Phthalocyanine-porphyrin hybrids

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Synthesis of *Meso*-Substituted Tetrabenzotriazaporphyrins: Easy Access to Hybrid Macrocycles**

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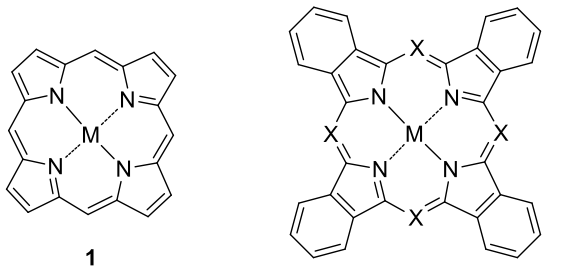
Dedicated to Professor Michael J. Cook on the occasion of his 70th Birthday.

Nature and synthetic chemistry have combined to provide a dazzling range of 18π-electron macrocyclic systems. They are exemplified by the parent structures porphyrin **1** and phthalocyanine **2** (Figure 1). Synthesis in particular has led to derivatives targeted for academic study and for applications in diverse fields of materials chemistry, photochemistry, biology and medicine. The research is reported in several thousand publications and summarized in comprehensive book series.[1]

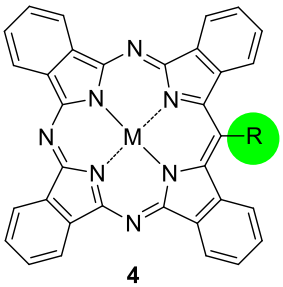


1
Porphyrin

2 X = N (Phthalocyanine)
3 X = C-H (Tetrabenzoporphyrin)

Figure 1. Parent structures porphyrin **1**, phthalocyanine **2** and tetrabenzoporphyrin **3** (M = metal or H, H).

Replacement of one or more of the bridging nitrogen atoms of phthalocyanine **2** by sp^2 carbon atoms leads to so-called hybrid structures – intermediate between the parent phthalocyanine and tetrabenzoporphyrin **3**.[2] Such hybrids are intrinsically fascinating because they offer potential to bridge the properties of the two systems and provide new chemistry within the field of macrocyclic chemistry. The present paper is concerned with the hybrid structure in which just one of the bridging aza groups is replaced by a carbon atom, *i.e.* tetrabenzotriazaporphyrin (TBTAP) **4** (Figure 2), a system that represents the most limited structural difference to a phthalocyanine within the series of hybrid compounds. Indeed, MO calculations[3] show that the molecular orbital systems of **2** and **4** are closely similar but with the TBTAP system developing a larger HOMO-LUMO energy difference leading to a small hypsochromic shift of the main visible region band. However, the principal difference that can be exploited within the TBTAP structure is the presence of the *meso* carbon. Apart from introducing a small dipole moment into the system, the structure affords the synthetic chemist the opportunity to develop chemistry unavailable to the phthalocyanine series. Thus, in short, functionalization of the *meso* position can provide a series of discrete, high-symmetry phthalocyanine type structures with functionality that can serve, for example, to attach the macrocycle uniquely to surfaces or can allow the ready construction of more complex materials, such as multi-macrocyclic systems.



4
Tetrabenzotriazaporphyrin
(TBTAP)

Figure 2. Tetrabenzotriazaporphyrin (TBTAP) **4** (M = metal or H, H; R = H for the parent structure).

While the fields of phthalocyanine and porphyrin research have become increasingly mature, the development of the chemistry of the hybrids has been very slow. Though examples of the hybrid structures were in fact first reported in the 1930's, largely as offshoots from the early seminal work on phthalocyanine macrocycles of that era,[4] the area has attracted substantially fewer than 200 publications to this day. This is despite a recent resurgence of interest in TBTAPs and analogues with fewer nitrogen bridges. A key reason for this is that the synthesis of such compounds has always proved challenging and this drawback has severely hindered their investigation. Indeed of the few publications referred to, only a small fraction attempt to address the inherent synthetic issues involved in their preparation.[2] These syntheses are mostly based on Linstead's original strategy whereby phthalonitriles are treated with an organometallic reagent such as methylmagnesium bromide at high temperature (Scheme 1).

