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Direct Synthesis of Magnesium Porphine via 1-Formyldipyrromethane

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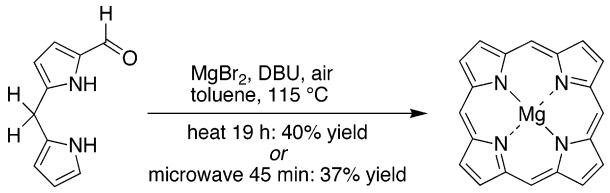
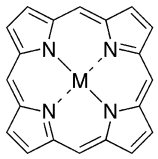


2 **Mg-1**

The reaction of 1-formyldipyrromethane (100 mM) in toluene at 115 °C containing DBU (10 mol equiv) and $MgBr_2$ (3 mol equiv) in the presence of air affords the magnesium chelate Mg(II) porphine in 30−40% yield. The advantages of the new method include simplicity, high concentration, chromatography-free purification, gram-scale synthesis, and avoidance of the poorly soluble free base porphine. Mg(II) porphine exhibits good solubility in common organic solvents and is a valuable core scaffold for derivatization.

Porphine (**1**, Chart 1) is the simplest porphyrin and represents the core macrocycle of naturally occurring and synthetic porphyrins. Due to the presence of eight open β-pyrrole sites and four open meso sites, porphine is a potential building block for the elaboration of porphyrin derivatives. In this regard, porphine undergoes selective monobromination at a β-position to give 2-bromoporphine.[1] On the other hand, Shi and Wheelhouse showed that the magnesium(II) chelate of porphine (**Mg-1**) undergoes tetrabromination to give magnesium(II) *meso*-tetrabromoporphine. Subsequent palladium-coupling reactions afforded tetraaryl A_4-tetraarylporphyrins, which included target porphyrins that are not easily available by other routes (e.g., with heterocyclic substituents).[2] Senge has shown that porphine reacts with organolithium reagents to provide meso-substituted A- or *cis*-A_2-porphyrins, which also are difficult to synthesize by other routes.[3] These reports provide a glimmer of the possible synthetic utility of porphine; however, the practical use of porphine in synthetic chemistry has been thwarted by two vexing and somewhat interrelated limitations: (1) lack of an efficient method of synthesis and (2) extremely low solubility of the free base porphine (**1**).

CHART 1



1: M = H, H
M-1: M = Mg(II), Zn(II), etc.

Methods for the synthesis of porphine span the past 70 years (see the Supporting Information).[4−16] The reactants employed include pyrrole and formaldehyde,[4,10] pyrrole-2-carboxaldehyde,[5] 2-(*N*,*N*-dimethylaminomethyl)pyrrole,[6] and 2-hydroxymethylpyrrole.[7−9,11,12] The best method to date employs condensation of 2-hydroxymethylpyrrole in an acidified biphasic mixture followed by oxidation with DDQ, which has afforded 30 mg of porphine in 15% yield.[12] An alternative method entails dealkylation of a tetra-*tert*-butylporphyrin or *meso*-tetrakis-(hexyloxycarbonyl)porphyrin in the presence of strong acid, which respectively affords porphine in 64−74%[14] or 77%[15] yield; however, this method obviously requires the preparation of the porphyrin precursor. Porphine also can be prepared in 31% yield by the reaction of 5,10,15,17-tetrahydrotripyrrin and 2,5-bis(hydroxymethyl)pyrrole[13] (or 2-hydroxymethylpyrrole[16]).

Thus, despite the structural simplicity of porphine, there remains no method of satisfactory yield, scale, and ease of implementation that enables the synthetic utility of porphine to be unlocked. The low yields of macrocycle formation with simple pyrrole compounds are mitigated by the easily available starting materials; however, separation of the poorly soluble porphine from the polymeric material in the crude reaction mixture remains tedious. The use of more elaborate precursors requires more synthetic effort than would seem warranted. Here we report an efficient, concise, and practical method for preparing **Mg-1**, which greatly facilitates access to this valuable compound, and from which free base porphine (**1**) is readily obtained.

