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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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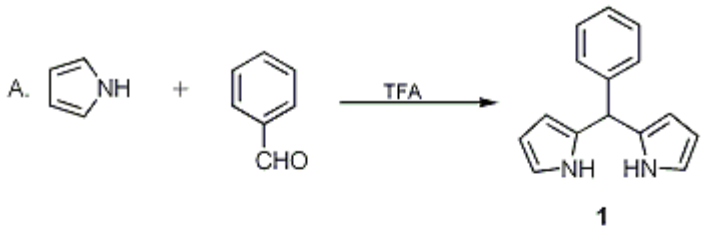
5-PHENYLDIPYRROMETHANE AND 5,15-DIPHENYLPORPHYRIN



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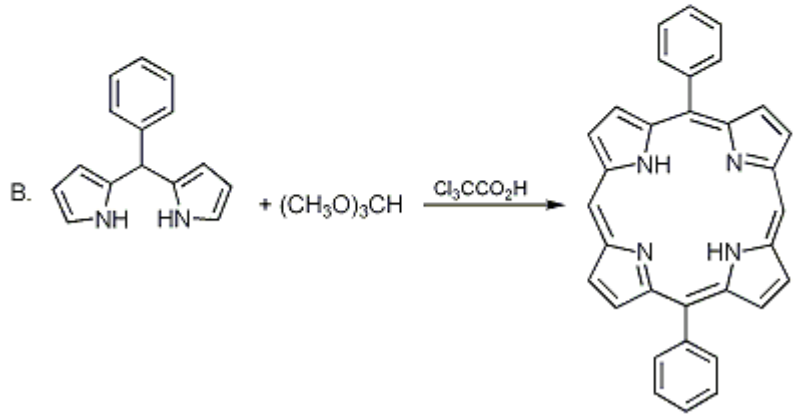

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1. Procedure

A. 5-Phenyldipyrromethane (**1**).[4] To a 250-mL, two-necked, round-bottomed flask equipped with a magnetic stir bar and fitted with a gas outlet connected to an oil bubbler are added freshly distilled pyrrole (150 mL, 2.16 mol) and benzaldehyde (6.0 mL, 59 mmol) (Note 1). The second neck of the flask is sealed with a rubber septum, and the mixture is deoxygenated by bubbling dry nitrogen through it for 15 min. Trifluoroacetic acid (0.45 mL, 5.8 mmol) is added in one portion by syringe, and the resulting mixture is stirred magnetically for 15 min at room temperature. Excess pyrrole (Note 2) is removed by rotary evaporation (5-20 mm) with warming (50-60°C) to yield a dark oil. The oil is taken up in a minimal amount (ca. 10 mL) of dichloromethane , and charged onto the top of a flash chromatography column (50 g of 230 - 400 mesh silica gel). The major fraction containing **1** and some higher oligomers is eluted with dichloromethane and collected (TLC is monitored with visualization using bromine vapor: Compound **1** turns bright red/orange, and the higher oligomers show beige to brown spots of lower R_f). Rotary evaporation of the solvent yields a tan oil that is transferred to a vacuum sublimation apparatus (50 mm × 200 mm) and subjected to high vacuum (0.01 mm). To allow residual pyrrole and solvent to escape, a slow heating rate (ca. 0.75°C/min) is maintained until visible sublimation sets in at approximately 120°C (Note 3). After sublimation ceases, the white crystalline sublimate consisting of **1** (8.57-8.83 g; 65-67%) is collected (Note 4).

