Heterocycles

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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

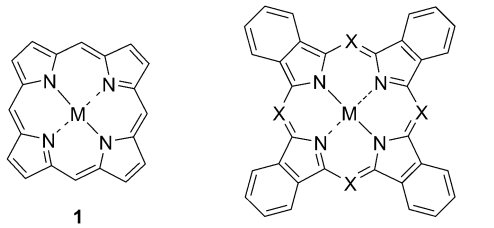

Figure 1. The parent structures porphyrin (**1**), phthalocyanine (**2**), and tetrabenzoporphyrin (**3**; M = metal or H, H).

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]

Replacement of one or more of the bridging nitrogen atoms of phthalocyanine (**2**) by sp^2-carbon atoms leads to so-called hybrid structures, which are intermediate between the parent **2** and tetrabenzoporphyrin (**3**).[2] Such hybrids are intrinsically fascinating because they offer the 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, that is, tetrabenzotriazaporphyrin (TBTAP; **4**;

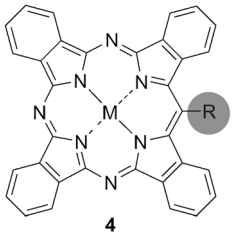

Figure 2. Tetrabenzotriazaporphyrin (TBTAP; **4**; M = metal or H, H; R = H for the parent structure).

Figure 2), a system which represents the most limited structural difference to a phthalocyanine within the series of hybrid compounds. Indeed, molecular orbital (MO) calculations[3] show that the molecular orbital systems of **2** and **4** are similar, with the TBTAP system developing a larger HOMO–LUMO energy difference, thus 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 atom. 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 and can serve, for example, to attach the macrocycle uniquely to surfaces or allow the ready construction of more complex materials, such as multi-macrocyclic systems.

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 1930s, 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. Reports are therefore very few in number, despite a recent resurgence of interest in TBTAPs and analogues having fewer nitrogen bridges. A key reason is that the synthesis of such compounds has always proved challenging, a drawback which 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[4b] original strategy whereby phthalonitriles are treated with an organ-

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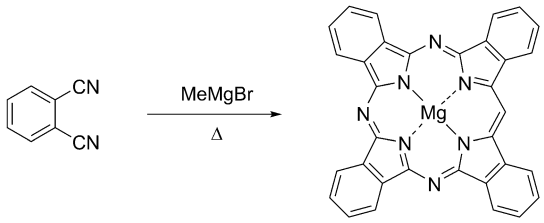


Scheme 1. Linstead's synthesis of parent tetrabenzotriazaporphyrin.[4b]

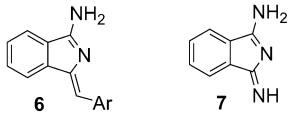
ometallic reagent such as methylmagnesium bromide at high temperature (Scheme 1).

Subsequent work has demonstrated that Grignard reagents and other carbon nucleophiles can therefore be employed at high temperatures to provide the meso-carbon atom. 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 which 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 atom 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 because of the 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.

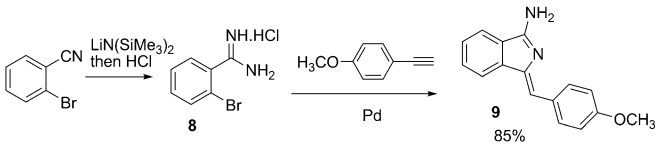
For our research on multichromophore arrays we identified meso-functionalized TBTAPs as ideal components, not least because we recognized that the core structure and properties would be unperturbed by chemistry performed on the meso-phenyl substituent (as in meso-phenyl porphyrins, the two rings will 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, the 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, and separation and isolation of the TBTAP product was also very difficult.

