphyrin analogue **25** in 25% yield (Scheme 8). Carbaporphyrin **25** also proved to be very insoluble but proton NMR data could be obtained for samples in $CDCl_3$ containing trace amounts of TFA. This results in protonation of the interior imine nitrogen to give cation **25**$H^+$, although it is possible that protonation is also occurring on the peripheral nitrogens. The results indicated that the system again retains a high degree of diatropic character. The internal CH gave an upfield singlet at −6.39 ppm, while the *meso*-protons gave rise to two 2H singlets in the downfield region at 10.32 and 11.68 ppm. Carbon-13 NMR data could not be obtained directly, but the HSQC spectrum

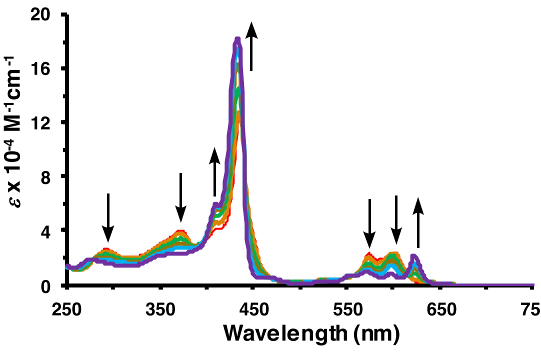


**Fig. 1.** UV–vis spectra of porphyrin **18** in $CHCl_3$ (red line) and with 1 equiv. (orange), 3 equiv. (green), 4 equiv. (light blue), 5 equiv. (dark blue) and 10 equiv. (purple) of TFA showing the formation of a protonated species.

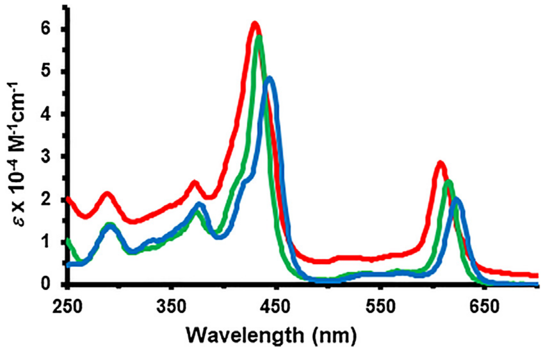
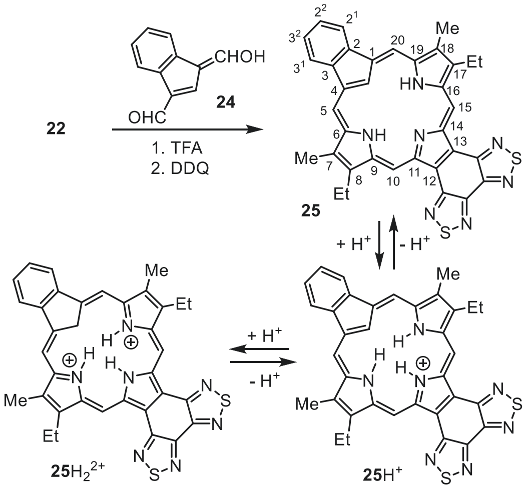


**Fig. 2.** UV–vis spectra of **Ni18** (red line), **Cu18** (green line) and **Zn18** (blue line) in chloroform.



**Scheme 8.** Synthesis of carbaporphyrin **25**.

showed that the *meso*-carbon resonances appear at 98.9 and 105.0 ppm. The UV–vis spectrum for **25** gave a Soret band at 447 nm and Q bands at 551, 597, 635 and 696 nm (Fig. 3). Addition of 10 equiv of TFA showed the formation of a new species with a Soret band at 470 nm and this was attributed to monocation **25**H$^+$. At much higher concentrations of TFA (40% TFA-CHCl$_3$), further changes are observed with the emergence of a Soret band at 457 nm and Q bands extending to 693 nm. The spectrum is consistent with C-protonated species such as **25**H$_2^{2+}$, but additional protonation may also be occurring on the external nitrogens.

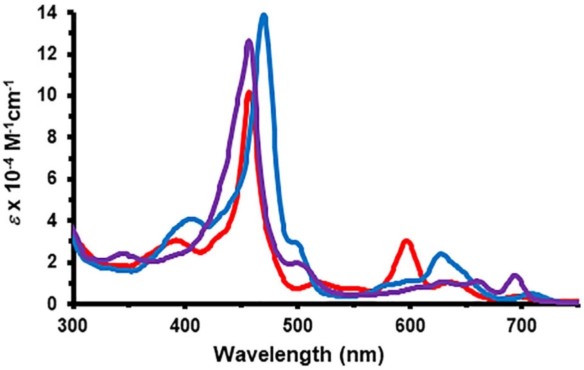


**Fig. 3.** UV–vis spectra of **25** in CHCl$_3$ (free base, red line), 1% TFA-CHCl$_3$ (blue line) and 40% TFA-CHCl$_3$ (purple line).

## Conclusion

Application of the Barton-Zard pyrrole synthesis allowed the preparation of an unusual bis(thiadiazolo)benzopyrrole ester by DBU-mediated condensation of 4-nitrobenzo[1,2-*c*:3,4-*c*']bis(1,2,5)thiadiazole with ethyl isocyanoacetate. Following cleavage of the ester unit, reaction with two equivalents of a chloromethylpyrrole in refluxing pyridine afforded a tripyrrane intermediate. This condensed with pyrrole or indene dialdehydes in the presence of TFA to give novel bis(thiadiazolo)benzoporphyrinoids. Both of the porphyrinoid products retained strongly aromatic characteristics but had highly modified UV–vis spectra. The metalated derivatives of the ring-fused porphyrin gave strong absorptions above 600 nm, values that approach those needed for applications in PDT.

## Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152576.

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