1. Strategy and Survey. Our approach for the synthesis of porphine, which has emerged from our prior studies of routes

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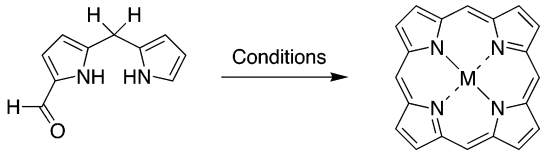
SCHEME 1



Conditions: Product, Yield

(A) (i) n-$PrNH_2$ M = Zn, 15%
(ii) $Zn(OAc)_2$, EtOH, reflux, 16 h

(B) $Pd(CH_3CN)_2Cl_2$, KOH, EtOH, reflux, 1 h M = Pd, 11%
(C) $MgBr_2$, DBU, air, toluene, 115 °C, 19 h M = Mg, 40%

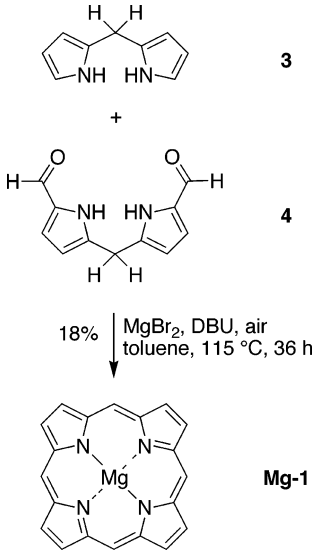
to *trans*-substituted porphyrins,[17,18] focused on methods that afford direct access to the metal chelate. A synthesis that affords direct access to the metalloporphine **M-1** would sidestep the difficult purification and handling problems of the poorly soluble free base porphine. In each case, we chose 1-formyldipyrromethane **2** as a potentially viable precursor to metal chelates of porphine. The conditions examined are shown in Scheme 1.

A. Formation of Zinc(II) Porphine. The reaction of a 1,9-diformyldipyrromethane with *n*-propylamine and subsequent reaction of the bis(imino)dipyrromethane with a dipyrromethane in the presence of $Zn(OAc)_2$ in refluxing ethanol exposed to air affords the zinc(II) complex of the *trans*-AB-porphyrin.[18] Although application of this method with the unsubstituted dipyrromethane resulted in little or no zinc porphyrin,[18] we examined the analogous self-condensation with 1-formyldipyrromethane **2**. Reaction of **2** with excess *n*-propylamine at room temperature afforded quantitatively the corresponding imine. The self-condensation of the latter was carried out in refluxing EtOH containing $Zn(OAc)_2$. Chromatographic workup afforded Zn(II) porphine (**Zn-1**) in 15% yield.

B. Formation of Palladium(II) Porphine. The self-condensation of a 1-acyldipyrromethane in refluxing ethanol containing KOH and a palladium reagent affords the corresponding palladium(II) chelate of a *trans*-A_2B_2-porphyrin.[17] Reaction of **2** under such basic, metalating conditions in refluxing ethanol [containing $Pd(CH_3CN)_2Cl_2$ and KOH][17] afforded palladium(II) porphine (**Pd-1**) in 11% yield. Palladium(II) porphine was purified by filtration through a silica pad. **Pd-1** and **Zn-1** have been prepared via other methods.[19]

C. Formation of Magnesium(II) Porphine. An extensive study was carried out to explore the generality of the basic, metalating conditions [$Pd(CH_3CN)_2Cl_2$ in EtOH containing KOH][17] for the self-condensation of 1-acylpyrromethanes. The study, which encompassed various metals, solvents, and bases, will be reported elsewhere. One key finding is that a Mg(II) salt (e.g., $MgBr_2$) in the presence of a non-nucleophilic base (e.g., DBU) provides an effective means for the self-condensation of 1-acyldipyrromethanes. The use of $MgBr_2$ and DBU stemmed from our study of magnesium insertion into porphyrins, wherein similar conditions in the absence of any oxygenic ligands afford the magnesium(II) porphyrin.[20] For the reaction

SCHEME 2



of **2**, the formyl group should be activated by coordination to magnesium(II) given the high affinity of magnesium(II) for oxygen. The non-coordinating solvent and non-nucleophilic base avoid competition by the solvent and base versus the 1-formyldipyrromethane in coordination to magnesium.