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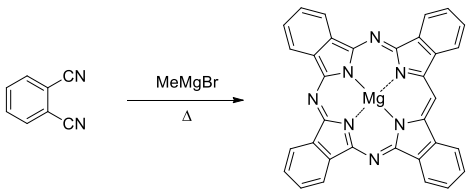
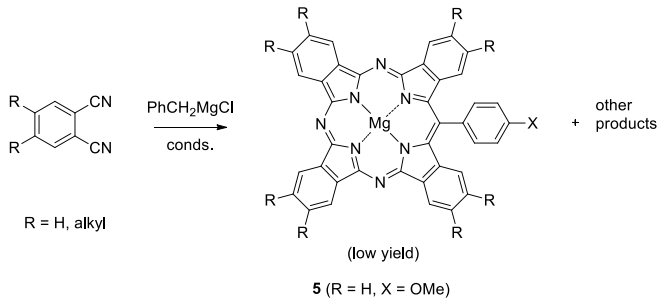


Scheme 1. Linstead's synthesis of parent tetrabenzotriazaporphyrin (TBTAP).[4b]

Subsequent work has demonstrated that Grignard reagents and other carbon nucleophiles can therefore be employed at high temperatures to provide the *meso*-carbon. However, all the reactions remain capricious and typically result in mixtures of products and low (typically <10%) yield of TBTAP.[5-9] A particular problem with these approaches is the lack of control in the syntheses that inevitably result in formation of other hybrids alongside the TBTAP. We have recently reported a particular example where the product distribution can be tailored to favor particular hybrids by careful control over the amount of Grignard reagent employed, but mixtures are still always formed.[9]

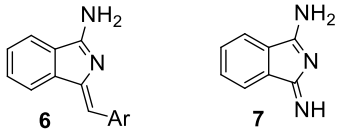
TBTAPs bearing a (functionalized) phenyl group on the *meso*-carbon are particularly attractive materials; they are the phthalocyanine hybrid analogues of the widely studied *meso*-phenylporphyrins. Synthesis of the parent *meso*-phenyl-TBTAP has been achieved using the reaction between benzyl-Grignard reagents and phthalonitrile but the reaction is low-yielding and unsatisfactory due to formation of a mixture of products (Scheme 2). Formation of analogues functionalized on the *meso*-phenyl group is even more challenging, and following this route requires formation of the appropriate benzyl Grignard reagent combined with low-yielding macrocycle formation.

For our research on multichromophore arrays we identified *meso*-functionalized TBTAPs as ideal components, not least because we recognized that the core structure and properties would be unperturbed by chemistry performed on the *meso*-phenyl substituent (as in *meso*-phenyl porphyrins, the two rings will lie perpendicular with their π-systems decoupled). We therefore required an efficient and versatile synthesis of such TBTAPs and investigated available routes leading to, in particular, *meso*-4-methoxyphenylTBTAP **5**.[7] As expected, in accordance with literature reports on similar attempted syntheses, the reaction between 4-methoxybenzylmagnesium chloride and phthalonitrile proved complex and low-yielding; separation and isolation of the TBTAP product was also very difficult.

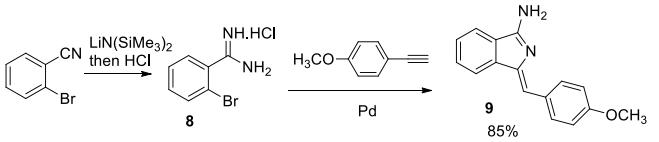


Scheme 2. The reaction of phthalonitriles with benzyl Grignard reagents under standard TBTAP-forming conditions; note that 3,6-dialkyl phthalonitriles cannot produce meso-aryl TBTAPs due to steric crowding.[9]

