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Tetrahedron Letters 49 (2008) 2236–2239
Tetrahedron Letters

Synthetic strategies and porphyrin building blocks for unsymmetrical multichromophores

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Received 22 November 2007; revised 5 February 2008; accepted 7 February 2008
Available online 10 February 2008

Abstract

A sequential use of halogenation, S_NAr, Sonogashira and/or Suzuki couplings together with the use of either mono-5-, 5,15- or 5,10-di-*meso*-substituted porphyrins allows the facile construction of unsymmetrical porphyrin dimers and trimers with different spatial orientation. The protocols established allow a convenient entry into multichromophores suitable for application in nonlinear optics and biomedicine.
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Keywords: Pd-catalyzed coupling; Porphyrins; Tetrapyrroles; Halogenation; Nonlinear optical limiting

Current advances in the use of porphyrins for photodynamic cancer therapy, solar energy conversion and as optical limiters and sensors necessitate the development of synthetic strategies.[1] Most of the applications mentioned require chromophores with a strong intramolecular dipole moment (e.g., push–pull systems) and long wavelength absorption. Suitable target compounds are multi-chromophore systems with appropriate functional groups. From a synthetic viewpoint, this necessitates the use of unsymmetrically substituted porphyrin building blocks in convergent or linear syntheses to construct porphyrin dimers or trimers with fine-tuned photophysical properties.

The last two decades have seen many advances in the synthesis of unsymmetrically substituted porphyrins, both through total synthesis[2a] and the use of organometallic reactions.[2b,c] Likewise, many di-, tri- and oligomeric porphyrin systems have been synthesized.[3] However, only a few methodological studies have targeted unsymmetrical multiporphyrin systems.[4] Here, we present preliminary results on the development of appropriate building blocks and synthetic sequences for the general preparation of di- and trimeric porphyrin systems with unsymmetrical substituent patterns and linker groups.

As several methods are available for the functionalization of the *meso* position of porphyrins, we chose porphyrins with free *meso* positions as starting materials. In order to allow for subsequent asymmetrization and to access different linker strategies, we used mono-,[5a] 5,10-di-[5a] and 5,15-disubstituted[5b] porphyrins. These have been shown to be useful starting materials for the preparation of various so-called ABCD porphyrins (Fig. 1).

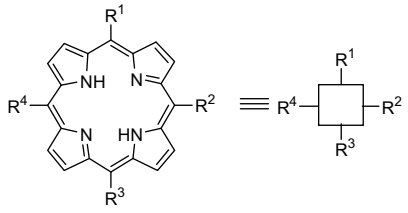

Fig. 1. ABCD–type porphyrin and the simplified formula used in other schemes.

