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Porphyrenediynes: synthesis and cyclization of *meso*-enediynylporphyrins

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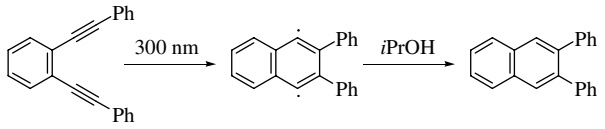
Abstract—Synthetic methodology to prepare porphyrinylethynyl enediynes has been developed. Compared to phenylethynyl derivatives, a bulky porphyrinic substituent on the alkyne significantly increases the thermal barrier toward Bergman cyclization and leads to multiple photolysis products.

The design and activation of enediyne pro-drugs that cleave DNA upon Bergman cyclization[1] remains a formidable synthetic challenge. The enediyne antitumor antibiotics utilize complex molecular architectures to control delivery and activation of enediyne warheads, leading to their potent cytotoxicity.[2] While the natural products and early synthetic models employ molecular strain to control the cyclization event,[3] recent synthetic efforts have focused on photochemical activation of simplified cyclic and acyclic enediynes.[4] The prototypical acyclic example is the cyclization of 1,2-bis(phenylethynyl)benzene, which affords 2,3-diphenylnaphthalene upon irradiation at 300 nm (Scheme 1).[5] As part of our program to combine porphyrins with enediynes, we have developed a methodology to incorporate porphyrinyl substituents on the enediyne alkyne. In addition to serving as a chromophore to potentially promote photocyclization at longer wavelengths, the porphyrin macrocycle can be readily functionalized to serve as an improved delivery system imparting solubility, tumor delivery, and DNA binding properties to enediyne pro-drugs.[6]



Scheme 1.

The first example of a porphyrin-enediyne hybrid was reported by the Smith group who prepared 2,3-diethynylporphyrin **1** (Fig. 1).[7] Upon heating to 190 °C, **1** undergoes thermal cyclization to afford picenoporphyrins via tandem radical cyclization with neighboring *meso*-phenyl substituents. Zaleski and co-workers later showed that this system cyclizes at room temperature in the presence of DDQ[8] and undergoes photocyclization via irradiation of the porphyrin Soret or Q bands.[9] Alternatively, phenylethynyl analogs afford only traces of photocyclized adducts at elevated temperatures[9] and are prone to photoreduction of the macrocycle.[10] We recently reported the synthesis and reactivity of *beta*-extended porphyrenediyne **2** that undergoes traditional Bergman cyclization followed by hydrogen atom abstraction from 1,4-cyclohexadiene.[11] More recently Jones and co-workers reported the synthesis and photocyclization of compound **3**, which incorporates *meso*-pyridyl substituents to aid delivery to biological targets.[12] An alternative method to combine porphyrin macrocycles with acyclic enediynes is to directly link them to the alkyne as in **4**. By connecting in this manner, the chromophore can become conjugated to the in-plane π-system of the enediyne isolated on the alkyne, whereas **1** and **2** are strictly conjugated to the enediyne out-of-plane π-system through the alkene.[13] In this Letter, we