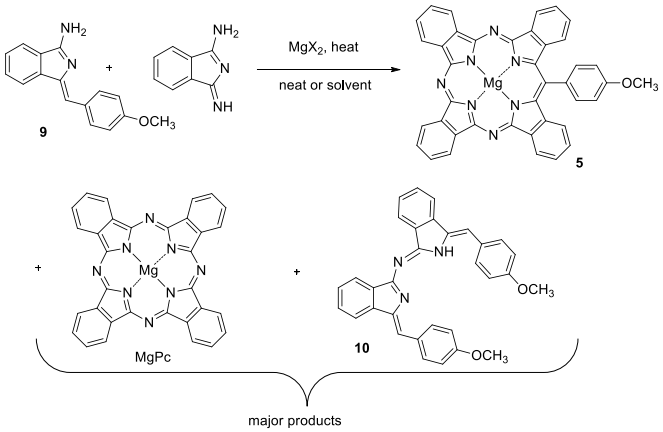
It was clear that the known strategies for synthesis of *meso*-substituted TBTAPs would never give useful or versatile access to the materials. Consequently we embarked on a new approach to TBTAP synthesis and conceived intermediates such as aminoisoindoline **6**; they are Ar-C analogues of diiminoisoindolines (**7**) that are frequently the precursors of choice in simple phthalocyanine synthesis. We reasoned that **6** would be incorporated during macrocycle formation, avoiding both the formation of other hybrids and unwanted byproducts.



Modern synthetic methodology is extremely powerful and transition-metal catalysis has become prominent. In particular for our purposes, methodology is now available for synthesis of the key intermediates like **6**. Our investigations remained focused on preparation of *meso*-4-methoxyphenylTBTAP **5**. So, following the methodology reported by Hellal and Cuny,[10] 4-bromobenzonitrile was treated with LiHMDS and hydrolyzed to give the HCl salt of bromoamidine **8**.[11] Treatment of **8** with 4-methoxyphenylacetylene, under palladium catalysis leads to cross-coupling and cyclization, yielding precursor **9** directly and in good yield (Scheme 3).



Scheme 3. Palladium catalyzed synthesis of substituted aminoisoindoline **9**.

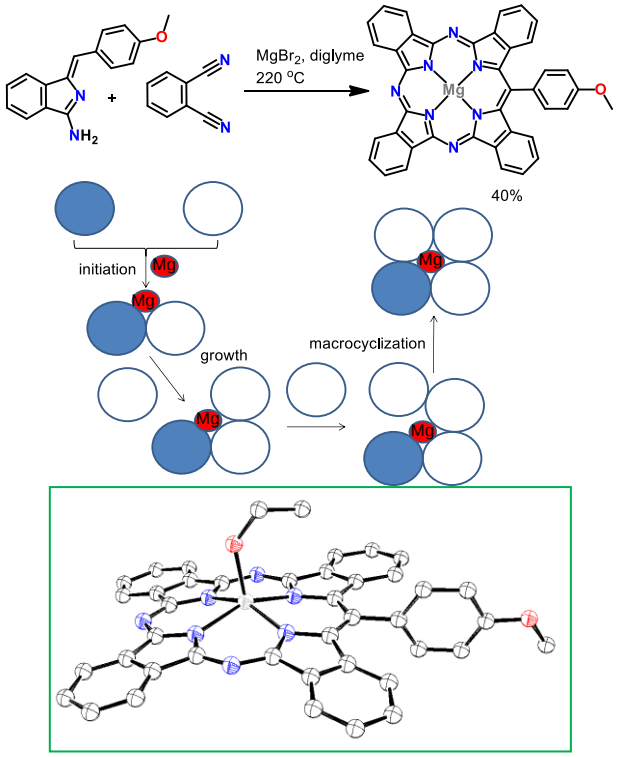


Scheme 4. First synthesis of *meso*-substituted TBTAP using aminoisoindoline **9** as precursor.

With intermediate **9** in hand we were in a position to employ modifications of typical conditions for macrocyclization. In the first set of experiments we selected diiminoisoindoline **7** as complementary macrocyclization partner and reactions with precursor **9** at high temperature in the presence of magnesium salt templates were performed (neat or in solvents such as quinoline, diglyme, DMF and dimethylaminoethanol) (Scheme 4). The required *meso*-4-methoxyphenylTBTAP **5** was indeed formed in these reactions, but the overall outcome was not satisfactory and two other products dominated in the product mixture. The first side-product was easily identified as magnesium phthalocyanine. Its formation is unsurprising because it is known to form from