It was clear that the known strategies for the 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 the aminoisoindoline **6**, Ar-C analogues of



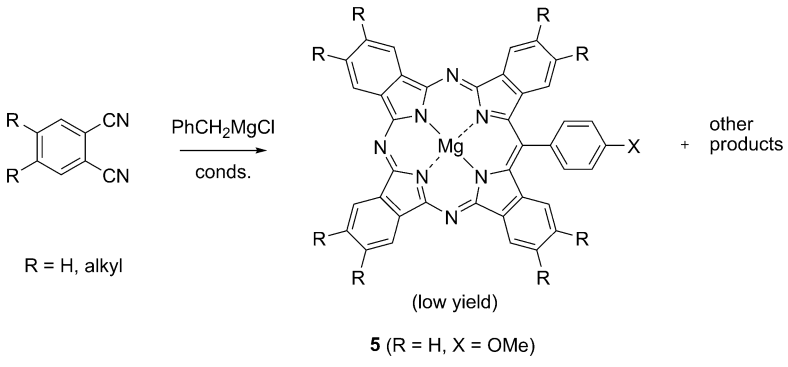
diiminoisoindoline (**7**), which are frequently the precursors of choice in simple phthalocyanine synthesis. We reasoned that **6** would be incorporated during macrocycle formation, thus avoiding both the formation of other hybrids and unwanted byproducts.

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 the preparation of **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 the bromoamidine **8** (Scheme 3).[11] Treatment of **8** with 4-methoxyphenylacetylene under palladium catalysis leads to cross-coupling and cyclization, thus yielding the precursor **9** directly and in good yield.

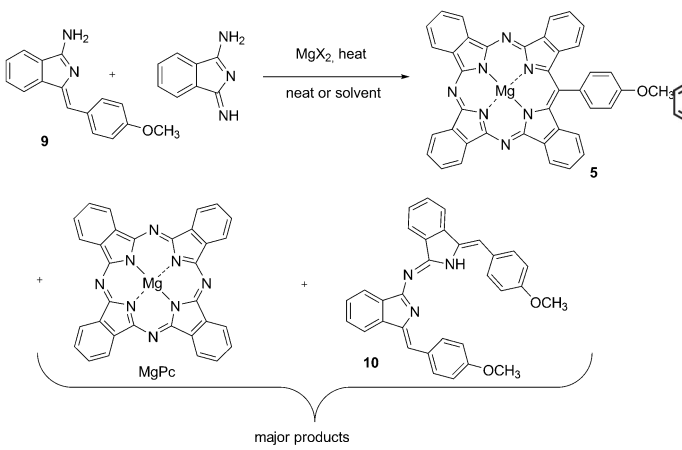


Scheme 3. Palladium-catalyzed synthesis of the substituted aminoisoindoline **9**.

With **9** in hand we were in a position to employ modifications of typical reaction conditions for macrocyclization. In the first set of experiments we selected **7** as complementary macrocyclization partner, and reactions with **9** at high temperature in the presence of magnesium salt templates were performed (neat or in solvents such as quinoline, diglyme, DMF, and



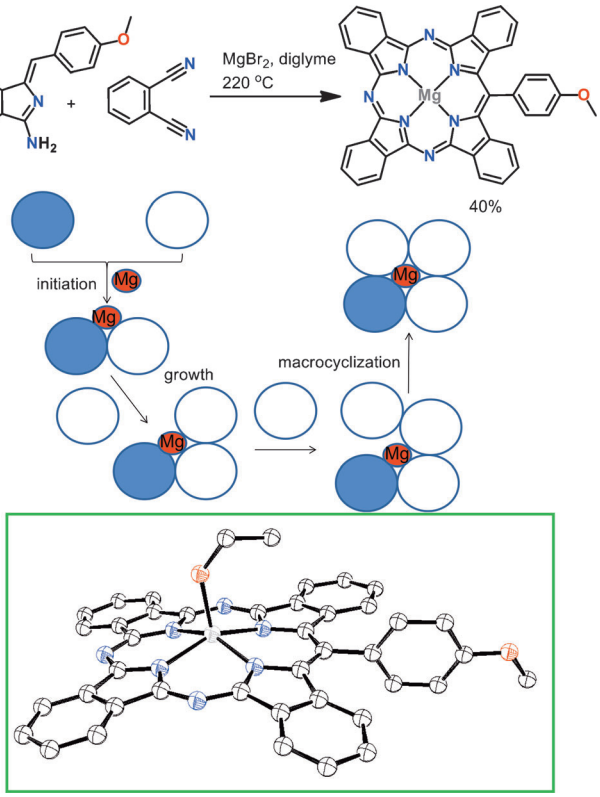
Scheme 2. The reaction of phthalonitriles with benzyl Grignard reagents under standard TBTAP-forming conditions. Note that 3,6-dialkyl phthalonitriles cannot produce meso-aryl TBTAPs because of steric crowding.[9]



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

dimethylaminoethanol; Scheme 4). The required **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 (MgPc). Its formation is unsurprising because it is known to form from **7** in the presence of a template ion at this high reaction temperature. The second major product 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.

