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Improved Synthesis of 10,20-Bis- and 5,10,15,20-Tetraethynylporphyrins via Ethynyl Protection with Dicobalt Octacarbonyl

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Abstract: *yields of the title compounds are improved by protection of the precursor propynal ethynyl groups with dicobalt octacarbonyl: Lindsey porphyrin synthesis results in brown cobalt-carbonyl-protected compounds which are oxidatively deprotected to yield green ethynyl-substituted porphyrins.*
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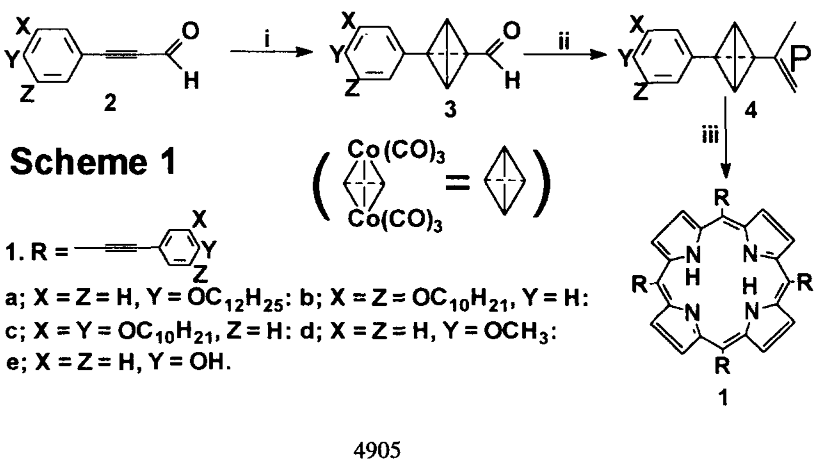
One-pot synthesis of 5,10,15,20-tetraethynylporphyrins[1a,b] **1** (trivially known as chlorphyrins because of their green colour) affords low yields and an unsymmetrical by-product.[1a] These problems are partially solved using the two-pot procedure of Lee and Lindsey[2b] (via a 5-substituted dipyrromethane),[1b,c] and we have prepared compounds **1a-c** that demonstrate discotic mesomorphism with 3rd-order non-linear optical (NLO) activity,[3,4] saturable- and reverse saturable absorption,[4] and photophysical properties commensurate with highly promising 2nd-generation photodynamic therapeutic (PDT) agents.[5]

The range of compounds **1** produced so far, however, is limited to those[1] capable of solublisation in chlorinated solvents. It has proved impossible to prepare for example the less soluble compounds **1d**, and **1e** because their precursors precipitate from the dichloromethane (DCM) reaction mixture prior to cyclisation. We report here a modification to our original synthesis that markedly improves yields of **1a** and 10,20-bisethynylporphyrins **5** and **6**, and allows entry to less organic-soluble compounds of these types.



Scheme 1

a; X = Z = H, Y = $OC_{12}H_{25}$: b; X = Z = $OC_{10}H_{21}$, Y = H: c; X = Y = $OC_{10}H_{21}$, Z = H: d; X = Z = H, Y = OCH_3: e; X = Z = H, Y = OH.

In the one-pot synthesis of compounds **1**, the presence of ethynyl groups seems to decrease porphyrin yields, purity, and solubility[6]. We decided to protect the ethynyl groups at the aldehyde stage, using dicobalt octacarbonyl (see Scheme 1).[7] Thus, the arylpropynal **2a**[1a] was stirred in THF with $Co_2(CO)_8$ at room temperature until effervescence (of CO) ceased. The $Co_2(CO)_8$ saturates the triple bond, giving the $Co_2(CO)_6$-ethynyl-protected aldehyde **3a** which, like $Co_2(CO)_8$, is chocolate brown in colour. The product was purified by column chromatography on silica gel and characterised by ir. This showed loss of the characteristic ethynyl band at 2196 cm^{-1}, and the appearance of terminal carbonyl groups centred on 2062 cm^{-1}. Proton nmr showed a downfield shift of 1 ppm for the aldehyde proton, now deshielded due to loss of the ethynyl moiety.

