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Multigram Synthesis of a Water-Soluble Porphyrazine and Derived *seco*-Porphyrazine Labeling Agents

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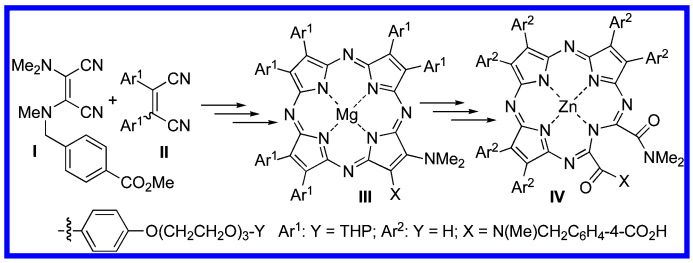
ABSTRACT



Porphyrazine III has been synthesized on a large scale (18.4 g), with minimal chromatographic purification by employing a novel one-pot, 3-step sequence. Two dinitrile precursors I and II, the latter of which consisted of a mixture of geometric isomers, were transformed, via the corresponding pyrroline diimines, into a mixture of III and the octa-Ar[1]-porphyrazine. Isolated macrocycle III was subsequently transformed into IV, a water-soluble *seco*-porphyrazine suitable for the labeling of biological vectors.

Photodynamic therapy[1] (PDT) is a noninvasive cancer treatment that uses a combination of visible light and a photosensitizing drug.[2] Following internalization of the photosensitizer in tumor cells, irradiation generates localized singlet oxygen, which may destroy the cancer.[3,4] Suitable photosensitizers for PDT include both porphyrins[5] and tetraazaporphyrins; the former class incorporates Photofrin, the first approved photochemical drug used for cancer therapy.[3] Porphyrins and tetraazaporphyrins are topologically related and differ by only the presence of *meso*-nitrogen atoms within the ligand framework. Tetraazaporphyrins can be further divided into phthalocyanines[6] and porphyrazines[7] (Pz). Vicinal diaminoporphyrazines readily undergo oxidative ring scission of the $R_2NC{=}CNR_2$ unit to provide the corresponding *seco*-porphyrazines. These macrocyclic compounds, as well as porphyrazines in general, may be of use

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for PDT and biomedical optical imaging[8] due to their intense Q-band in the UV−vis spectrum and, in many cases, excellent singlet oxygen quantum yield[9] on photosensitization.

While a number of procedures have been developed recently for the synthesis of metalated and free-base porphyrazines,[10] the magnesium ion-templated Linstead macrocyclization[11] of acyclic maleonitriles is still the most widely used method for the preparation of these macrocycles. For the synthesis of unsymmetrical porphyrazines, the statistical co-macrocyclization of two different (*Z*)-dinitriles (represented by A and B) is currently the only viable method for their synthesis. This procedure results in the formation of a mixture of porphyrazines A_4Pz, A_3BPz, both *cis*- and *trans*-A_2B_2Pz, AB_3Pz, and B_4Pz, the ratios of which depend on the ratios of the precursor dinitriles A and B. Such reactions are frequently plagued with poor yields and difficulties with purification. Previously, we have used a ROM-polymerization-capture release strategy to tackle this shortcoming.[12] In this paper, we wish to describe the multigram scale synthesis of an A_3B porphyrazine **15** and its application to the synthesis of the *seco*-porphyrazine **1** (Figure 1), a current candidate

