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A New Route to *meso*-Formyl Porphyrins

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Abstract: Prior syntheses of porphyrins bearing *meso*-formyl groups have generally employed the Vilsmeier formylation of an acid-resistant copper or nickel porphyrin. A new approach for the synthesis of free base porphyrins bearing one or two (cis or trans) *meso*-formyl substituents entails the use of a dipyrromethane bearing an acetal group at the 5-position, a dipyrromethane-1-carbinol bearing an acetal group at the 5-position or carbinol position, or a dipyrromethane-1,9-dicarbinol bearing an acetal group at a carbinol position. Treatment of the resulting *meso*-acetal-substituted free base porphyrin to gentle acidic hydrolysis yields the corresponding *meso*-formyl porphyrin.

Formyl-substituted porphyrinic macrocycles provide versatile intermediates and target molecules in bioorganic and materials chemistry. Notable reactions of the porphyrinic formyl group include classical reactions of aldehydes (e.g., Wittig,[1−3] Grignard,[2,4] McMurry,[5] Schiff's base,[6−8] Knoevenagel[7,9])[10] as well as reaction with pyrrole or a dipyrromethane leading to multi-porphyrinic architectures.[11] The formyl group also has been exploited in supramolecular chemistry wherein the oxygen of the formyl group binds to the apical site on a neighboring metalloporphyrin.[12] Although a few formyl-porphyrinic compounds occur naturally (e.g., chlorophyll *b*), most must be synthesized de novo. The generic method for introducing a formyl group to a porphyrinic macrocycle entails Vilsmeier formylation.[10] Vilsmeier formylation, either with the traditional DMF/$POCl_3$[6,13] or the more recent $HC(OMe)_3$/TFA or $SnCl_4$,[3] can only be carried out with metalloporphyrins that are stable toward strong acids (e.g., copper or nickel chelates). Hence, formylation typically requires three steps: (1) insertion of copper into a free base porphyrin, (2) formylation of the copper chelate, and (3) demetalation of copper to give the free base porphyrin bearing the formyl group. The removal of copper generally requires strongly acidic conditions such as TFA in H_2SO_4. The yield of the Vilsmeier formylation is typically quite high (though mixtures of polyformylated metalloporphyrins are known[10,14,15]). However, the requirement for a three-step procedure, use of strong acid, and limited control over the site of formylation presents obvious limitations.

There exists a need for a milder and more direct procedure for preparing formyl porphyrins. Two routes to porphyrins bearing distinct patterns of meso substituents include (1) the self-condensation of a dipyrromethane-1-carbinol, affording *trans*-A_2B_2-porphyrins,[16] and (2) the reaction of a dipyrromethane and a dipyrromethane-1,9-dicarbinol, affording porphyrins with up to four different meso substituents (ABCD-porphyrins).[17] We considered that the incorporation of a latent formyl synthon in a dipyrromethane, dipyrromethane-1-carbinol, or dipyrromethane-1,9-dicarbinol would enable a direct, mild synthesis of formyl porphyrins. A recent paper by Trova et al. outlined the condensation of a dipyrromethane bearing a 5-carboethoxy or 5-*N*,*N*-dimethylaminocarbonyl group with an aldehyde to give the corresponding *trans*-A_2B_2-porphyrin.[18] Such groups upon further transformation could provide a complementary entry into *meso*-formyl porphyrins. In this paper, we describe the synthesis of four dipyrromethane or acyldipyrromethane components, each bearing one or two latent *meso*-formyl groups and explore their utility in rational routes to porphyrins.

5-Formylporphyrins. We initially examined the use of a 5-(dithiolan-2-yl)dipyrromethane as a precursor to porphyrins bearing a latent formyl group, but upon porphyrin formation, the *meso*-dithiolane group was partially lost, yielding a mixture of porphyrins (see Supporting Information). While the origin of the fragmentation reaction was not clear, we turned to the use of an acetal protecting group. The acid-catalyzed reaction of glyoxal with neopentyl glycol provided a mixture of

(1) (a) Callot, H. J. *Tetrahedron* **1973**, *29*, 899−901. (b) Arnold, D. P.; Gaete-Holmes, R.; Johnson, A. W.; Smith, A. R. P.; Williams, G. A. *J. Chem. Soc., Perkin. Trans. 1* **1978**, 1660−1670. (c) Burrell, A. K.; Officer, D. L. *Synlett* **1998**, 1297−1307.