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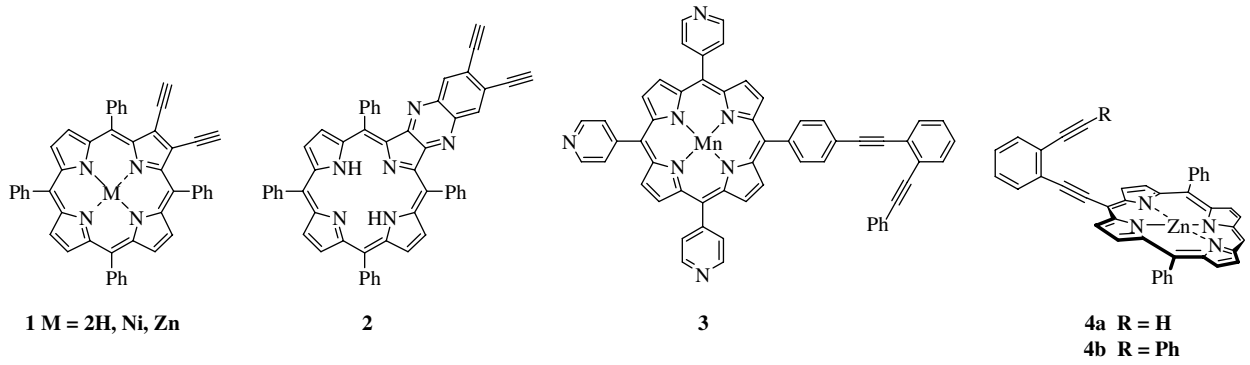
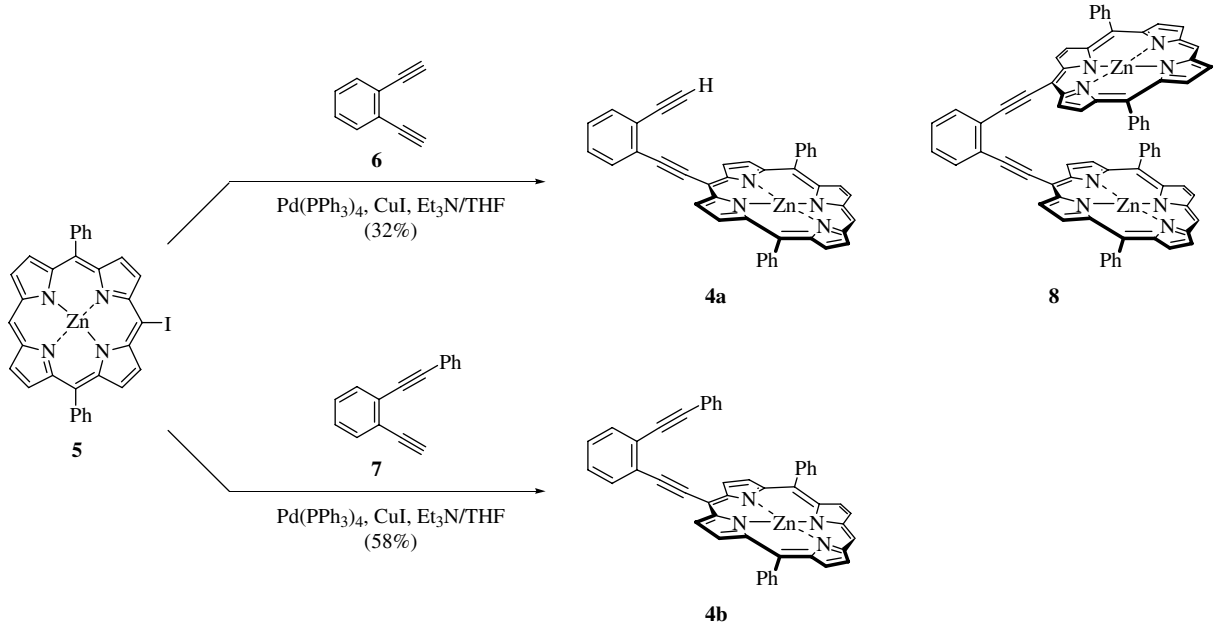


Figure 1. Structures of porphyrenediynes.

report the synthesis of porphyrenediyne models **4a** and **4b** and their respective thermal and photochemical reactivities.

The synthetic route toward *meso*-enediynylporphyrins was adapted from the preparation of *meso*-ethynyl porphyrins described by Dolphin.[14] Coupling zinc(II)-5-iodo-10,20-diphenylporphyrin **5** with 1,2-diethynylbenzene **6**[15] or 1-ethynyl-2-(phenylethynyl)benzene **7**[16] gave porphyrenediynes **4a** and **4b**, respectively, in 32% and 58% yields (Scheme 2). THF was required as a solvent for these reactions to improve solubility of the iodoporphyrin, and optimal yields were obtained when **6** and **7** were slowly added to a solution of **5** to limit self-coupling of the terminal alkynes. A second porphyrinic product, tentatively assigned as the bis-coupled adduct **8** by ^{1}H NMR, UV–visible and nominal mass data, was also obtained from the reaction with **6** but was too unstable to fully characterize.