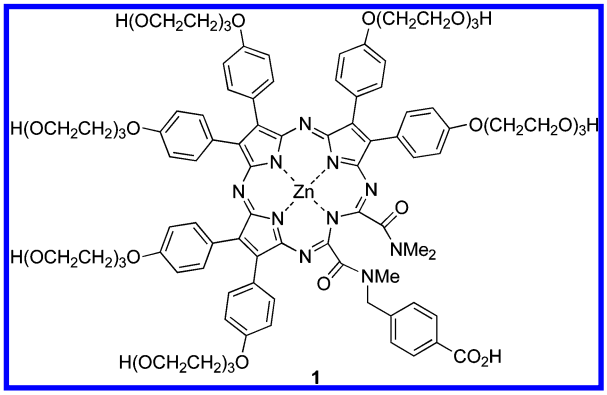
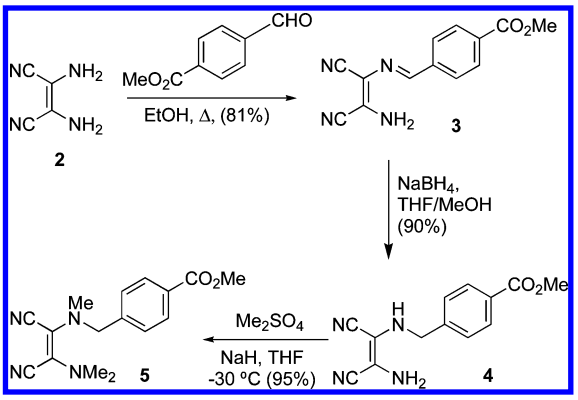


Figure 1. *seco*-Porphyrazine photosensitizer.

for PDT studies. Photosensitizer **1** possesses (i) polyethylene glycol chains, to enhance water solubility and facilitate the internalization of dye in cells, (ii) a carboxylic acid moiety, used for bioconjugation,[13] and (iii) the *seco* functionality, which provides high singlet oxygen quantum yields.[9] We now report an efficient, concise chromatography-minimized synthesis via Linstead macrocyclization of pyrroline diimines.

Utilizing the protocol of Sheppard and co-workers, maleonitrile **5** was prepared in three steps from commercially available diaminomaleonitrile **2** (Scheme 1).[14] Heating ma-

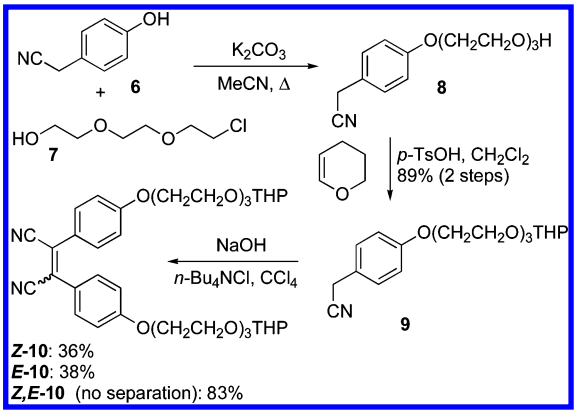
Scheme 1



leonitrile **2** in ethanol in the presence of methyl 4-formylbenzoate yielded the imine **3**, which was reduced with sodium borohydride in THF and methanol to give the amine **4** in 73% yield over the two steps. Subsequent methylation with dimethyl sulfate gave maleonitrile **5** in 95% yield.

Maleonitrile **10** was prepared from phenol **6** by alkylation with chloride **7** to give the alcohol **8** in quantitative yield (Scheme 2). Following protection of **8** by dihydropyran to

Scheme 2



give **9**, oxidative coupling with carbon tetrachloride under basic conditions[15] gave a mixture of maleonitrile ***Z*-10** and

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(11) Linstead, R. P.; Whalley, M. *J. Chem Soc.* **1952**, 4839.
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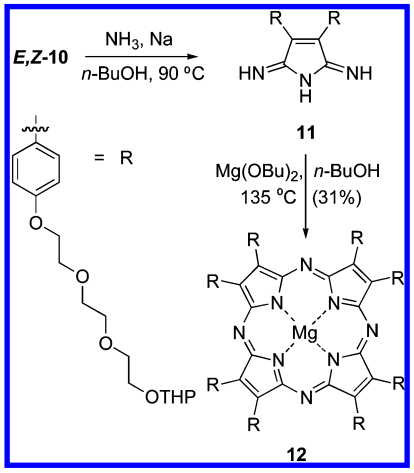
fumaronitrile ***E*-10** isolated in 36% and 38% yields, respectively, by chromatography on silica gel. In our hands, however, this separation could not be easily performed on more than a 5 g scale since larger scale separations resulted in partial THP-deprotection and/or degradation. These difficulties were avoided by using the mixture of geometric isomers directly in the next step without separation. It is noteworthy that this three-step sequence could be performed on a 100 g scale of the starting phenol **6** to provide the mixture of dinitriles ***E*,*Z*-10** in 83% (150 g) overall yield.