(2) Arnold, D. P.; Johnson, A. W.; Mahendran, M. *J. Chem. Soc., Perkin. Trans. 1* **1978**, 366−370.

(3) (a) Montforts, F.-P.; Scheurich, G.; Meier, A.; Haake, G.; Höper, F. *Tetrahedron Lett.* **1991**, *32*, 3477−3480. (b) Ando, A.; Yamazaki, M.; Komura, M.; Sano, Y.; Hattori, N.; Omote, M.; Kumadaki, I. *Heterocycles* **1999**, *50*, 913−918.

(4) Runge, S.; Senge, M. O. *Tetrahedron* **1999**, *55*, 10375−10390.

(5) (a) Vicente, M. G. H.; Smith, K. M. *J. Org. Chem.* **1991**, *56*, 4407−4418. (b) Jaquinod, L.; Nurco, D. J.; Medforth, C. J.; Pandey, R. K.; Forsyth, T. P.; Olmstead, M. M.; Smith, K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1013−1016.

(6) Johnson, A. W.; Oldfield, D. *J. Chem. Soc. C* **1966**, 794−798.

(7) Witte, L.; Fuhrhop, J.-H. *Angew. Chem., Int. Ed.* **1975**, *14*, 361−363.

(8) (a) Ponomarev, G. V. *Chem. Heterocycl. Compd.* **1996**, *32*, 1263−1280. (b) Ponomarev, G. V.; Morozova, Y. V.; Yashunsky, D. V. *Chem. Heterocycl. Compd.* **2001**, *37*, 253−255.

(9) Schlözer, R.; Fuhrhop, J.-H. *Angew. Chem., Int. Ed.* **1975**, *14*, 363.

(10) Ponomarev, G. V. *Chem. Heterocycl. Compd.* **1994**, *30*, 1444−1465.

(11) (a) Wasielewski, M. R.; Johnson, D. G.; Niemczyk, M. P.; Gaines, G. L., III; O'Neil, M. P.; Svec, W. A. *J. Am. Chem. Soc.* **1990**, *112*, 6482−6488. (b) Johnson, D. G.; Niemczyk, M. P.; Minsek, D. W.; Wiederrecht, G. P.; Svec, W. A.; Gaines, G. L., III; Wasielewski, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 5692−5701.

(12) Balaban, T. S.; Bhise, A. D.; Fischer, M.; Linke-Schaetzel, M.; Roussel, C.; Vanthuyne, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2140−2144.

(13) Inhoffen, H. H.; Fuhrhop, J.-H.; Voigt, H.; Brockmann H., Jr. *Justus Liebigs Ann. Chem.* **1966**, *695*, 133−143.

(14) (a) Ponomarev. G. V.; Kirillova, G. V.; Maravin, G. B.; Babushkina, T. A.; Suboch, V. P. *Chem. Heterocycl. Compd.* **1979**, *15*, 622−629. (b) Ponomarev, G. V.; Kirillova, G. V.; Maravin, G. B.; Babushkina, T. A.; Suboch, V. P. *Chem. Heterocycl. Compd.* 630−633.

(15) (a) Smith, K. M., Bisset, G. M. F., Tabba, H. D. *J. Chem. Soc., Perkin. Trans. 1* **1982**, 581−585. (b) Smith, K. M.; Bisset, G. M. F.; Case, J. J.; Tabba, H. D. *Tetrahedron Lett.* **1980**, *21*, 3747−3750.

(16) Rao, P. D.; Littler, B. J.; Geier, G. R., III; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 1084−1092.

(17) Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323−7344.

(18) Trova, M. P.; Gauuan, P. J. F.; Pechulis, A. D.; Bubb, S. M.; Bocckino, S. B.; Crapo, J. D.; Day, B. J. *Bioorg. Med. Chem.* **2003**, *11*, 2695−2707.