B. 5,15-Diphenylporphyrin (**2**).[5] A 1-L, one-necked, round-bottomed flask equipped with a

magnetic stir bar and a 250-mL, pressure-equalizing, dropping funnel fitted with an argon inlet adaper is charged with a solution of 5-phenyldipyrromethane (**1**) (0.5 g, 2.3 mmol) in 630 mL of dichloromethane (Note 5). Trimethyl orthoformate (18 mL, 0.165 mol) is added in one portion (Note 6). The flask is wrapped in aluminum foil, stirred magnetically, and a solution of trichloroacetic acid (8.83 g, 54 mmol) in 230 mL of dichloromethane is added dropwise over 15 min. The resulting solution is stirred in the dark for 4 hr, whereupon excess acid is quenched by adding 15.6 mL of pyridine in one portion. The solution is stirred for 17 hr, while still protected from light. Finally, air is bubbled into the solution for 10 min, and the reaction mixture is stirred for 4 hr open to air and light. The solvent is removed by rotary evaporation (25°C, 20 mm), and the residue is further concentrated under high vacuum (0.01 mm) for 17 hr. The solid residue is dissolved in 100 mL of dichloromethane , and silica gel (5 g, 230-400 mesh) is added to the solution. The solvent is evaporated and the crude product, adsorbed on silica gel, is loaded onto the top of a chromatography column packed with 50 g of 230-400 mesh silica gel. The product is eluted with 70:30 dichloromethane/hexane. The combined eluants are concentrated under reduced pressure, and the residue is triturated with 50 mL of methanol . The solid crystalline product is recovered by filtration (Note 7). The purple crystals are air-dried and recrystallized from a mixture of toluene (15 mL) and pyridine (0.1 mL) to give **2** (0.073-0.104 g; 14-20%) as lustrous purple plates (Note 8).

2. Notes

1. Pyrrole was obtained from Lancaster Synthesis Inc. , and all other chemicals were obtained from Aldrich Chemical Company, Inc. and used as received.
2. Excess pyrrole is required to maximize formation of dipyrromethane. Lowering the pyrrole/benzaldehyde ratio favors formation of higher oligomers and polymers. Unreacted pyrrole is recovered by distillation after the reaction is complete and can be recycled.
3. A slow heating rate and application of vacuum are crucial to avoid bumping of the crude oil onto the cold finger.
4. The spectral and analytical properties for **1** are as follows: mp 102.0-102.5°C (lit.[6] 100.2-101.1°C), the submitters observed 104°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.47 (s, 1 H), 5.92 (br s, 2 H), 6.15 (d, 2 H, J = 2.8), 6.69 (br s, 2 H), 7.20-7.34 (m, 5 H), 7.90 (br s, 2 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 43.9, 107.1, 108.3, 117.1, 126.8, 128.3, 128.5, 132.3, 141.9 ; IR (CH_2Cl_2) cm^{-1}: 3440, 3020, 2970, 1590, 1555, 1485, 1440, 1420, 1390, 1110, 1080, 1020, 965, 880, 780 ; HRMS M^+ calcd for $C_{15}H_{14}N_2$: 222.1157, found: 222.1156 ; Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C. 80.83; H, 6.38; N, 12.42.
5. High dilution conditions are necessary to maximize cyclotetramerization at the expense of linear polymerization.
6. Trimethyl orthoformate is used in excess relative to 5-phenyldipyrromethane to promote reaction between these two species, because dipyrromethanes alone, in common with pyrroles, undergo self-condensation under acidic conditions to yield polypyrroles.
7. The use of a fritted filter unit (Millipore) fitted with Millipore HVLP 04700 filter discs (0.45 μm) was found to be advantageous and allows essentially quantitative recovery of crystalline product.
8. Addition of pyridine to the recrystallization solvent is necessary to ensure that the porphyrin is present in the free base form during crystallization. Crystallization without pyridine results in recovery of product contaminated with porphyrin hydrochloride salts. The spectral and analytical properties for **2** are as follows: mp >300°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: −3.12 (br s, 2 H), 7.80-7.84 (m, 6 H), 8.28 (dd, 4 H), 9.09 (d, 4 H, J = 4.2), 9.40 (d, 4 H, J = 4.8), 10.32 (s, 2 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 105.2, 119.0, 126.9, 127.6, 130.9, 131.5, 134.7, 141.2, 145.0, 147.0 ; IR (CH_2Cl_2) cm^{-1}: 3020, 2960, 1410, 1230, 950, 890, 850, 760 ; UV-vis ($CHCl_3$) λ_{max} (ε): 405nm (412000), 500nm (18100), 535nm (5150), 574nm (5720), 629nm (1450) ; HRMS M^+ calcd for $C_{32}H_{22}N_4$: 462.1844, found: 462.1847 . Anal. Calcd for $C_{32}H_{22}N_4$: C, 83.09; H, 4.79; N, 12.11. Found: C, 82.84; H, 4.53; N, 12.02.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