Thus, the reaction was carried out with a mixture of **2** (100 mM) in toluene at 115 °C containing DBU (10 mol equiv vs **2**) and $MgBr_2$ (3 mol equiv) in the presence of air. After 8 h, **Mg-1** was present, in part as a precipitate, together with unreacted starting material. After 19 h, TLC analysis of the crude reaction mixture revealed the presence of **Mg-1**, polar polymeric material, and no starting material **2**. The workup entailed (i) concentration of the reaction mixture, treatment of the resulting residue with THF, and filtration to remove polymeric material and inorganic salts; (ii) washing the filtrate with water to remove DBU; and (iii) crystallization from ethanol/water to afford **Mg-1** in 40% yield. Note that **Mg-1** was previously prepared by metalation of **1**.[2]

Several related condensations were explored under analogous conditions. The attempted self-condensation of pyrrole-2-carboxaldehyde, or the condensation of dipyrromethane (**3**) and paraformaldehyde, gave no **Mg-1**. However, the condensation of dipyrromethane (**3**) and 1,9-diformyldipyrromethane (**4**) afforded **Mg-1** in 18% yield (Scheme 2).

2. Scalable Synthesis of Mg-1. The reasonable yield and operational simplicity of **Mg-1** formation prompted examination of the reaction at the multigram scale. We investigated three routes for the multigram synthesis of **Mg-1**, each of which employed $MgBr_2$ and DBU in toluene at ~115 °C. In Method I, the self-condensation of **2** (6.97 g) for 19 h afforded **Mg-1** (2.68 g, 40% yield) in a single batch process. In Method II, the self-condensation of **2** was carried out by using microwave irradiation in an effort to achieve faster reaction. The reaction at 115 °C under otherwise standard conditions (toluene, 100 mM of **2**, 3 mol equiv of $MgBr_2$, and 10 mol equiv of DBU) was completed in ~45 min. Subsequent crystallization afforded **Mg-1** in 37% yield (0.031 g, 0.50 mmol scale). In both methods, the crude **Mg-1** was purified by crystallization (and without chromatography); however, the synthesis of the precursor **2** requires chromatography thereby limiting the scale of reaction. We sought to overcome this limitation.

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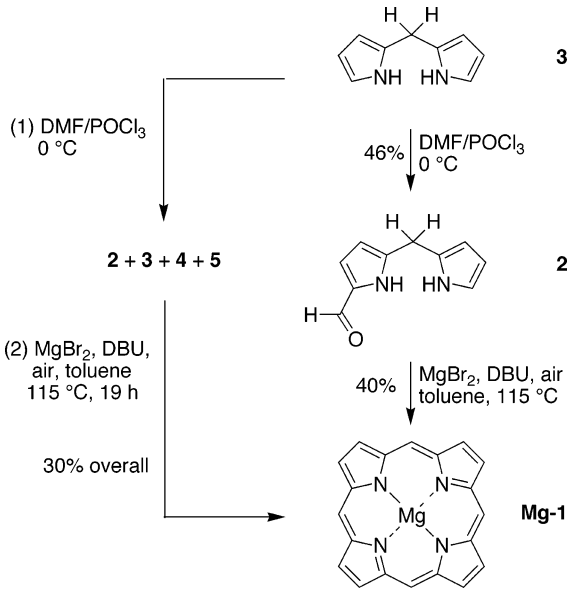
SCHEME 3