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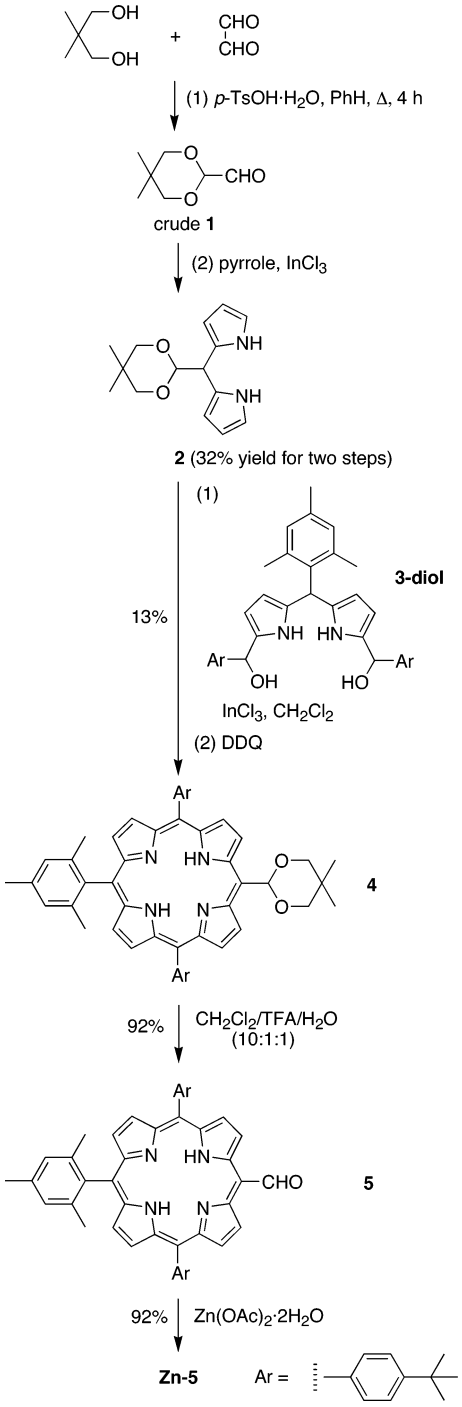
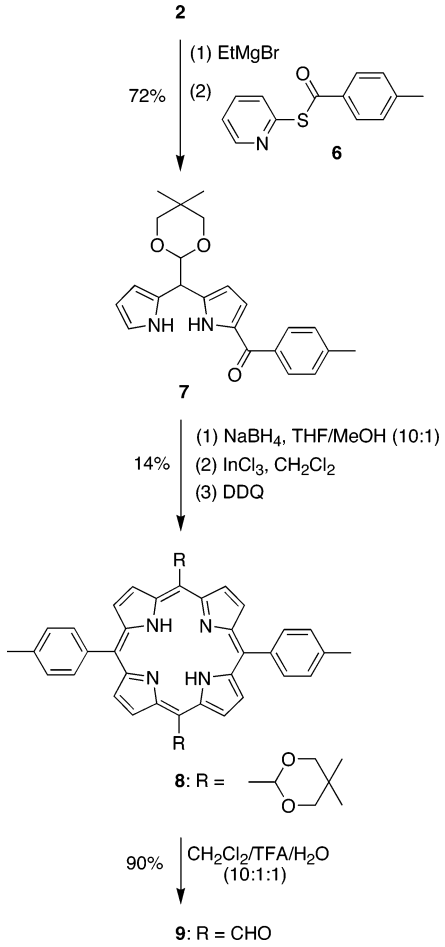
SCHEME 1



the monoacetal **1**[19] and the bis-acetal. Our efforts to isolate the monoacetal from the crude reaction mixture by distillation provided the glyoxal monoacetal **1** in only 4% yield rather than the reported yield of 50%.[19] Treatment of **1** with excess pyrrole in the presence of $InCl_3$ following a standard procedure[20] afforded the acetal-dipyrromethane **2** in 70% yield. Given the difficulty of isolating pure **1** and the ease of isolation of **2**, crude **1** was employed directly in the dipyrromethane-forming reaction. In this manner, **2** was obtained from glyoxal in 32% overall yield.

SCHEME 2



The condensation of dipyrromethane **2** with **3-diol** (prepared by the $NaBH_4$ reduction of 1,9-diacyldipyrromethane **3**[17]) was carried out in the standard manner[17,21] in the presence of $InCl_3$ followed by oxidation with DDQ. Acetal-porphyrin **4** was obtained cleanly in 13% yield. Hydrolysis of the acetal in porphyrin **4** was carried out using a biphasic mixture of CH_2Cl_2, TFA, and water (10:1:1)[22] at room temperature to afford *meso*-formyl porphyrin **5** in 92% yield. Metalation of **5** with $Zn(OAc)_2{\cdot}2H_2O$ gave the zinc porphyrin **Zn-5** in 92% yield (Scheme 1).