As an initial approach to the A_3B porphyrazine, dinitriles **5** and ***Z*-10** (1:6 ratio) were co-macrocyclized under Linstead conditions[11] by reflux in *n*-butanol in the presence of freshly prepared magnesium butoxide to give the desired transesterified A_3BPz **14**, along with the symmetrical A_4Pz **12**. Chromatography on silica gel gave pure A_3B **14** in 36% isolated yield. This method of purification on quantities larger than 500 mg, however, is prohibitively time-consuming due to the high polarity and strong aggregation of the macrocycles. We consequently sought to develop another strategy to allow the scale-up of this synthesis. Importantly, any such procedure would ideally utilize both ***E*-** and ***Z*-10** as their separation is an obvious bottleneck in the synthetic sequence. It has been reported that Linstead macrocyclization can be performed with not only *Z*-dinitriles but also pyrroline diimines. These latter compounds may be considered as analogues of the initial intermediates in Linstead macrocyclization, and can be obtained by reaction of a dinitrile with ammonia in the presence of a catalytic amount of sodium in ethylene glycol.[16] Under these reaction conditions, isomerization of either the dinitrile or a subsequent reaction intermediate occurs meaning both *Z* and *E* dinitriles yield the corresponding, geometrically locked, pyrroline diimine. Indeed, the reaction of the mixture of dinitriles ***E*,*Z*-10** with ammonia in *n*-butanol or ethylene glycol, at 100 °C, afforded the corresponding pyrroline diimine **11** (Scheme 3). This

Scheme 3



compound, however, is highly polar and although it can be purified by chromatography, its poor stability renders the process difficult and subject to low yields. Instead, a one-pot reaction was developed. The pyrrolidine diimine was generated in situ, and used directly without isolation in the crossed Linstead macrocyclization reaction.[11,17] The crude pyrroline **11** was prepared by reaction of dinitriles ***E*,*Z*-10** with ammonia in anhydrous *n*-butanol, and the resulting solution of **11** was directly added to a freshly prepared solution of magnesium butoxide in *n*-butanol.

Reflux for 16 h gave the desired symmetrical (A_4) Pz **12** (31%). This protocol was applied to the synthesis of the unsymmetrical A_3B porphyrazine **14**. Dinitriles ***E*,*Z*-10** and **5** (7:1 ratio) were heated for 16 h in *n*-butanol at 95 °C with a catalytic amount of sodium, under a constant flow of gaseous ammonia (Scheme 4).[16] The mixture of crude pyrrolines **11** and **13** in butanol was immediately added to a preformed solution of magnesium butoxide in *n*-butanol. After 48 h at reflux, the crude mixture of A_4Pz **12** and A_3BPz **14** was saponified to give a mixture of A_3BPz **15**,[18] A_4Pz **12**, and minor impurities. Macrocycle **15** could be purified by chromatography on amberlyst A_{21} or more conveniently silica gel, which afforded the acid **15** in 33% overall yield from dinitrile **5** for the three steps of the synthesis. This process could be successfully applied to 120 g of starting dinitriles ***E*,*Z*-10** and **5**, providing 18.4 g of A_3BPz **15** after three steps and a single chromatographic purification. Such a scale is unusual for unsymmetrical porphyrazines, and these compounds are usually prepared on a small scale (<500 mg) due to low yields and difficulties in purification. To complete the synthesis of the potential PDT photosensitizer **1**, the acid **15** was esterified by *n*-butanol under Yamaguchi conditions,[19] giving ester **14** in