5,15-Diphenylporphyrin was, until recently, inaccessible in quantities suitable for use as a porphyrin model compound. The two classic synthetic porphyrins most commonly used in model studies, 2,3,7,8,12,13,17,18-octaethylporphyrin and 5,10,15,20-tetraphenylporphyrin, give access to stable, organic-solvent-soluble molecules with unsubstituted meso-positions and unsubstituted β-positions, respectively. 5,15-Diphenylporphyrin represents a unique model porphyrin, in that it is stable, freely soluble in a range of organic solvents (chloroform, dichloromethane, tetrahydrofuran), and presents two unsubstituted meso-positions and eight unsubstituted β-positions in the same molecule. The chemical properties peculiar to this molecule are only beginning to be explored, but they have already allowed the synthesis of novel ethynyl-linked porphyrin arrays as models of light-harvesting antenna systems,[7] and the development of a new bioconjugation method,[8] the key step of which was direct iodination of 5,15-diphenylporphyrin, a reaction that had either failed, or proved uncontrollable, on all other porphyrins.

To the submitter's knowledge the synthesis of 5,15-diphenylporphyrin has been reported on only two previous occasions. Both syntheses relied on the reaction of dipyrromethane, a relatively air-sensitive compound, with benzaldehyde. Treibs and Haberle[9] reported a 3% yield for this reaction and noted it was "hard to access", while Manka and Lawrence[10] claimed a 92% yield. In the submitter's hands, however, the yield for the latter method could not be reproduced, and neither detailed experimental data, nor a measure of purity for the product, was available. The method presented here, therefore, represents the first reliable procedure for synthesizing analytically pure 5,15-diphenylporphyrin. The method requires only standard solvents and reagents. It should also be noted that this synthetic route contains a novel purification of 5-phenyl-dipyrromethane by sublimation, which obviates the need for large scale chromatography[4] to obtain gram quantities of this intermediate. Indeed, reactions giving 12 g of analytically pure product in 44% yield from pyrrole and benzaldehyde are practical. A yield of 54% has been reported for the synthesis of 5-phenyldipyrromethane from pyrrole and a triazolinedione ylide.[6] However, this method gave only milligram quantities of product and required purification by centrifugal chromatography. The condensation of 5-phenyldipyrromethane with trimethyl orthoformate to yield 5,15-diphenylporphyrin is also unusual as the only previous use of this method appears to have been in the synthesis of 5,15-diphenyl-2,3,7,8,12,13,17,18-octamethylporphyrin from 1,9-dicarboxy-2,3,7,8-tetramethyl-5-phenyldipyrromethane.[5] Note that in this latter reaction a yield of 13% was reported, while the submitter's adaptation of these conditions to the synthesis of 5,15-diphenylporphyrin from 5-phenyldipyrromethane resulted in a 21% yield.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

5-Phenyldipyrromethane:
1H-Pyrrole, 2,2'-(phenylmethylene)bis- (12); (107798-98-1)

5,15-Diphenylporphyrin:
Porphine, 5,15-diphenyl- (8,9); (22112-89-6)

Pyrrole:
1H-Pyrrole (9); (109-97-7)

Benzaldehyde (8,9); (100-52-7)

Trifluoroacetic acid:
Acetic acid, trifluoro- (8,9); (76-05-1)

Trimethyl orthoformate:
Orthoformic acid, trimethyl ester (8);
Methane, trimethoxy- (9); (149-73-5)

Trichloroacetic acid:
Acetic acid, trichloro- (8,9) (76-03-9)