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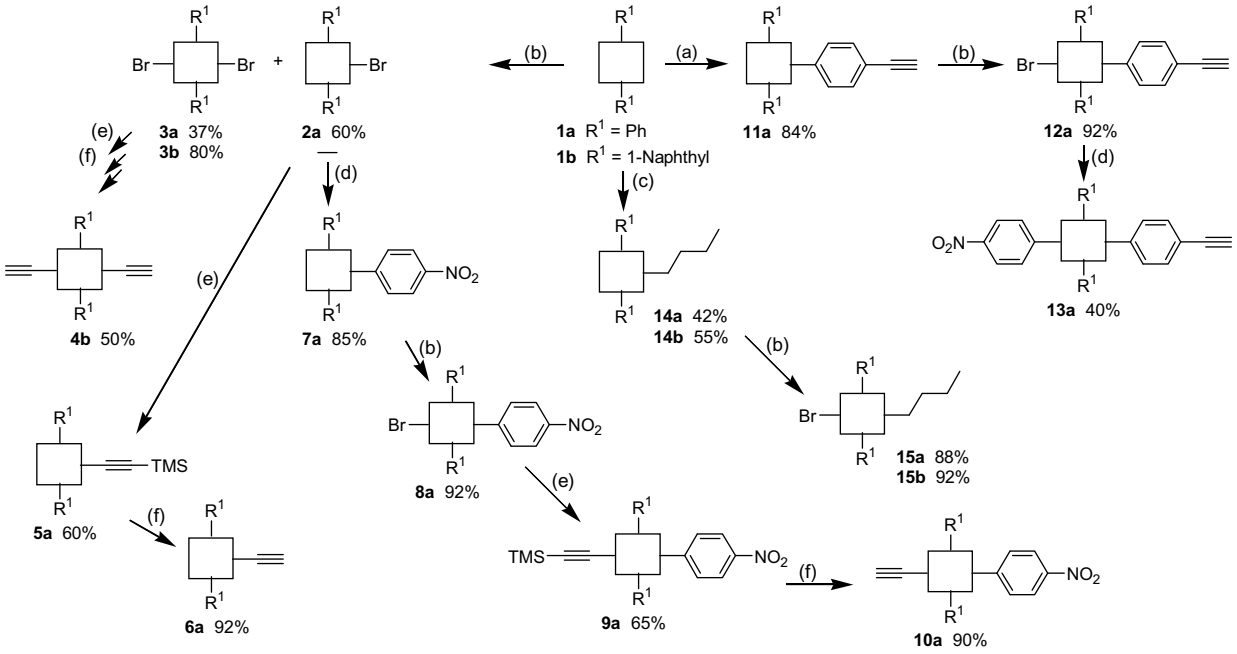
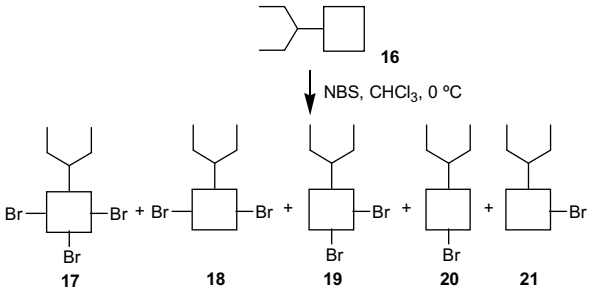
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.029



Scheme 1. Synthesis of monomeric porphyrin building blocks. Reagents and conditions: (a) 1-bromo-4-ethynylbenzene (15 equiv), Et_2O, *n*-BuLi (30 equiv), H_2O (2 mL), DDQ (15 equiv), −78 °C; (b) NBS (1.1 equiv), pyridine (1 mL), $CHCl_3$ (40 mL), 0 °C; (c) *n*-BuLi (6 equiv), H_2O (1 mL), DDQ (6 equiv), THF (40 mL), −78 °C; (d) 4-nitrophenylboronic acid pinacol ester (12 equiv), K_3PO_4 (25 equiv), $Pd(PPh_3)_4$ (0.1 equiv); (e) ethynyltrimethylsilane (1.1 equiv), CuI (0.25 equiv), $Pd(PPh_3)_2Cl_2$ (0.1 equiv); (f) 0.3 mL TBAF 1 M solution in THF, CH_2Cl_2.

Due to their utility in nonlinear optical porphyrins,[1c] for the present study, we concentrated on alkynyl-linked systems. These are conveniently prepared via Pd-catalyzed coupling reactions and require appropriate bromo and alkynyl precursors. Thus, the initial step involved either bromination with NBS[6] or arylation with RLi[2c,7] of the free base porphyrins. *meso* Halo- and alkyne-substituted porphyrins are important precursors for multiporphyrin chromophores.[8] A large number of conjugated porphyrins have been prepared using simple synthetic tools and easily accessible porphyrins (**1a**, **1b**) in good yields (Scheme 1). The ethynylphenyl motif was smoothly inserted in a one-step reaction by treatment with aryllithium reagents.[8a] Sequences of reactions were used to introduce the acetylene moiety, for example, bromination (affording **8a**), the introduction of TMS protected acetylene via a Sonogashira coupling reaction[8c] (giving **9a**) followed by the removal of the TMS group to afford precursor **10a**. Similarly, monobromination of **1a** to afford compound **2a** in good yield and subsequent Suzuki coupling[8b] enabled the introduction of, for example, a 4-nitrophenyl residue for the preparation of push–pull systems.[8g] Alternatively, alkyl substituted compounds **14** are accessible via reaction with *n*-BuLi and can then be brominated to **15** to serve as precursors for subsequent couplings.