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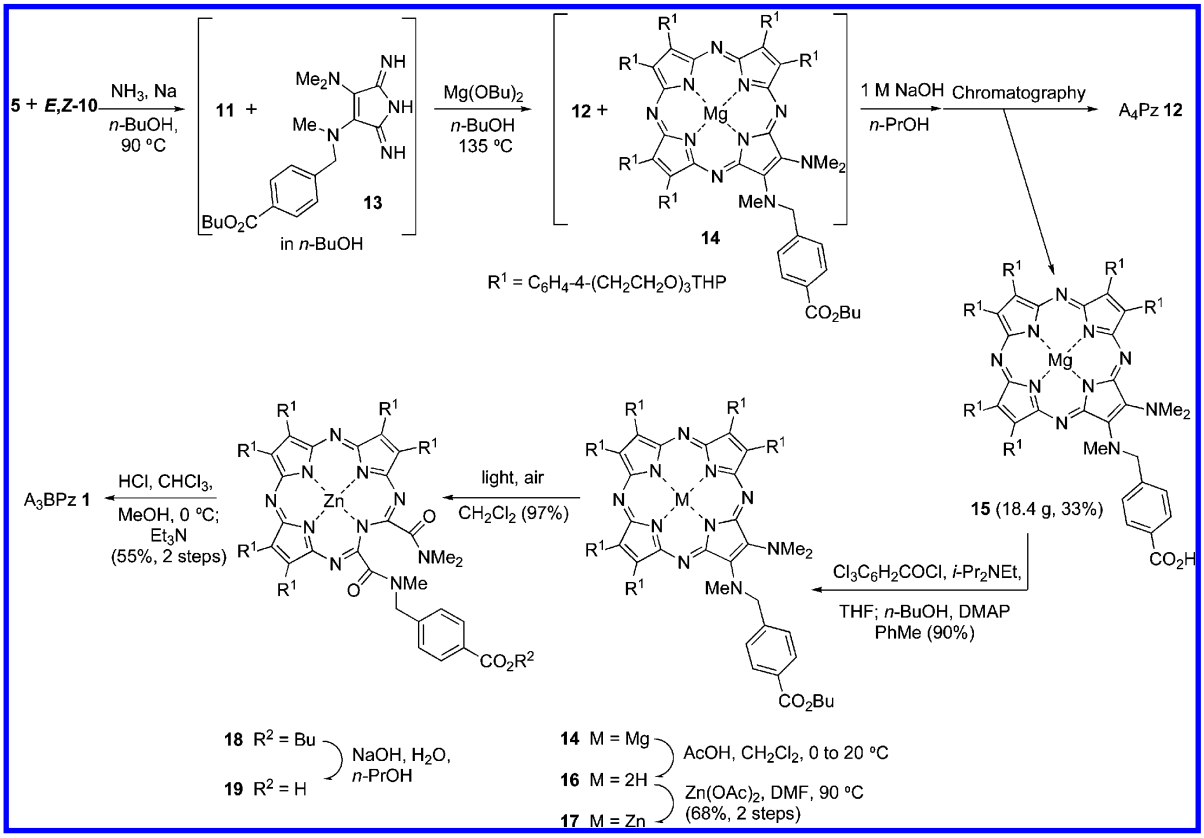
(17) It is possible that the macrocyclization reaction involves a sodium template and late transmetalation; see ref 10c.
(18) A_3BPz **15** was obtained in 72% yield when the reaction was performed with chromatographically purified **14**.
(19) (a) Inanaga, J.; Hirata, K.; Katsuki, T.; Yamaguchi, M. A. *Bull. Chem. Soc. Jpn*. **1972**, *52*, 1989. (b) Haslam, E. *Tetrahedron* **1980**, *36*, 2409.

Scheme 4



89% yield. Subsequent treatment with acetic acid yielded pure demetalated Pz **16**, which was remetalated with zinc acetate in DMF to give the zinc Pz **17** in 68% global yield. Exposure to air and light at room temperature in CH_2Cl_2 gave the *seco*-Pz **18** (97%).[8] Finally, saponification with NaOH in *n*-propanol and acidic deprotection of the THP protecting groups gave the target Pz **1**, which could be purified on lipophilic Sephadex to give **1** (55%).

In conclusion, a large-scale synthesis of a new highly functionalized, water-soluble *seco*-porphyrazine has been achieved. This is a suitable compound for the labeling of biomolecules for imaging and PDT studies. This synthetic procedure has allowed the preparation several grams of the desired Pz **15** in one single reaction sequence in good overall yield.

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Supporting Information Available: Experimental procedures and characterization data for all products and ^1H NMR and/or ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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