The Vilsmeier formylation[21] of dipyrromethane (**3**)[22] affords a mixture composed of the target 1-formyldipyrromethane (**2**), unreacted **3**, 1,9-diformyldipyrromethane (**4**), and an unknown byproduct (tentatively assigned as 2-formyldipyrromethane (**5**)) in a ratio of 24:8:5:1. The mixture typically is chromatographed to isolate pure **2**. Given that **2** self-condenses to give **Mg-1**, and **3** + **4** also react to give **Mg-1**, we examined the porphine-forming reaction with use of the crude Vilsmeier formylation mixture, which contains **2**, **3**, and **4**. Thus, in Method III, the crude Vilsmeier reaction mixture was concentrated. The resulting mixture (7.34 g) was dissolved in toluene, treated with DBU and $MgBr_2$ (10 and 3 mol equiv vs the original quantity of **3**, respectively), and heated at 115 °C for 19 h whereupon **2**−**4** were completely consumed. The chromatography-free purification as described above afforded **Mg-1** in 30% yield (1.98 g, 40 mmol scale) (Scheme 3).

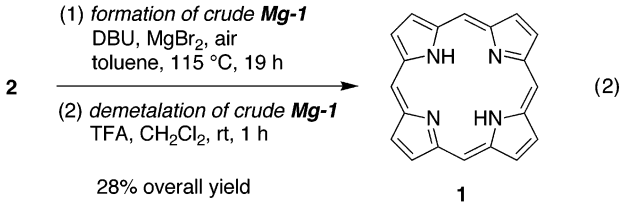
The ^{1}H NMR analysis of the crude Vilsmeier reaction mixture (7.34 g) gave a molar composition of **2**, **3**, **4**, **5**, and DMF of 24:8:5:1:5, corresponding to 25.5 mmol of **2**, 8.5 mmol of **3**, and 5.3 mmol of **4**. The combined reactions of **2** → **Mg-1** (in yields ranging from 5% to 47%) and **3** + **4** → **Mg-1** (in yields ranging from 100% to 0%) can account for the observed yield of **Mg-1**. It may be coincidental that yields of 40% and 16% for the respective reactions, which are nearly identical with those of the constituent reactions alone, fit the observed data (see the Supporting Information for analysis). Regardless of the exact contributions by each reaction, this streamlined, entirely chromatography-free procedure offers a simple and fast method for preparing multigram quantities of **Mg-1**.

3. Stoichiometry. The overall stoichiometry for the reaction shows the requirement for a base and an oxidant (eq 1). The

$$\mathbf{2} + \mathbf{2} + MgBr_2 \rightarrow \mathbf{Mg\text{-}1} + 2HBr + 2H_2O + 2e^- + 2H^+ \quad (1)$$

base is required, minimally, to neutralize the 2 equiv of HBr liberated upon metal complexation. A $2e^-/2H^+$ oxidant is required to form the unsaturated macrocycle. Oxygen present in air would seem a likely source for the oxidizing equivalents. However, the microwave-mediated reaction in a degassed flask gave **Mg-1** in 32% spectroscopic yield. An alternative oxidant could be the formyl group of **2**, or the imine moiety of DBU. In the latter regard, the reaction with 2,2,6,6-tetramethylpiperidine in place of DBU gave **Mg-1** in only 4.5% spectroscopic yield. The essential requirement for both $MgBr_2$ and DBU was validated by omission experiments, where the reaction of **2** carried out in the absence of either DBU or $MgBr_2$ gave no porphine.

4. Synthesis of Porphine 1. A direct route to **1** was examined by demetalation of crude **Mg-1** (eq 2). Thus, reaction of **2** in



toluene at 115 °C containing $MgBr_2$ and DBU afforded crude **Mg-1**. The reaction mixture was concentrated followed by filtration. Treatment of crude **Mg-1** with dilute TFA in CH_2Cl_2 afforded the free base porphine **1** in 28% overall yield.