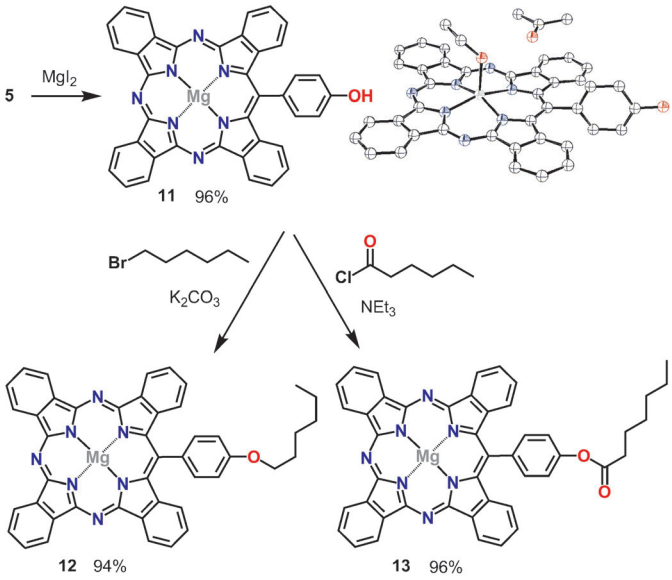
Like the Grignard reagent route, this approach therefore also appears to be of limited value, thus leading to two self-condensations which result in irreversible formation of MgPc and **10**. However, with more careful matching of the reactivities of the substrates we were able to transform this synthesis 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, the 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 reaction conditions (220 °C, Mg^{2+}) macrocyclization is also induced so the growing oligomer cyclizes when it is four units long, presumably with expulsion of ammonia (Scheme 5). More subtle variations improved the reaction additionally. 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 **5** and **9**. Addition of DABCO to the reaction mixture results in release and complete consumption of the starting material **9** and correspondingly improved yield.



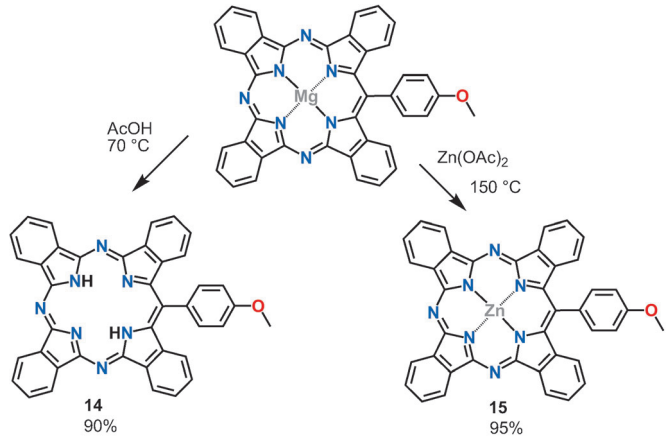
Scheme 5. Efficient synthesis of the magnesium meso-(4-methoxyphenyl) TBTAP **5** and its X-ray crystal structure. Thermal ellipsoids shown at 50% probability.

The final optimized synthesis is straightforward to perform and reproducible, thus giving impressive yields of around 40%, values which are considered normal and acceptable in the formation of simple symmetrical phthalocyanine analogues. Isolation is also significantly simplified, and the availability of **5** in quantities has allowed additional chemistry to be explored to produce important additional derivatives. Crystals suitable for X-ray crystallography have been obtained for **5** (and three other 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 the meso-4-hydroxyphenylTBTAP **11**. This sequence is particularly important because it yields the first meso-phenyl TBTAP which bears a reactive functional group ready for further elaboration. The transformation employs magnesium iodide as a 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 reaction conditions in excellent yields. As predicted, the UV/Vis absorption profiles for **5** and **11**–**13** are essentially identical (see the Supporting Information).

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



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; thermal ellipsoids shown at 50% probability), and the crystal structures for **12** and **13** are shown in the Supporting Information.



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

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