5,15-Diformylporphyrins. Two routes were investigated for the synthesis of 5,15-diformylporphyrins. Each route employs the self-condensation of the carbinol derived from a 1-acyldipyrromethane. The routes differ only in whether the acetal group is located at the 5-position or attached to the 1-acyl group of the 1-acyl-dipyrromethane.

The route that employs a dipyrromethane-monocarbinol bearing the acetal at the 5-position begins with dipyrromethane **2**. Treatment of **2** under the standard

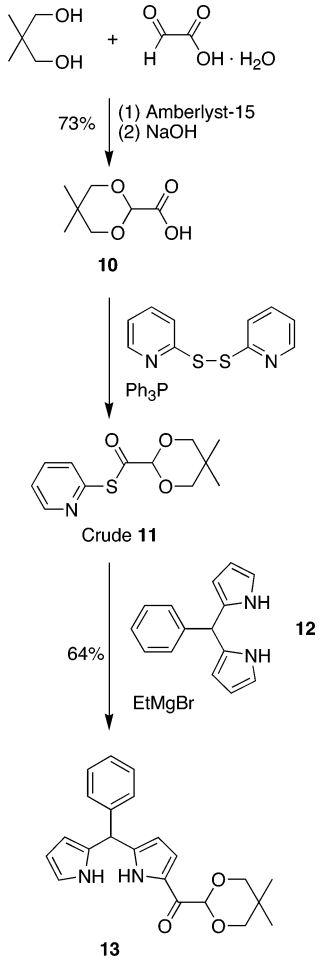
(19) Blanc, A.; Hamedi-Sangsari, F.; Chastrette, F. J. U.S. Patent 4,835,320.

(20) Laha, J. K.; Dhanalekshmi, S.; Taniguchi, M.; Ambroise, A.; Lindsey, J. S. *Org. Process Res. Dev.* **2003**, *7*, 799−812.

(21) Geier, G. R., III; Callinan, J. B.; Rao, P. D.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2001**, *5*, 810−823.

(22) Lindsey, J. S.; Brown, P. A.; Siesel, D. A. *Tetrahedron* **1989**, *45*, 4845−4866.

SCHEME 3



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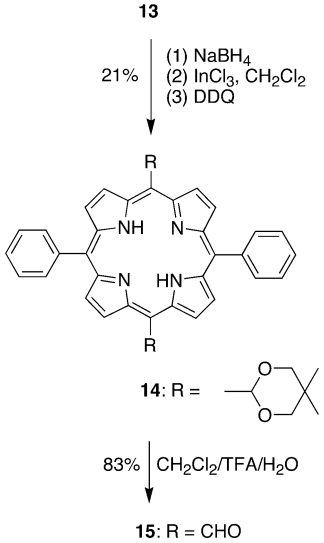
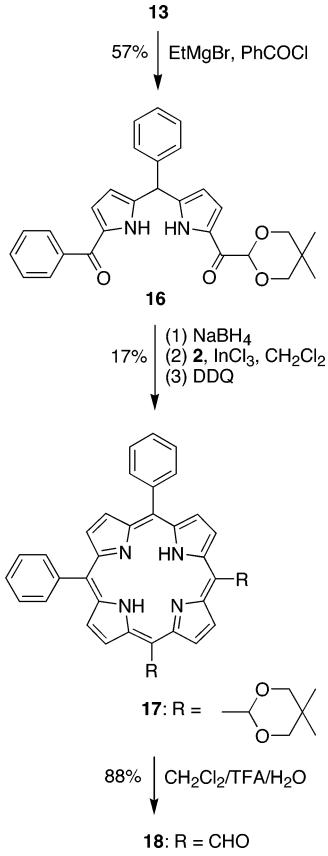


conditions for 1-acylation[16] with pyridyl thioester **6**[16] afforded the 1-acyldipyrromethane **7** in 72% yield. Reduction of **7** with $NaBH_4$ and self-condensation[16,21] of the resulting dipyrromethane-monocarbinol **7-OH** in the presence of $InCl_3$ followed by oxidation with DDQ gave porphyrin **8** in 14% yield. Hydrolysis of the two acetal groups in porphyrin **8** with CH_2Cl_2/TFA/H_2O (10:1:1) gave 5,15-diformylporphyrin **9** in 90% yield (Scheme 2).