5. Outlook. One of the intrinsic problems in porphine chemistry is the poor solubility of **1** in common organic solvents. Among the various chelates prepared, the general trend in solubility in common organic solvents (CH_2Cl_2, THF, MeOH, diethyl ether, toluene) is as follows: **Pd-1** < **1** ≪ **Zn-1** ≪ **Mg-1**. The solubility of **Mg-1** in common organic solvents is sufficiently high to perform routine operations (purification, NMR characterization) and reactions at concentrations (1−50 mM) typical of those for porphyrinic compounds. The satisfactory solubility of **Mg-1** and its availability in gram quantities without any chromatography makes this simple macrocycle quite attractive for synthetic manipulation. The overall yield of **Mg-1** is 17% in a chromatography-free, 3-reaction sequence beginning with pyrrole and paraformaldehyde. In conjunction with the results obtained by Shi and Wheelhouse[2] (bromination of **Mg-1** and subsequent palladium-coupling reactions), the door appears open to the synthesis of porphyrins bearing meso substituents (e.g., ethenyl, ethynyl, heterocyclic, sterically hindered) not easily available by other methods.

Experimental Section

Porphine (1). A sample of DBU (7.5 mL, 50 mmol, 10 mol equiv versus **2**) was added to a suspension of **2** (0.871 g, 5.00 mmol, 100 mM) in toluene (50 mL). $MgBr_2$ (2.76 g, 15.0 mmol, 3 mol equiv) was added in a single portion. The reaction mixture was heated at 115 °C with exposure to air for 19 h. On the basis of TLC analysis no starting material was observed. The reaction mixture was concentrated. The resulting residue was twice treated with THF (100 mL), stirred vigorously for 20 min at room temperature, and filtered through a Buchner funnel. The filtrate was concentrated (filtrate 1). The filter cake was mixed with THF (100 mL) and heated to reflux for 1 h to release residual bound **Mg-1**. The mixture was filtered through a second Buchner funnel to remove insoluble black material, and the filter cake was washed with THF (5 × 10 mL), affording filtrate 2. Filtrates 1 and 2 were combined, concentrated, and dissolved in diethyl ether (300 mL). The resulting solution was washed (water, brine), dried (Na_2SO_4),

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and concentrated. The resulting crude product was dissolved in CH_2Cl_2 (100 mL) and treated with TFA (1.93 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized by addition of TEA (3.5 mL, 25 mmol), washed (water, brine), and concentrated. Crystallization (THF/water 1:2.5) afforded a shiny brown solid (0.220 g, 28%): ^{1}H NMR (THF-d_8) δ −3.86 to −3.93 (br s, 2H), 9.57 (s, 8H), 10.43 (s, 4H); ^{13}C NMR (THF-d_8) δ 104.8, 132.4−132.6 (br); LD-MS obsd 309.6; FAB-MS obsd 311.1311, calcd 311.1297 [$(M + H)^+$, $M = C_{20}H_{14}N_4$]; λ_{abs} 396, 490, 564 nm.

1-Formyldipyrromethane (2). A sample of DMF (30 mL) was treated with $POCl_3$ (4.50 mL, 49.2 mmol) at 0 °C under argon with stirring for 10 min (Vilsmeier reagent). A solution of **3** (5.85 g, 40.0 mmol) in DMF (120 mL) at 0 °C under argon was treated with the freshly prepared Vilsmeier reagent (25 mL, 41 mmol), and the resulting solution was stirred for 1.5 h at 0 °C. The reaction mixture was poured into a mixture of 2 M NaOH (300 mL) and CH_2Cl_2 (200 mL) at 0 °C. The resulting blue reaction mixture was stirred for 20 min at 0 °C. The reaction mixture turned orange-brown. The organic phase was washed (saturated aqueous NH_4Cl (200 mL), water, and brine), dried (Na_2SO_4), and concentrated to give a red, oily crude product. The remaining DMF was removed under high vacuum (1 h, 50 °C), resulting in a light-pink solid. Column chromatography [silica, $CH_2Cl_2 \rightarrow CH_2Cl_2$/ethyl acetate (5:1)] gave a yellow solid (3.198 g, 46%). The data (^{1}H NMR, mp, elemental analysis) were consistent with those obtained from samples prepared via earlier routes.[21]