The ^{1}H NMR spectra of porphyrenediynes **4a** and **4b** readily confirmed their molecular structures. In both **4a** and **4b**, a 1H singlet is observed for the lone remaining *meso*-hydrogen near 10.3 ppm along with four 2H doublets for the porphyrin *beta*-hydrogens ranging from 10.1 to 8.7 ppm. The remaining phenyl hydrogens are observed from 8.3 to 7.4 ppm while the terminal alkyne in **4a** appears at 4.61 ppm. Similar shifts are observed in the ^{1}H NMR spectrum of **8**, with the exception of one porphyrin *beta*-hydrogen shifted upfield to 7.73 ppm. The lack of molecular symmetry in **4a** and **4b** was further confirmed by the appearance of four distinct alkyne resonances between 100 and 80 ppm in ^{13}C NMR spectroscopy. In the UV–visible absorbance spectrum of **4a** the porphyrin Soret band is red-shifted to 435 nm, compared to 411 nm for zinc(II)-5,15-diphenylporphyrin, with *Q*-bands noted at 561 and 603 nm. Similar trends are observed in **4b** with the Soret band shifted to 440 nm and *Q*-bands at 565 and 617 nm, while the Soret band for diporphyrin **8** is observed at 424 nm. These absorptions are consistent with a *meso*-ethynylporphyrin and demonstrate conjugation between the porphyrin and enediyne π-system.[17] Molecular modeling[18] of **4b** indicates that the porphyrin macrocycle is rotated out



Scheme 2.

of the plane of the arenediyne and, as a result, the chromophore is more efficiently conjugated to the in-plane enediyne π-system isolated on the alkyne.

The thermal reactivity of porphyrenediynes **4a** and **4b** toward Bergman cyclization in the solid state has been investigated by differential scanning calorimetry (DSC). Although DSC has recently been shown to be a very crude measure of relative reactivity for enediynes,[19] comparing porphyrenediynes **4a** and **4b** with their respective starting terminal enediynes provides insight into the steric demands imposed by porphyrin substitution. An irreversible exotherm indicative of Bergman cyclization is observed for porphyrenediyne **4a** beginning at ~230 °C (Fig. 2) while that of **6** is observed beginning at ~130 °C. In comparison, the onset temperature for porphyrenediyne **4b** is observed at ~270 °C whereas **7** displays an onset temperature at ~150 °C. Not surprisingly, adding a porphyrinyl substituent to the terminal alkyne of **6** or **7** increases the onset temperature by approximately 100–120 °C. In comparison, adding one phenyl substituent (in going from **6** to **7**) increases the onset temperature by only 20 °C. Finally, addition of two phenyl substituents, generating 1,2-bis(phenylethynyl)benzene, increases the onset temperature to ~280 °C.

To identify and characterize the Bergman cyclized product, the solution reactivity of porphyrenediyne **4a** in the presence of a hydrogen atom donor was examined. Heating a solution of porphyrenediyne **4a** in 1,2,4-trichlorobenzene containing 10% 1,4-cyclohexadiene (CHD) at 250 °C for 96 h yielded the cyclized adduct **9** in 26% yield after preparative thin layer chromatography (Scheme 3). No other porphyrinoid products were observed by TLC, UV or NMR analysis. During the course of the reaction the solution changed from the characteristic green color of *meso*-ethynylporphyrins to the red color of *meso*-aryl derivatives. The ^{1}H NMR spectrum shows the loss of the terminal alkyne signal observed in **4a** and the presence of three new aromatic signals at 8.67, 8.41 and 8.08 ppm consistent with a *meso*-(2′-naphthyl) substituent.[20] The UV–visible spectrum shows a Soret band at 417 nm, which is blue-shifted 18 nm compared to **4a** as expected for the loss of the *meso*-ethynyl group, with one prominent *Q*-band observed at 545 nm. Furthermore, FAB HRMS gave a molecular ion peak at *m*/*z* 650.1450, confirming the addition of two hydrogen atoms. The increased steric hindrance and higher temperature required for the thermolysis of **4b**, however, led to degradation of the porphyrenediyne upon heating to 300 °C.

