Phenylpyrroles by Suzuki Cross Coupling and a Synthesis of Type I Tetramethyltetraphenylporphyrin

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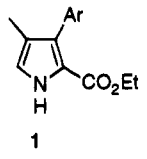
During the course of studying the oxophlorin to oxaporphyrin conversion[1,2] in heme catabolism catalyzed by heme oxygenase, it appeared desirable to prepare aryl-substituted porphyrins with no methine (*meso*) substituents.[3] A literature survey indicated that except for a few octaphenylporphyrin derivatives,[4] only a very limited number of *meso*-unsubstituted β-aryl porphyrins were known. Almost all of these were reported in a paper by Ono et al.[5] utilizing the Barton–Zard method[6] to construct the necessary 3-arylpyrrole precursors (**1**). The subsequent conversion of **1** to the tetraarylporphyrins, via the reduced pyrrylmethanol, however, did not always result in a single product, and more often than not, a mixture of (type I, II, III, and IV) porphyrins was obtained. In fact, the prototype of this class of porphyrins, **2**, has never been convincingly established.[5b]



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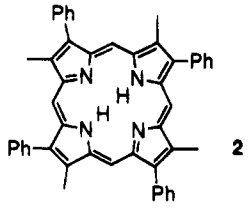
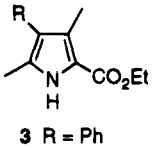


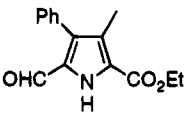
2

In an initial attempt to prepare **2**, we made ethyl 4-methyl-3-phenylpyrrole-2-carboxylate (**1**, R = Ph) from nitroalkene and converted the pyrrole into porphyrin following the literature protocol.[5] The resultant mixture of porphyrins, as evidenced by multiple ^{1}H NMR signals for the meso protons, proved to be hopelessly difficult to separate on a preparative scale. We were therefore forced to look for alternative methods.

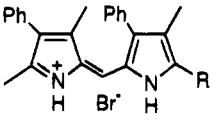
A suitable pyrrole starting material for the classical Fischer type-I porphyrin synthesis is **3**. This pyrrole was made from benzyl methyl ketone and ethyl acetoacetate oxime in low yield and appeared in the literature only once as an IR reference compound.[7] We decided to prepare **3** from the easily available bromopyrrole **4** and phenylboric acid using Pd(0)-catalyzed cross coupling[8]—a versatile reaction which, as far as we can determine, has not been applied to pyrrole synthesis.[9] The reaction was conducted in DMF to give essentially a quantitative yield. Having prepared this pyrrole, we converted it to the aldehyde **5**, and after hydrolyzing off the ethyl ester group, the carboxylic acid forms of **3** and **5** were condensed to give the dipyrrylmethene **6**. For achieving good yields in type-I porphyrin synthesis, it is customary to treat a dipyrrylmethene such as **6** with slightly more than 1 equiv of bromine before being heated in formic acid to effect the ring closure.[10,11] The purpose of bromine



3 R = Ph
4 R = Br



5



6 R = CO_2H
7 R = Br

is to remove the carboxyl group and partially brominate the 2-pyrryl methyl group. Unfortunately, this procedure, as we realized afterwards, introduced bromo groups on the phenyl ring. From mass spectra, one could readily see up to four bromine atoms present in this mixture of product, the separation of which was not feasible. It appeared that the bromination of the phenyl substituents is at least as competitive as the bromination of the 2-pyrryl methyl group under the reaction conditions. To avoid the unwanted bromination, it was necessary to remove all free bromine before the ring formation step. We worked out a different procedure to prepare the 2-bromodipyrrylmethene **7**. When the hydrolyzed acid form of **3** in acetic acid was treated with 2.5 equiv of bromine at room temperature, a deep red solution formed instantly. Without delay, a stream of air was blown over the solution to remove most volatile material. The residue was then stirred with ether (to induce crystallization) and a small amount of cyclohexene (bromine scavenger) to yield red crystalline **7**, free from occluded bromine (perbromide). The cyclization of **7** was conducted in the old fashioned way—fused in malic acid at 160 °C—to give isomerically pure type-I tetramethyltetraphenylporphyrin in 24% yield, quite acceptable for this type of reaction. In principle, **6** could be brominated cleanly by using no more than 1 equiv of bromine. The practical problem often encountered is that this type of dipyrrylmethene is either a noncrystalline gum which makes accurate calculation of Br_2 difficult or it does not dissolve well at room temperature. Therefore, the one-step preparation of the bromodipyrrylmethene **7** is the preferred route.