5-Monosubstituted porphyrins with three free *meso* positions available for further asymmetric functionalization are important precursors for multiporphyrin systems.[5a] We used the soluble porphyrin **16**[5a] to elaborate an entry into substituted porphyrins with different regio-

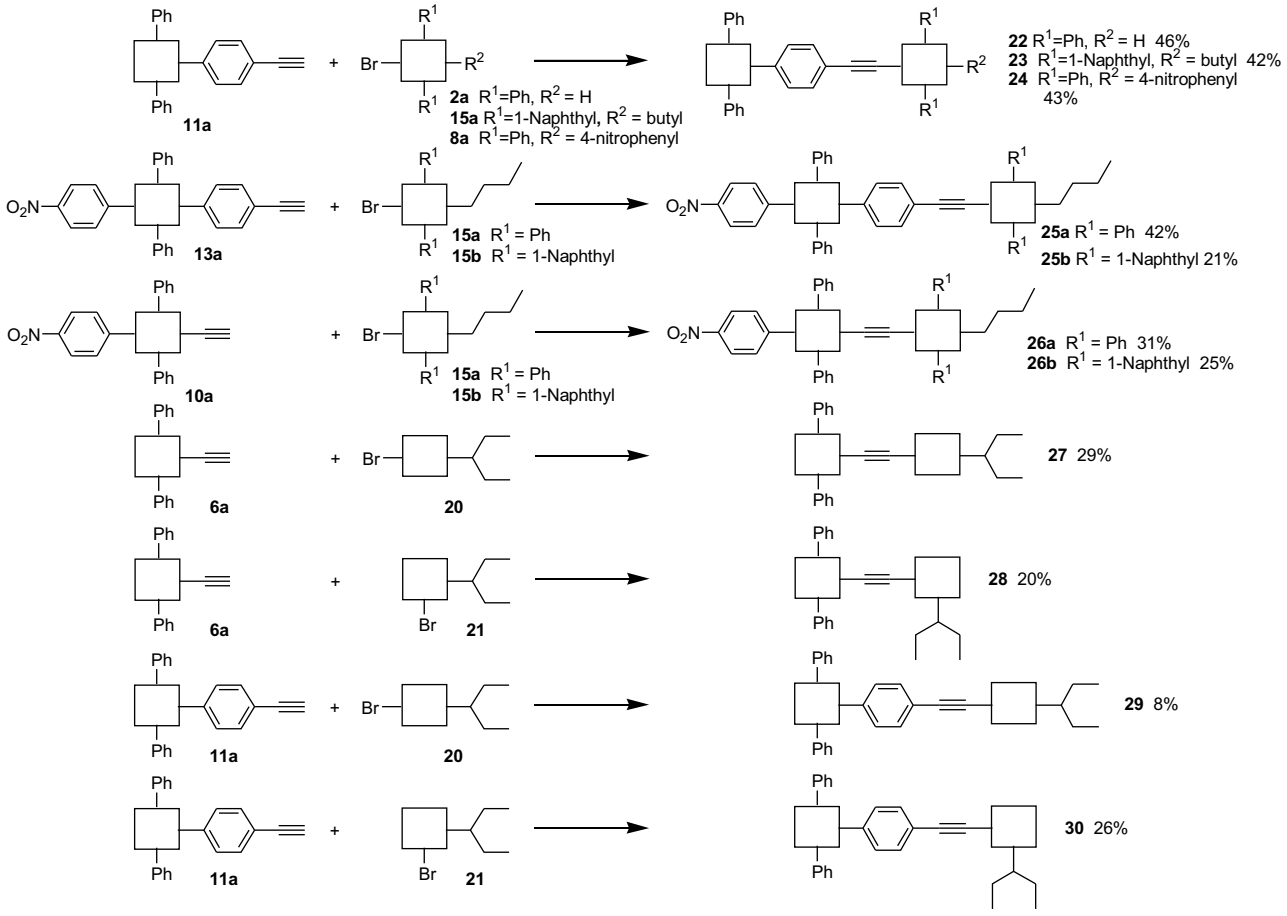


eq. NBS	16	17	18+19	20	21
3	-	93%	-	-	-
1.5	-	2%	5%	31%	16%
1	5%	-	4%	60%	21%
0.8	10%	-	4%	41%	14%

Scheme 2. Bromination of **16** and product distribution based on the equivalence of NBS.

chemical arrangements of *meso* bromo substituents. As shown in Scheme 2, with smaller amounts of NBS the yield of tribrominated porphyrin **17** decreased in favour of the less brominated porphyrins **20** and **21**. Thus, depending on the conditions, an entry into mono- to tribrominated porphyrins is possible; with a preference for bromination in the 'trans' 15-position relative to the alkyl residue. Compound **17**, obtained easily with 3 equiv of NBS, can be used to quickly construct porphyrin tetramers with two different porphyrin units in a unique 10, 15, 20 orientation.[9]

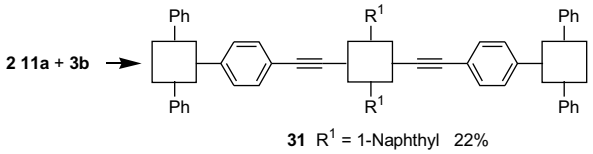
Our approach to porphyrin dimers linked by acetylene and ethynylphenyl bridges involved optimized Pd-mediated



Scheme 3. Synthesis of porphyrin dimers. Reagents and conditions: $AsPh_3$ (2 equiv), $Pd_2(dba)_3$ (0.1 equiv), THF (20 mL), TEA (4 mL), 65 °C, nitrogen.

