Tetrahedron Letters,Vol.28,No.27,pp 3069-3070,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

AN IMPROVED SYNTHESIS OF TETRAMESITYLPORPHYRIN

Richard W. Wagner, David S. Lawrence, and Jonathan S. Lindsey*

Department of Chemistry, Carnegie Mellon University
4400 Fifth Avenue, Pittsburgh, Pennsylvania 15213

Abstract: We report a simple two-step one-flask procedure for the synthesis of tetramesitylporphyrin in 29% yield. Pyrrole and mesitaldehyde react at room temperature to form tetramesitylporphyrinogen. The addition of an oxidant yields the porphyrin. Macrocycle formation and oxidative aromatization are thus performed separately. The reaction at higher temperature results in a lower yield of porphyrin.

Porphyrins sterically-encumbered by peripheral substituents have been used as synthetic models for a variety of porphyrin-mediated processes in biological systems.[1] The archetype of sterically-hindered porphyrins is *meso*-tetramesitylporphyrin (TMP), which has been the target of synthetic efforts for three decades. Despite prolonged interest, the standard protocol for the preparation of TMP as well as most sterically-hindered porphyrins involves the use of sealed bomb reactions at high temperatures. In a recent optimization of the original procedure,[2] mesitaldehyde, pyrrole, pyridine, and anhydrous zinc acetate were reacted at 175°C under Ar for three days in a sealed vessel, followed by workup and chromatography to afford TMP in 4.5% yield.[3] The inconvenience and low yield of this procedure present obvious limitations which we have sought to overcome.

We recently developed a new synthetic strategy for the preparation of tetraphenylporphyrins.[4] Pyrrole and benzaldehyde react with trace acid catalysis at room temperature to afford the tetraphenylporphyrinogen at thermodynamic equilibrium. The addition of a quinone oxidant affords tetraphenylporphyrin in 40-50% yield. Though benzaldehydes bearing multiple functionalities in the meta and para positions are easily converted to the corresponding porphyrin, ortho-substituted aldehydes react poorly, and mesitaldehyde fails altogether. We now present an extension of this methodology for the fast and efficient synthesis of tetramesitylporphyrin.

Pyrrole and mesitaldehyde (10^{-2} M) reacted readily at room temperature in dry $CHCl_3$ upon addition of BF_3-etherate. After 1 h the product distribution was estimated to consist of tetramesitylporphyrinogen (30%), dipyrrylmethenes (5%), unreacted mesitaldehyde (5%), unreacted pyrrole, and open-chain polypyrrylmethanes. The addition of a quinone oxidant (DDQ at 25°C, 1 min, (31%); or p-chloranil at 61°C, 1 h (32%)) converted the porphyrinogen to the porphyrin and the polypyrrylmethanes to polypyrrylmethenes. The crude reaction

product was freed of starting materials, quinone, and polypyrrylmethene species by washing with methanol, affording tetramesitylporphyrin in 29% yield.

The highest yield of porphyrin was obtained at intermediate concentrations (10^{-2} M) of mesitaldehyde and pyrrole, in analogy with unhindered aromatic aldehydes.[4] When the condensation of mesitaldehyde and pyrrole was performed in refluxing $CHCl_3$, the yield of porphyrin was lower and the yield of dipyrrylmethenes increased.[5] Elevated temperatures are not necessary to form porphyrinogen macrocycles, the natural precursors to porphyrins.[4] The synthesis of more complex sterically-hindered porphyrins via this gentle procedure is currently underway.

Experimental: A 2-L three neck round-bottomed flask fitted with a septum, reflux condenser, and nitrogen inlet port was charged with 1 L of $CHCl_3$ (distilled from K_2CO_3), mesitaldehyde (1.475 mL, 10 mmol, 10^{-2} M), and pyrrole (694 μL, 10 mmol, 10^{-2} M). After purging the solution with N_2 for 5 min, BF_3-etherate[6] (1.320 mL, 3.3 mmol, 3.3 x 10^{-3} M) was added via syringe. The room temperature reaction was monitored by removing 50 μL aliquots, oxidizing with excess DDQ, followed by absorption spectrophotometry.[4] At the end of 1 h, p-chloranil (1.844 g, 7.5 mmol) was added in powder form and the reaction was gently refluxed (61°C) for 1 h. The reaction mixture then was rotary evaporated to dryness, and the crude dry product was washed with methanol (75 mL) until the filtrate was clear.[7] The polypyrrylmethenes are highly soluble in methanol, have no properties characteristic of tars, and were removed with ease. The final product (576 mg, 29%) was greater than 95% pure as evidenced by TLC, HPLC, and fluorescence excitation and emission spectroscopy. Visible (CH_2Cl_2:ethanol 3:1) λ in nm (log ε) 403 sh, 418 (5.63, fwhm 10 nm), 480 sh (2.95), 514 (4.20), 547 (3.57), 590 (3.70), 647 (3.48). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.61 (8 H, s), 7.27 (8 H, s), 2.62 (12 H, s), 1.85 (48 H, s), -2.51 (2 H, bs).

Acknowledgment: This work was supported by Research Corporation, NIH (GM 36238), and the Donors of the Petroleum Research Fund administered by the American Chemical Society.

1. Suslick, K. S.; Reinert, T. J. *J. Chem. Ed.* **1985**, *62*, 974-983. Gold, K. W.; Hodgson, D. J.; Gold, A.; Savrin, J. E.; Toney, G. E. *J. Chem. Soc., Chem. Commun.* **1985**, 563-564. Suslick, K.; Cook, B.; Fox, M. *J. Chem. Soc., Chem. Commun.* **1985**, 580-583.

2. Eaton, S. S.; Eaton, G. R. *J. Am. Chem. Soc.* **1975**, *97*, 3660-3666.
Badger, G. M.; Jones, R. A.; Laslett, R. L. *Aust. J. Chem.* **1964**, *17*, 1028-1035.

3. Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243-6248.

4. Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969-4970.
Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827-836.

5. The Zn-dipyrrylmethene from 2,6-dichlorobenzaldehyde and pyrrole was isolated from refluxing collidine (171°C) in 40% yield, but the porphyrin yield was only 3.7%. See: Hill, C. L.; Williamson, M. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1228-1229.

6. The BF_3-etherate was used as obtained from Aldrich Chemical Company.

7. This methanol wash procedure is superior to chromatography, and also is applicable to unhindered tetraphenylporphyrins.

(Received in USA 9 March 1987)