An expedient synthesis of substituted tetraaryltetrabenzoporphyrins†

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A simple route to tetraaryltetrabenzoporphyrins (Ar_4TBPs) is developed; the procedure allows for the introduction of substituents on both benzo- and phenyl-rings and employs readily available, inexpensive components.

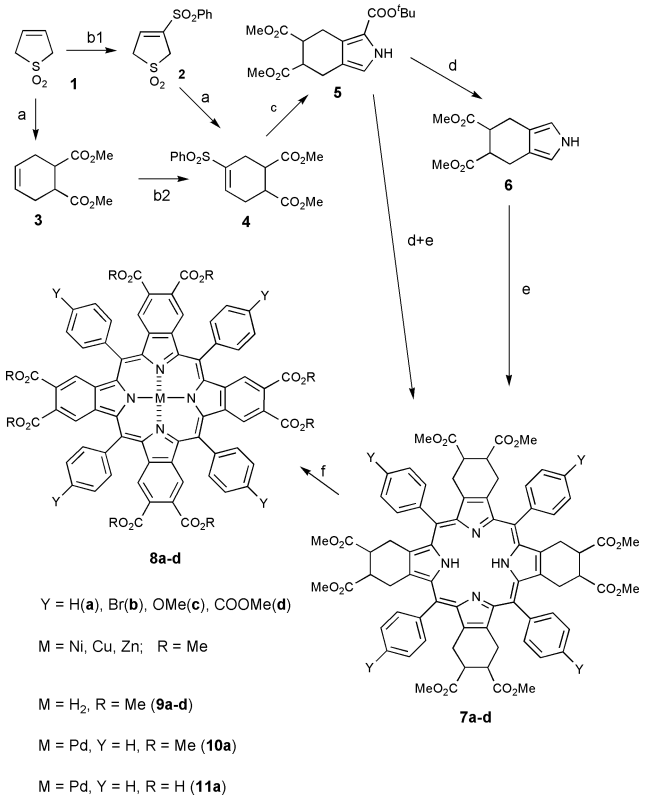
Tetrabenzoporphyrins (TBP's) and their metal complexes have rapidly gained popularity as versatile near infra-red dyes. The spectrum of their applications encompasses PDT (photodynamic therapy),[1a] non-linear optical absorption,[1b] optical limiting[1c] and dioxygen measurements *in vivo* by phosphorescence quenching.[1d] Due to solubility considerations the *meso*-tetraarylsubstituted TBP's (Ar_4TBP) have proven to be the most useful, especially those bearing functional groups in benzo and/or in *meso*-phenyl rings, which permit their further derivatization. However, until very recently all synthetic methods leading to Ar_4TBPs were based on a high temperature condensation between phthalimide and phenylacetic acids,[2a] or similar donors of benzo- and phenyl-groups.[2b] The harsh conditions of this process (fusion at 350–400 °C) allowed for only a few inert substituents, such as alkyl groups or halogens,[3] to be introduced into the TBP macrocycle. In addition, low yields and complex, virtually inseparable mixtures of products[4] made the whole method quite impractical.

Since the obvious precursor of the Ar_4TBP cycle, isoindole, is highly unstable, the recent search for more convenient synthetic protocols centered around isoindole-precursors, *i.e. c*-annelated pyrroles. These are available *via* Barton–Zard isocyanoacetate chemistry and have proven to be useful for the synthesis of other symmetric extended porphyrins.[5] Two methods of TBP synthesis of this kind were reported to date. Both methods are based on the Barton–Zard reaction and involve the initial synthesis of either cycloalkyl[6] or bicycloalkenyl fused porphyrins.[7] These intermediate porphyrins are then aromatized by either base catalyzed elimination of sulfinate[6] or the thermal retro-Diels–Alder extrusion of ethylene.[7] The latter method affords Ar_4TBPs in excellent yields; however, the synthesis of the isoindole precursors themselves, *i.e.* bicycloalkenyl fused pyrroles, involves hazardous compounds such as nitroethyl acetate. Here we report an alternative route to the Ar_4TBP system, which is both simple and general. The procedure allows for the introduction of substituents in both benzo- and *meso*-phenyl rings while employing only inexpensive and readily available components.