coupling reactions in order to link the free base porphyrins under mild conditions. For optical applications we targeted the push–pull dimers **25a**,**b** connected through an ethynylphenyl linker and bearing either naphthyl or phenyl substituents. Their synthesis involved the coupling of **13a** with the appropriate *meso*-halogenated porphyrin (Scheme 3). Using similar pathways, the more conjugated push–pull dimers **26a**,**b** were prepared in good yields. Furthermore, porphyrins **20** and **21** were used for the synthesis of the acetylene linked dimers **27** and **28** and the ethynylphenyl linked dimers **29** and **30**. Depending on which porphyrin monomer carries the bromo or acetylenic group, dimers with opposite orientations of the intramolecular dipole are accessible (e.g., **24** vs **25a**). These compounds allow for further modifications as a wide range of reactions can be performed at the free *meso* positions (e.g., linkage to bioconjugates) and different metals can be inserted into the dimers to further fine-tune their physical properties.

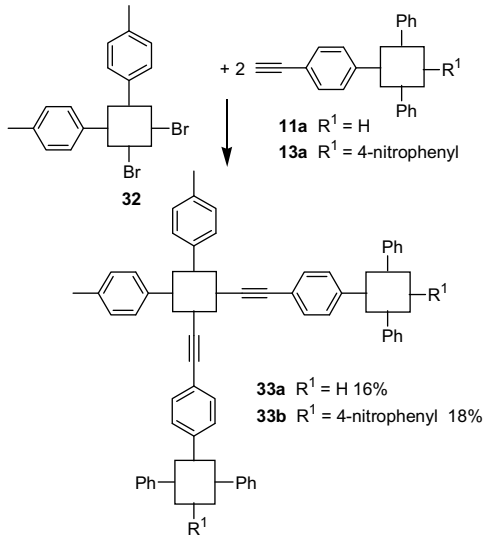
Similarly, linear porphyrin trimers are easily constructed using 2 equiv of an alkylporphyrin and a dibromoporphyrin (Scheme 4). For example, the reaction of **11a** with **3b** gave trimer **31** in 22% yield. Again, the terminal porphyrin units contain a free *meso* position amenable for further synthetic manipulations. As expected, the absorption spectrum of **31** in CH_2Cl_2 gives two sharp Soret bands at 413 nm and