The Suzuki cross coupling conditions seem to offer a high yielding and convenient approach to various aryl substituted pyrroles. To test the generality of this reaction, dibromopyrrole **8** was reacted with phenylboric acid. Again, the diphenylpyrrole **9** was obtained in 95%

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(5) (a) Ono, N.; Kawamura, H.; Bougauchi, M.; Maruyama, K. *Tetrahedron* **1990**, *46*, 7483. (b) In a short note by Ono, N.; Maruyama, K. *Chem. Lett.* **1989**, 1237, an alleged **2** of unknown purity was believed to have been synthesized. However, the MS provided for this material was not **2**.
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(9) The Suzuki coupling reaction has recently been applied to brominated *meso*-tetraphenylporphyrins, see Zhou, X.; Zhou, Z.; Mak, T. C. W.; Chan, K. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2519. For related Pd-catalyzed couplings, see the following: (a) DiMagno, S. G.; Lin, V. S.-Y.; Therien, M. J. *J. Org. Chem.* **1993**, *58*, 5983. (b) Morris, I. K.; Snow, K. M.; Smith, N. W.; Smith, K. M. *J. Org. Chem.* **1990**, *55*, 1231. (c) Arnold, D. P.; Nitschinsk, L. J. *Tetrahedron Lett.* **1993**, *34*, 693. (d) Ali, H.; van Lier, J. E. *Tetrahedron* **1994**, *50*, 11933. (e) Boyle, R. W.; Johnson, C. K.; Dolphin, D. *J. Chem. Soc., Chem. Commun.* **1995**, 527.
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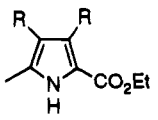
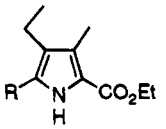
yield. This pyrrole can be converted to the previously



8 R = Br
9 R = Ph



10 R = I
11 R = Ph

known octaphenylporphyrin either by the same dipyrrylmethene strategy reported here or by cyclization via the 5-acetoxymethyl derivative as described in the literature.[12] Likewise, 2-iodopyrrole such as **10** was coupled successfully with phenylboric acid to give **11** with an excellent yield. This example demonstrates a novel way to connect pyrrole α-position(s) to other heterocycles (e.g. thiophene, furan, etc.) from which "expanded" macrocycles[13] may be constructed. The general availability of many aromatic boron compounds and the remarkable tolerance of functional groups during the coupling reaction likely will open the door to many interesting pyrroles whose potential is now being explored.

Experimental Section

Phenylboric acid and $Pd(PPh_3)_4$ were supplied by Aldrich Chemical Co.

Ethyl 4-Methyl-3-phenyl-2-pyrrolecarboxylate (1, Ar = Ph). Ethyl isocyanoacetate (385 mg, 3.43 mmol) was added to a THF solution (10 mL) of 1-phenyl-2-nitropropene[14] (550 mg, 3.37 mmol) cooled in an ice bath. To this solution, DBU (760 mg, 5 mmol) in THF (10 mL) was added dropwise over 30 min. The reaction mixture was stirred at room temperature overnight, poured into 15% HCl solution and extracted with CH_2Cl_2. The extracts were washed with water and dried over Na_2SO_4. The crude product was purified by column chromatography using silica gel (CH_2Cl_2) to give an oil: yield 415 mg (54%); ^1H NMR (300 MHz, in $CDCl_3$) δ 9.23 (br, 1 H), 7.51–7.22 (m, 5 H), 6.79 (s, 1 H), 4.15 (q, 2 H), 2.01 (s, 3 H), 1.13 (s, 3 H); HRMS, found *m/e* 229.1085 for M^+, $C_{14}H_{15}NO_2$ requires 229.1103. Anal. Calcd: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.07; H, 6.60; N, 6.08. This pyrrole was reported[5b] without data.