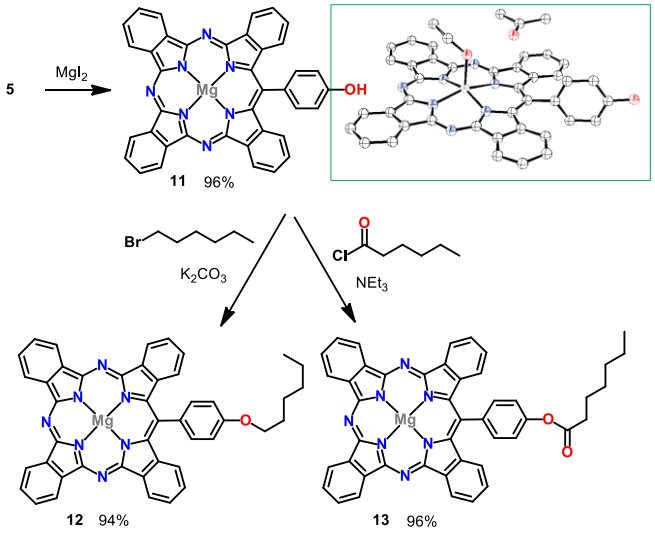
diiminoisoindoline **7** in the presence of a template ion at this high reaction temperature. The second major product (red) was characterized as the self-condensation product **10** formed solely from **9**. This intermediate can in principle also act as a precursor to TBTAP, but in practice it does not lead to significant formation of this macrocyle when re-subjected to the reaction conditions in the presence of more diiminoisoindoline.

Like the Grignard reagent route, this approach therefore also appears to be of limited value, leading to two self-condensations that result in irreversible formation of PcMg and **10**. However, with more careful matching of reactivities of the substrates we were able to transform this synthesis into the first useful and versatile method for accessing *meso*-substituted TBTAPs. Specifically, the key to success is exchanging diiminoisoindoline with less reactive (in terms of self-macrocyclization) phthalonitrile. The direct formation of MgPc is therefore avoided. At 220°C in the presence of magnesium ions, however, reaction between **9** and phthalonitrile is initiated, and the rate of this reaction is competitive with its self-condensation. After this initiation, further additions of phthalonitrile no doubt lead to oligomer formation. Under these same conditions (220°C, Mg^{2+}) macrocyclization is also induced so the growing oligomer cyclizes when it reaches 4 units long, presumably with expulsion of ammonia (Scheme 5). More subtle variations improved the reaction further. Controlled addition of **9** to the heated mixture of the other reaction components minimizes its self-condensation. Separate evidence also implied strong complex formation between the magnesium TBTAP **5** and starting material **9**. Indeed chromatography of early reaction mixtures led to isolation of 1:1 mixtures of Mg-TBTAP **5** and **9**. Addition of DABCO to the reaction mixture results in release and complete consumption of starting material **9** and correspondingly improved yield.



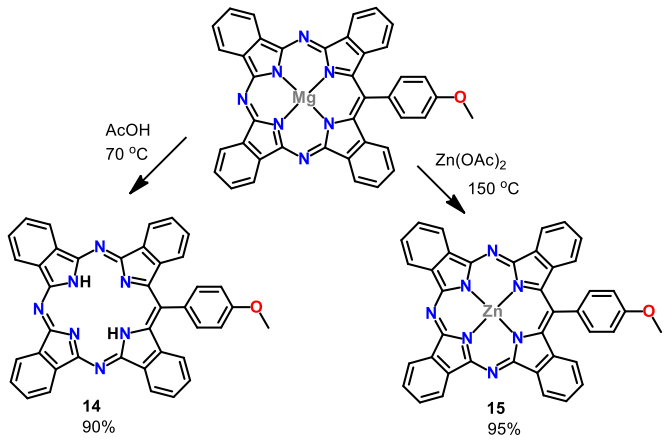
Scheme 5. Efficient synthesis of magnesium *meso*-(4-methoxyphenyl) TBTAP **5** and its X-ray crystal structure.