The protected aldehyde **3a** was then reacted with an equimolar amount of pyrrole under Lindsey conditions using $BF_3.Et_2O$ as catalyst.[2a] After oxidation with DDQ, the reaction solution remained chocolate brown, but tlc (on silica gel) showed consumption of **3a**. Interestingly, when the brown tlc spot was exposed to light it eventually turned green, indicating the presence of compound **1a**.

The product (a *meso*tetra{$Co_2(CO)_6$-ethynyl-protected}porphyrin, **4a**) was then cleanly separated by column chromatography on silica gel. Uv/visible spectroscopy gave no clear indication of a porphyrin, as the usual sharp B and Q bands were indistinct. Instead, exceptionally broad, weak bands were observed around 420 and 500-650 nm. To ascertain that the $Co_2(CO)_6$-protected porphyrin **4a** had indeed been produced, a sample of compound **1a**, prepared by the previous route,[1a,b] was treated with $Co_2(CO)_8$. The green colour disappeared during 1 hour, to give a chocolate-brown solution which had extremely broad, weak uv/visible bands in the 420 nm and 500-650 nm regions. The broadness of the peaks shows the electron-withdrawing influence of the eight cobalt centres (which depopulate the porphyrin excited state).[8]

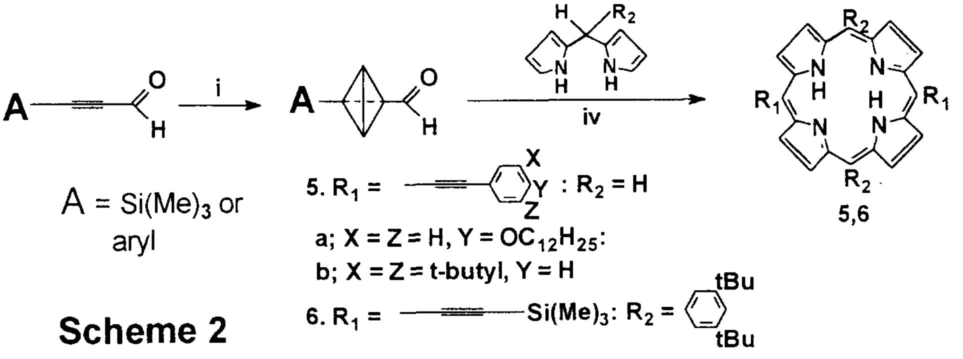
Seyferth, *et. al.* used ceric ammonium nitrate (CAN) to oxidatively deprotect $Co_2(CO)_6$-protected diarylacetylenes.[7b] We used the milder oxidising agent ferric perchlorate for quantitative deprotection; indeed, CAN destroys the porphyrin macrocycle. Thus, a brown DCM solution of **4a**, shaken at room temperature with excess methanolic ferric perchlorate, quantitatively produces a deep green solution which, after purification by column chromatography, gave a good yield of compound **1a** (35% from **2a** without any by-product); a 10-fold increase in yield over our previous one-pot route.[1a] Following the tlc observation above, we were also able to generate the compound **1a** photochemically by exposing a solution of the $Co_2(CO)_6$-ethynyl-protected porphyrin to light in the presence of silica gel during several hours.[9] Presumably, the porphyrin excited state generated next to the protected ethynyl groups, serves to oxidatively remove that protection.

Protecting the ethynyl groups with $Co_2(CO)_8$ increases the solubility of a *meso*tetraethynylporphyrin. This allowes the synthesis of previously inaccessible (i.e., less organic-soluble) compounds **1**, e.g., the 4-methoxy-substituted **1d** and the 4-hydroxy-substituted **1e**, both from **3d**. The latter (**1e**) was prepared by demethylation of **4d** (with boron tribromide in DCM at -80°C)[10] prior to deprotection with methanolic ferric perchlorate. We shall report more fully on the synthesis and properties of **1d** and **1e** at a later date.