SCHEME 5



The route that employs a dipyrromethane-monocarbinol bearing the acetal at the 1-carbinol position requires the synthesis of an appropriate acetal-containing Mukaiyama reagent. The reaction of glyoxylic acid monohydrate with neopentyl glycol in the presence of Amberlyst-15 ion-exchange resin (as described for homologous compounds)[23] provided a mixture of the desired acetal-acid **10** and an acetal-ester byproduct. Hydrolysis of the mixture with 20% aqueous NaOH afforded **10** in 73% yield. The Mukaiyama reaction[24] of **10** with 2,2′-dipyridyl disulfide and Ph_3P provided pyridyl thioester **11**, which proved to be difficult to purify. The crude reaction mixture containing **11** was used in the next step. Thus, acylation of 5-phenyldipyrromethane (**12**)[20] in the standard manner[16] with the crude **11** afforded the 1-acyldipyrromethane **13** in 64% yield (Scheme 3).

Reduction of **13** with $NaBH_4$ gave the dipyrromethane-monocarbinol **13-OH**, which upon self-condensation[16,21] in the presence of $InCl_3$ followed by oxidation with DDQ provided porphyrin **14** in 21% yield. Hydrolysis of the two acetal groups in porphyrin **14** in CH_2Cl_2/TFA/H_2O (5:1:1) afforded the 5,15-diformylporphyrin **15** in 83% yield (Scheme 4).

5,10-Diformylporphyrins. Acylation of 1-acyldipyrromethane **13** with benzoyl chloride by the standard

(23) Newman, M. S.; Chen, C. H. *J. Org. Chem.* **1973**, *38*, 1173−1177.
(24) Araki, M.; Sakata, S.; Takei, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1777−1780.
(25) (a) Fenyo, D.; Chait, B. T.; Johnson, T. E.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **1997**, *1*, 93−99. (b) Srinivasan, N.; Haney, C. A.; Lindsey, J. S.; Zhang, W.; Chait, B. T. *J. Porphyrins Phthalocyanines* **1999**, *3*, 283−291.

procedure[17] provided the 1,9-diacyldipyrromethane **16** in 57% yield. Reduction of **16** with $NaBH_4$ gave the dipyrromethane-dicarbinol **16-diol**, which upon condensation with dipyrromethane **2** in the presence of $InCl_3$ followed by oxidation with DDQ afforded porphyrin **17** in 17% yield. Hydrolysis of the two acetal groups in porphyrin **17** in CH_2Cl_2/TFA/H_2O (5:1:1) afforded the 5,10-diformylporphyrin **18** in 88% yield (Scheme 5).

Spectroscopic Characterization. Each porphyrin was characterized by absorption spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy (except **9** and **15** due to poor solubility), laser-desorption mass spectrometry (LD-MS),[25] and FAB-MS. The acetal-substituted porphyrins (**4**, **8**, **14**, **17**) exhibited typical absorption spectra, with the characteristic Soret band in the 416−419 nm region. The corresponding formyl-porphyrins exhibited red-shifted Soret bands. The magnitude of the shift varied from 9 nm (one formyl, **5**), to ∼12 nm (5,15-diformyl, **9**, **15**), to 23 nm (5,10-diformyl, **18**). The IR spectra showed bands at 1672 cm^{-1} to 1674 cm^{-1} (one formyl, **5**; 5,15-diformyl, **15**; 5,10-diformyl, **18**) and at 1666 cm^{-1} (5,15-diformyl, **9**). In each formyl-porphyrin, the formyl proton resonated as a distinctive singlet at 12.3−12.5 ppm. The formyl carbon gave a resonance at 195.13 ppm (one formyl, **5**) and at 194.77 ppm (5,10-diformyl, **18**). Each porphyrin gave the expected molecule ion peak upon LD-MS analysis.

Conclusion

Acetal-substituted dipyrromethane, dipyrromethane-1-carbinol, and dipyrromethane-1,9-dicarbinol components can be used in rational routes for forming porphyrins. Gentle acid hydrolysis of the resulting *meso*-acetal porphyrins affords the corresponding *meso*-formyl porphyrins. The conversion of acetal-substituted dipyrromethane species to free base porphyrins complements the traditional Vilsmeier formylation of metalloporphyrins.

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Supporting Information Available: Complete experimental section, including the synthesis of 5-(dithiolan-2-yl)-dipyrromethane, 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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