In our approach, the common precursor of the synthesis is the inexpensive sulfolene **1**‡ (Scheme 1), which is converted to a tetrahydroisoindole *via* the Diels–Alder reaction with an appropriate dienophile,[8] followed by the introduction of the phenylsulfonyl group and subsequent Barton–Zard-type reaction of the resulting vinyl sulfone.[9] Tetrahydroisoindoles are further introduced into Lindsey condensation, giving tetracyclohexanoporphyrins, which are finally aromatized.

The first successful application of this approach to the synthesis of the substituted Ar_4TBPs is shown in Scheme 1.§

Sulfolene **1** is converted to 3-phenylsulfonyl-3-sulfolene[10] **2** (b1) using earlier published procedures.[11] Alternatively, Diels–Alder adduct **3** with dimethyl maleate (DMM) is obtained in 85% yield (a). Both products, **3** and **2**, are further transformed into sulfone **4**. Compound **3** reacts with PhSCl, which is followed by oxidation and elimination of HCl (b2); **2** participates in the similar Diels–Alder reaction (a) with DMM.[12] Sulfone **4** reacts with *tert*-butyl isocyanoacetate (c)[13] yielding cyclohexanopyrrole **5** in 70–95% yield, which is deprotected and decarboxylated by TFA in CH_2Cl_2 (d) in 35–40% yield. Pyrrole **6** obtained in this way is introduced into the Lindsey condensation (e),[14] which produces porphyrins **7a**–**d** in 25–35% yields. Alternatively, porphyrins **7a**–**d** can be obtained by directly reacting cyclohexanopyrrole **5** with benzaldehydes under Alder–Longo conditions (d+e), in which case deprotection–decarboxylation occurs *in situ* in the presence of TsOH. Such simplification of the synthesis is especially practical when yields of the one-pot procedure (8–12%) are comparable with yields of the stepwise decarboxylation-condensation (8–14%). Noteworthy is that in all cases porphyrins **7a**–**d** were isolated as dications rather than as free-bases (evidenced by UV-VIS



Scheme 1 *Reagents and conditions*: a, DMM, py, 140 °C, pressure tube, 85%; b1, (i) PhSCl. CH_2Cl_2; (ii) Et_3N; (iii) Oxone, MOH, 86% for three steps; b2, (i) PhSCl, CH_2Cl_2; (ii) MCPBA; (iii) DBU, 81% for three steps; c, $CNCH_2CO_2{}^tBu$, ^tBuOK, THF, Ar, 0 °C, 80–95%; d, TFA–CH_2Cl_2, Ar, rt, 35–40%; e, (i) YC_6H_4CHO, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (ii) DDQ, 25–35% for two steps; d + e, YC_6H_4CHO (X = H), AcOH, TosOH, CH_2Cl_2, 8–12%; f, (i) $M(OAc)_2$, MeOH–$CHCl_3$; (ii) DDQ, THF or MeCN, reflux, M = Zn, Cu, Ni, 98% for two steps.

† Electronic supplementary information (ESI) available: experimental data. See http://www.rsc.org/suppdata/cc/b0/b008816l/

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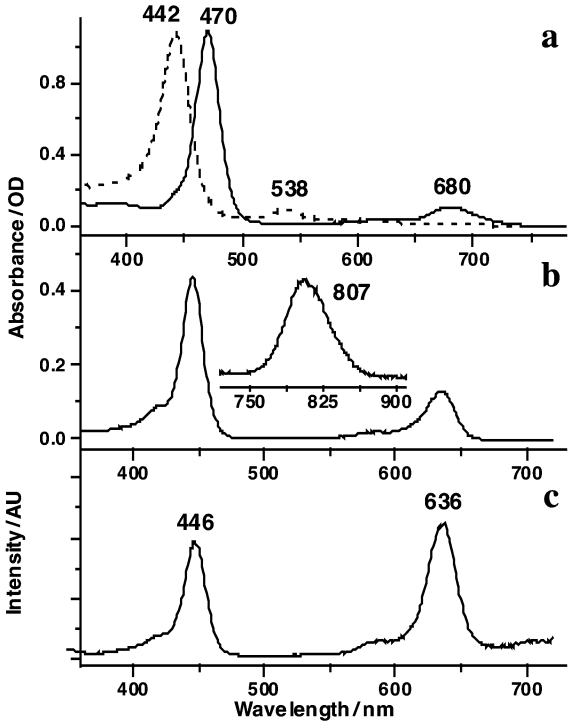