We have also prepared 10,20-bisarylethynylporphyrins **5a** and **5b** (unsubstituted in their 5- and 15-*meso*positions) in good yields (46%) via $Co_2(CO)_8$-ethynyl protection of the precursor arylpropynal (Scheme 2). Interestingly, these compounds could not be prepared using unsubstituted dipyrromethane and *unprotected* arylpropynal. Although compounds **5** proved somewhat unstable to light and air, it was possible to identify them by uv-visible spectroscopy (B band at 434 nm, two main Q bands at 587 and 674 nm) and their characteristic ^{1}H-nmr spectra (i.e., for **5b**, an AB spin-pattern of β-hydrogen resonances centred on 9.53 ppm, J_{AB} = 4.38 Hz, and a low-field singlet at 10.1 ppm for the two 5,15-*meso*-protons).

As previously observed,[1c] this reaction is sensitive to conditions for if the reaction temperature is too high, or the reaction time too long, scrambling[11] of the porphyrinogen occurs to yield, on oxidation, mixtures of mono-, di- (5,10- and 5,15-), and triarylethynylporphyrins that are difficult to separate. Even so, mixtures of the 5,15- and 5,10-*bis*(arylethynyl)porphyrins are produced. The 5,10-isomer was identified again by the splitting pattern of its β-pyrrolic protons, this time into two AB spin systems.

Therien *et. al.*[12] and Anderson *et. al.*[1c] have both prepared 5,15-bisaryl-10,20-bisethynylporphyrins. In particular, Anderson achieved low yields (19%) of compound **6** by reaction of a 5-(3',5'-di-t-butylphenyl)-substituted dipyrromethane with trimethylsilylpropynal in DCM, using $BF_3.Et_2O$ as catalyst. We have found, however, that prior protection of this aldehyde with $Co_2(CO)_8$ (see Scheme 2), reaction with the same 5-substituted dipyrromethane, followed by oxidative deprotection of the thus formed $Co_2(CO)_6$-protected porphyrin with ferric perchlorate, gave a higher yield of **6** (40% from the unprotected aldehyde, identical spectroscopically with Anderson's compound)[1c] with very little contamination by the 5,10-bis(trimethylsilylethynyl)porphyrin isomer. We also obtained cleaner samples and similar yields of the precursor 5-substituted dipyrromethane,[1c] using $BF_3.Et_2O$ in place of trifluoroacetic acid as the catalyst for coupling pyrrole to the aryl aldehyde.



Scheme 2

Interestingly (and unlike the synthesis of compounds **1**), deprotection of the ethynyl groups to form **5** (and more slowly **6**) occurs spontaneously as the porphyrinogen is oxidised. The amount of DDQ is just enough to oxidise the porphyrinogen: there is insufficient to oxidatively remove the $Co_2(CO)_6$ protecting groups. As light was excluded from the reaction, the deprotection is unlikely to involve formation of an adjacent oxidising porphyrin excited state, as with compounds **1**. Also, attempts to reprotect the ethynyl moieties of **5** with $Co_2(CO)_8$ failed. We have yet to establish and substantiate a satisfactory mechanism for this spontaneous deprotection.

In conclusion, we have used $Co_2(CO)_8$ to protect the ethynyl groups of precursor propynals, for the preparation of *meso*ethynyl-substituted porphyrins **1**, **5**, and **6**. in good yields by one-pot procedures. The added solubility afforded by the $Co_2(CO)_6$-protecting groups in the cyclisation step, permitted production of the less soluble **1d** and **1e** which could not be prepared by our previous routes.[1a,b] We believe this finding opens up a synthetic route to compounds **1** with a larger range of substituents, and therefore applications, e.g., water-soluble chlorphyrins for PDT and the production of conducting[13] and/or electroluminescent[14] polymers. However, the low stability of compounds **5** precludes their possible application as calamitic liquid crystals.[15]

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9. Key to reactions outlined in Scheme: i; $Co_2(CO)_8$/THF/r.t.: ii; pyrrole/$BF_3.Et_2O$/DCM/-25°C: iii; $Fe(ClO_4)_3$/MeOH or SiO_2/light: iv; dipyrromethane/$BF_3.Et_2O$/DCM/-25°C. All new compounds gave satisfactory elemental analyses. Arylpropynals were synthesised as reported previously.[1a] $Co_2(CO)_6$-protected arylpropynals were identified by ir and nmr and were used without further purification.
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