Scheme 4. Synthesis of the linear porphyrin trimer **31**. Reagents and conditions: $AsPh_3$ (2 equiv), $Pd_2(dba)_3$ (0.1 equiv), THF (20 mL), TEA (4 mL), 65 °C, nitrogen.

451 nm, respectively, and the Q bands are red-shifted by 57 nm relative to that of **11a** and by 23 nm relative to that of dimer **23** indicating their potential for biomedical applications.

Even more intriguing was the possibility of using 5,10-disubstituted porphyrins for the construction of multiporphyrin systems with 'rectangular' geometry.[5a] They have already been used as building blocks for the synthesis of symmetric square shaped π-conjugated porphyrin oligomers using Glaser couplings.[10] Our recent results on the potential of monomeric push–pull 5,10-A_2B_2 porphyrins[11] for nonlinear optical applications encouraged us to expand our studies to rectangular trimeric systems as NLO materials. These were easily accessible by bromination of the 5,10-disubstituted porphyrins affording **32** followed by a



Scheme 5. Synthesis of porphyrin trimers with rectangular geometry. Reagents and conditions: $AsPh_3$ (2 equiv), $Pd_2(dba)_3$ (0.1 equiv), THF (20 mL), TEA (4 mL), 65 °C, nitrogen.

Pd-catalyzed coupling reaction with 2 equiv of precursors **11a** and **13a**, respectively, to yield dimers **33** (Scheme 5).

Similar to trimer **31**, the absorption spectrum of the rectangular trimers **33a**,**b** exhibited a split Soret band and a bathochromic shift of the Q bands due to the electronic coupling of the subunits. The optical limiting (OL) properties of the multiporphyrins were investigated using the open-aperture *z*-scan technique with 6 ns laser pulses at 532 nm.[12] All the compounds examined exhibited reverse saturable absorption (RSA) under incident focal intensities ranging from about 0.05 to approximately 0.10 GW cm^{-2}. Preliminary studies showed the rectangular trimer **33a** to possess outstanding OL properties in comparison to the linear compound **31** with the same number of porphyrin units. The OL performances of the dimers examined (**22**, **23**, **25a**,**b**, **29** and **30**) were better or comparable to the linear trimer **31** but did not exceed those of **33a**.

Currently, we are optimizing the reactions described herein. The preliminary results indicate that judicious choice of the starting materials and appropriate planning of the sequence of coupling and functionalization reactions allow the rapid generation of a variety of unsymmetrical multichromophoric systems or precursors with enhanced optical properties. The synthetic strategies are equally amenable for the construction of amphiphilic porphyrin dimers and trimers for use in photodynamic therapy and will be useful precursors for the preparation of larger, superstructured systems.

Acknowledgement

This work was generously supported by the Science Foundation Ireland (Research Professorship SFI 04/RP1/B482 and SFI 06/RFP/CHO044).

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9. Initial studies showed that **17** can be converted to the 5-(1-ethylpropyl)-10,15,20-tri(2-trimethylsilylethynyl)porphyrin in 49% yield, which subsequently was deprotected to 5,10,15-triethynyl-(20-(1-ethylpropyl)porphyrin in 63% yield.
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12. *z*-Scans: Q-switched Nd:YAG laser with a pulse repetition rate of 10 Hz; samples dissolved in DMF; $c = 0.01$ g L^{-1}. The beam was spatially filtered to remove the higher order modes and tightly focused with a 9 cm focal length lens as described in Ref. 11.