Fig. 1 (a) Absorption spectra of porphyrin **7a** in CH_2Cl_2 (solid line) and in pyridine (dashed line); (b) absorption spectrum of Pd-tetrabenzoporphyrin **11a** in water (pH 8.0). Insert shows uncorrected emission (phosphorescence) spectrum of **11a** in deoxygenated solution; (c) excitation spectrum of **11a** (corrected for the lamp intensity) related to the emission at 807 nm.

spectroscopy Fig. 1a). The dications could be fully deprotonated only in the presence of such bases as Et_3N or pyridine, which suggests that **7a**–**d** exhibit unusually high basicity.[15] The porphyrins **7a**–**d** were converted to their respective metal complexes and aromatized by refluxing with an excess of DDQ (f),[16] giving the MAr_4TBPs (M = Ni, Cu, Zn) **8a**–**d** in nearly quantitative yields. Interestingly, free-base porphyrins could not be aromatized under such conditions, most likely due to the formation of dications, which are apparently not oxidized by DDQ. The net yield of the entire sequence is 3–8%. Given that all starting compounds are readily available, this synthesis can afford gram quantities of substituted Ar_4TBPs in a single preparation.

Zn complexes **8a**–**c** could be quantitatively demetalated by treatment with TFA in CH_2Cl_2, to give free-base tetrabenzoporphyrins **9a**–**c**. The Pd complex of tetraphenyloctamethoxycarbonyltetrabenzoporphyrin **10a** was formed quantitatively upon reacting the free-base porphyrin **9a** with $PdCl_2$ in refluxing benzonitrile. Finally, the methoxycarbonyl groups of **10a** were deesterified ($NaOH–THF–H_2O$), giving tetraphenyloctacarboxytetrabenzoporphyrin **11a**, well soluble in basic aqueous solutions. The absorption and emission spectra of **11a** are shown in Fig 1b. The near infra-red emission with λ_{max} at 807 nm (phosphorescence) is completely quenched in the presence of molecular oxygen. In deoxygenated water solutions this phosphorescence has a lifetime of 107 μsec and a quantum yield of about 10%, which makes metalloporphyrin **11a** well suited for the lifetime oxygen sensing.[1d] Intriguingly the phosphorescence of **11a** has a significantly higher intensity if excited at the weaker Q-band, than at the Soret band. The corrected excitation spectrum of **11a**, recorded at a very high dilution (absorbance at Soret maximum (440 nm) 0.05 OD), is shown in Fig. 1c. Since no emission was observed directly from the S_2-state, such behavior is most likely due to the existence of uncommon non-radiative pathways of S_2 deactivation.

In summary, we have developed a new method of synthesis of Ar_4TBPs, which employs inexpensive, readily available starting materials. The method allows introduction of functional groups in both benzo- and phenyl- rings, thus providing a general route to the modified tetrabenzoporphyrin system. Newly synthesized tetrabenzoporphyrins were found promising basic phosphors for oxygen measurements by phosphorescence quenching.

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Notes and references

‡ The IUPAC name for sulfolene is 2,5-dihydro-1*H*-thiophene-1,1-dioxide.

§ Newly synthesized porphyrins were characterized by ^1H NMR and MALDI-TOF mass spectrometry. The details of the analysis are given in the ESI†. The UV-VIS and phosphorescence spectroscopy was performed as described elsewhere.[1d]

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12 Interestingly, the Diels–Alder reaction between sulfolene **1** and DMM leads almost quantitatively to the *trans*-isomer of **3**, while the reaction of **2** with DMM produces predominantly the *cis*-isomer of **4**. The latter can also be synthesized from the commercially available *cis*-tetrahydrophthalic anhydride. The *trans*-isomer, however, affords higher yields (up to 95%) in the following Barton–Zard condensation with *tert*-butyl isocyanoacetate.

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