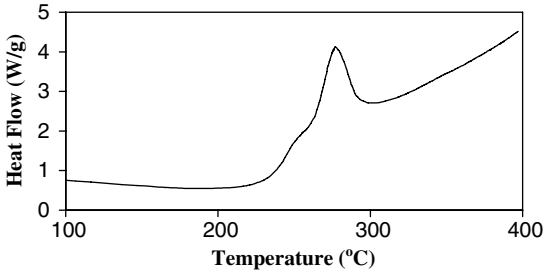
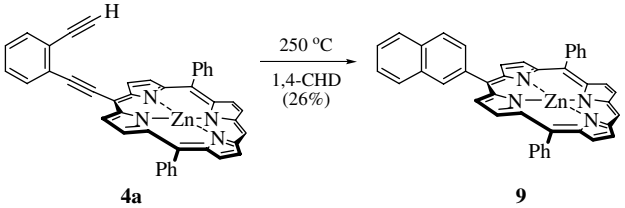


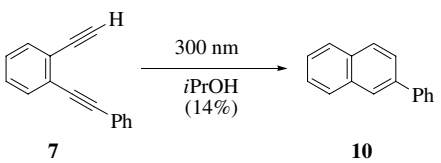
Figure 2. DSC scan of porphyrenediyne **4a**.

The photochemical reactivity of **4a** was next examined by irradiation with 300 nm light in THF/*i*PrOH. However, no trace of cyclized product **9** is observed and the starting porphyrenediyne is degraded within 5 h. To demonstrate the ability of terminal enediynes to photocyclize, irradiation of phenyl derivative **7** in *i*PrOH at 300 nm for 5 h resulted in complete consumption of the enediyne, and 2-phenylnaphthalene **10** was obtained in 14% yield (Scheme 4). Under identical conditions, the previously reported 1,2-bis(phenylethynyl)benzene[5] reacts more slowly to produce 2,3-diphenylnaphthalene in <10% yield with 20% recovered starting material. In the photolysis of the phenylethynyl derivatives a significant amount of polymeric material is obtained as characterized by a broad absorbance throughout the aromatic region in the crude ^{1}H NMR spectrum.

Irradiation of the Soret band of **4a** with 419 nm light results in slow degradation of the porphyrenediyne with >50% starting material recovered after 5 h along with trace products and baseline material observed by TLC. The limited reactivity of porphyrenediyne **4a** compared to **7** toward photo-Bergman cyclization underscores the effect of steric bulk on the alkyne termini.[9] However, upon heating the photolysis reaction to 140 °C, trace quantities of cyclized product **9** are observed by TLC along with multiple colored products with nearly identical Rf values. In addition to the formation of **9**, competing reactions such as alkyne reduction,[5] porphyrin reduction,[9,10] fulvene formation[21] and indene formation[22] may be occurring. Recent theoretical calculations[21] suggest C1–C5 cyclization to fulvene derivatives is competitive with C1–C6 Bergman cyclization when bulky groups are present at the alkyne termini, which may partly explain the formation of multiple photolysis products from **4a** compared to the clean cyclization of **7**. Similar results are obtained upon irradiation of porphyrenediyne **4b** with 419 nm light. Mass analysis of the crude products obtained from pho-



Scheme 3.



Scheme 4.

tolysis of **4a** and **4b** at 419 nm indicate formation of multiple photoadducts with molecular weights two, four, and six mass units higher than the starting material, as expected for a mixture derived from competing cyclization and reduction pathways.

In conclusion, we have developed the syntheses of porphyrenediynes in which the porphyrin macrocycle is conjugated to the in-plane π-system of an arenediyne. The presence of a porphyrinic substituent on the alkyne induces a large thermal barrier toward cyclization and lowers the overall efficiency of the photo-Bergman cyclization, thereby allowing alternative reactions to become competitive upon irradiation at 419 nm. In the presence of an appropriate electron donor such as DNA, however, C1–C5 photocyclization may become the dominant reaction pathway to generate a more lethal enediyne pro-drug capable of four hydrogen atom abstractions.[22] Work in this direction is currently in progress.

Acknowledgements

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Supplementary data

Experimental conditions and spectral data for compounds **4a**, **4b** and **9** are available in Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.164.

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