The final optimized synthesis is straightforward to perform and reproducible, giving impressive yields of around 40% - values that are considered normal and acceptable in the formation of *simple* symmetrical phthalocyanine analogues. Isolation is also significantly simplified, and the availability of magnesium *meso*-4-methoxyphenylTBTAP **5** in quantity has allowed further chemistry to be explored to produce important additional derivatives. Crystals suitable for crystal X-ray crystallography have been obtained for *meso*-4-methoxyphenylTBTAP **5** (and 3 subsequent derivatives – see below)[12]. These are the first reported crystal structures for *meso*-substituted TBTAPs. The reaction sequences are complementary and shown in Schemes 6 and 7. The first sequence (Scheme 6) demonstrates smooth demethylation to yield *meso*-4-hydroxyphenylTBTAP **11**; this is a particularly important step because it yields the first *meso*-phenyl TBTAP that bears a reactive functional group ready for further elaboration. The transformation employs magnesium iodide as reagent[13] to ensure the integrity of the central metal ion is maintained. Subsequent functionalization through ether and ester bond-formation is straightforward and achieved using conventional conditions in excellent yields. As predicted, the UV-Vis absorption profiles for **5**, **11-13** are essentially identical (Supporting Information).



Scheme 6. Demethylation of **5** to give the corresponding phenol **11**, and its re-alkylation/acylation; the X-ray crystal structure for **11** is shown (H-atoms omitted for clarity), and the crystal structures for **12** and **13** are shown in Supporting Information.

In complementary fashion (Scheme 7), de-metallation is achieved by treatment with acetic acid at 70°C, conditions that leave the methyl ether intact. Re-metallation is then possible, but single step transmetallation with zinc is also smoothly accomplished directly from the magnesium TBTAP **5**.



Scheme 7. Demetallation and transmetallation of **5**.

In summary, for the first time a straightforward, versatile, high yielding synthesis of *meso*-substituted tetrabenzotriazaporphyrins (TBTAPs) is available, giving access to a range of new materials suitable for elaboration into bespoke derivatives and structures. The breakthrough stems from a new approach to synthesis of TBTAPs from precursors like **9** that are themselves easily accessed using modern palladium catalysis. Aminoisoindoline **9** acts as initiator for macrocyclization, providing the hybrid's *meso*-carbon *and* its functionalization. The straightforward new synthesis and good yields of functionalized TBTAPs that have been obtained herald the prospect of facile development of TBTAP chemistry. The synthetic versatility and potential is demonstrated for the parent magnesium *meso*-4-methoxyphenylTBTAP **5** where conditions to exclusively demethylate or demetallate are described, giving further precursors suitable for functionalization. The first crystal structures for *meso*-substituted TBTAPs are also reported.

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[12] CCDC 948596 (**5**), CCDC 948597 (**11**), CCDC 948598 (**12**), and CCDC 948599 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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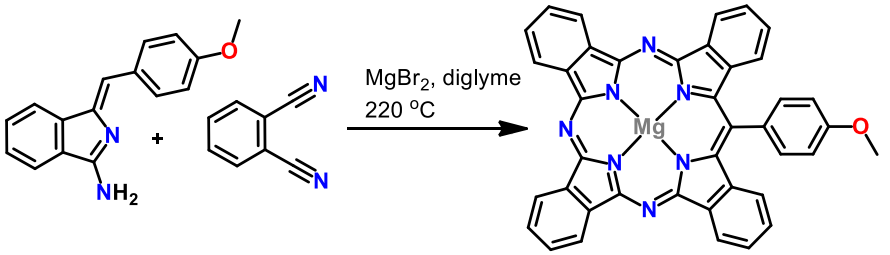
Phthalocyanine-porphyrin hybrids

Alejandro Díaz-Moscoso*, Graham J. Tizzard, Simon J. Coles and Andrew N. Cammidge*_____ **Page – Page**

Synthesis of *Meso*-Substituted Tetrabenzotriazaporphyrins: Easy Access to Hybrid Macrocycles



[i]

Hybrid structures that lie between the ubiquitous phthalocyanine and porphyrin scaffolds are fascinating materials. Until now, all but the simplest parent compounds have been extremely difficult to prepare and isolate. A straightforward, high yielding synthesis of *meso*-derivatized tetrabenzotriazaporphyrins (TBTAPs) is described, unlocking access to new materials suitable for elaboration into bespoke derivatives and structures.

[ii]