Method I: Synthesis of Mg-1 from 1-Formyldipyrromethane. A sample of **2** (6.97 g, 40.0 mmol) in a 1000-mL oven-dried round-bottomed flask was treated with anhydrous toluene (400 mL). The resulting suspension was heated to 80 °C, whereupon DBU (60 mL, 400 mmol, 10 mol equiv) was added dropwise under vigorous stirring in 10 min. The resulting solution was stirred for 5 min, during which the temperature increased from 80 °C to 98 °C and the mixture darkened. $MgBr_2$ (22.1 g, 120 mmol, 3 mol equiv) was added in one portion under vigorous stirring. The reaction flask was attached to a reflux condenser and heated at 115 °C with exposure to air. On the basis of TLC analysis (silica, CH_2Cl_2/ethyl acetate 5:1) and absorption spectroscopy, porphyrin formation was complete in 19 h. The reaction mixture was concentrated. The resulting residue was treated with THF (2 × 200 mL). The mixture was stirred vigorously for 20 min at room temperature, and then filtered through a Buchner funnel. The filtrate was concentrated (filtrate 1). The filter cake was mixed with THF (200 mL) and heated to reflux for 1 h to release residual bound **Mg-1**. The mixture was filtered through a second Buchner funnel to remove insoluble black material, and the filter cake was washed with THF (10 × 10 mL), affording filtrate 2. Filtrates 1 and 2 were combined and concentrated. The resulting crude product was dissolved in diethyl ether (1 L), washed [water (200 mL) and brine (5 × 200 mL); in both cases small amounts of MeOH and Na_2SO_4 were added to facilitate phase separation], and concentrated. Crystallization (ethanol/water 1:3) afforded a purple solid (2.681 g, 40%): mp >370 °C; ^{1}H NMR (THF-d_8) δ 9.47 (s, 8H), 10.26 (s, 4H); ^{13}C NMR δ 105.8, 132.6, 150.0; LD-MS obsd 331.9; FAB-MS obsd 332.0929, calcd 332.0912 ($C_{20}H_{12}N_4Mg$); λ_{abs} 402, 536 nm.

Method II: Microwave-Assisted Synthesis of Mg-1. A sample of **2** (0.087 g, 0.50 mmol) was placed in a 10-mL glass tube containing a magnetic stir bar. Toluene (5 mL) and DBU (0.750 mL, 5.02 mmol) were added. The resulting mixture was stirred for 5 min and treated with $MgBr_2$ (0.276 g, 1.50 mmol). The vessel was sealed with a septum and subjected to microwave irradiation at 300 W. The protocol was as follows: (1) room temperature to 115 °C (irradiation ∼30 s), (2) hold at 115 °C (irradiation for 15 min; temperature overshot to 130 °C and then stabilized after 1−2 min), (3) allow to cool to ∼60 °C (∼3 min), (4) heat to 130 °C (irradiation ∼20−30 s), (5) hold at 115 °C (irradiation for 15 min), and (6) allow to cool to room temperature. The reaction mixture was diluted with THF and filtered. The filter cake was washed with THF (total ∼300 mL). The filtrate was concentrated. The residue was dissolved in diethyl ether (∼500 mL) and washed with water (100 mL) and brine (200 mL). The organic phase was concentrated, and the resulting purple solid was crystallized twice from ethanol/water (1:3, 20 mL) to afford purple-violet crystals (31 mg, 37%) with characterization data (^{1}H NMR, absorption, LD-MS, FAB-MS) consistent with those for samples prepared via other methods.

Method III: Synthesis of Mg-1 from Crude 1-Formyldipyrromethane. Vilsmeier formylation of **3** (5.85 g, 40.0 mmol) was performed following the above procedure. The resulting crude pink solid (7.34 g) was used without purification. Following Method I, the crude product was dissolved in toluene (400 mL) and treated with DBU (60 mL, 400 mmol, 10 mol equiv versus **3**) and $MgBr_2$ (22.1 g, 120 mmol, 3 mol equiv versus **3**). Crystallization afforded **Mg-1** as a purple solid (1.98 g, 30%). The data (^{1}H NMR, ^{13}C NMR, absorption, and FAB-MS) were consistent with those obtained from samples prepared via other methods.

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Supporting Information Available: Table of prior routes to porphine; additional experimental procedures and information; and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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