Ethyl 3,5-Dimethyl-4-phenyl-2-pyrrolecarboxylate (3). To a stirred solution of **4**[15] (500 mg, 2.03 mmol) and $Pd(PPh_3)_4$ (80 mg, 0.07 mmol) in DMF (15 mL) under argon was added Na_2CO_3 (550 mg, dissolved in minimum amount of water) and phenylboronic acid (275 mg, 2.25 mmol). The mixture was magnetically stirred and refluxed under argon overnight. The mixture was then allowed to cool, and inorganic solids were removed by filtration. The filtrate was diluted with the same amount of dichloromethane and thoroughly washed with several portions of water to remove DMF. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography on silica gel afforded **3** (468 mg, 95%): mp 138–140 °C (lit.[7] mp 143–144 °C); ^1H NMR ($CDCl_3$) δ 8.77 (br, 1 H), 7.40 (t, 3 H), 7.28 (d, 1 H), 7.23 (d, 1 H), 4.33 (q, 2 H), 2.29 (s, 3 H), 2.26 (s, 3 H), 1.37 (t, 3 H); MS, *m/e* for $C_{15}H_{17}NO_2$ calcd 243.1, found 243.3.

Ethyl 5-Formyl-3-methyl-4-phenyl-2-carboxylate (5). To a 20-mL acetic acid solution of **3** (2.15 g, 8.85 mmol) was added lead tetraacetate (11 g, 25 mmol). The solution was heated for 45 min over a steam bath before being cooled and poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and evaporated to give a crude product which was flash chromatographed on silica gel column (CH_2Cl_2) to afford **5** (1.9 g, 84%): mp 98–99 °C; ^1H NMR δ 9.72 (br, 1 H), 9.49 (s, 1 H), 7.58–7.32 (m, 5 H), 4.38 (q, 2 H), 2.30 (s, 3 H), 1.38 (t, 3 H); HRMS, found 257.1070 for M^+, $C_{15}H_{15}NO_3$ requires *m/e* 257.1052. Anal. Calcd: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.21; H, 5.83; N, 5.43.

Attempted Synthesis of 2 from 5. The pyrrole ester **3** (1.1 g, 4.5 mmol) in ethanol (10 mL) was hydrolyzed by heating with NaOH (0.5 g in 4 mL H_2O) on a steam bath for 1 h. The solution was diluted with H_2O (50 mL) and acidified with 10% HCl. The precipitated pyrrole acid was collected by filtration and dried in vacuo. The pyrrole aldehyde ester **5** (1.16 g, 4.5 mmol) was saponified and isolated similarly. The two products were stirred in acetic acid (5 mL) to which HBr (48%, 1 mL) was added. The dark mixture was heated on a steam bath for 10 min before being cooled; no crystalline solid (**6**) was observed after standing 3 h at 23 °C and then half a day at 5 °C. The mixture was pumped dry and redissolved in anhydrous formic acid (10 mL). Bromine (0.4 mL, 7.3 mmol) was added, and the mixture was heated to reflux in an oil bath (120 °C). After refluxing for 2 h, the condenser was removed and the solvent was evaporated. The residue was dried with a stream of air and extrated with $CHCl_3$ and water. The dark colored material in the organic phase was washed with more water and purified by column chromatography on silica gel with hexane/CH_2Cl_2. The porphyrin band isolated was further purified by preparative TLC plates. MS of this material showed that it contains multiple of bromo-substituents beyond what was expected for **2**.

2-Bromo-4,3′-diphenyl-3,2′,4′-trimethyl-5,5′-dipyrrylmethene Hydrobromide (7). The pyrrole ester **3** (1.1 g, 4.5 mmol) was dissolved in ethanol (10 mL) to which a NaOH solution (0.5 g in 4 mL H_2O) was added. The mixture was heated to reflux on a steam bath for 1 h before the solvent was removed on a rotovap. The residue was dissolved in H_2O (20 mL) to which 8 N HCl was added carefully until the pH of the solution became acidic. The precipitated white pyrrole acid was collected by filtration and dried in vacuo. To this solid (920 mg, 4.2 mmol) suspended in acetic acid (3 mL) and stirred with a magnetic stirrer in the open air, a bromine solution made by 0.6 mL of bromine and 1 mL of acetic acid was added all at once through a pipette. The dark colored mixture was stirred at room temperature for about 20 s before a stream of air from a pipette was blown into the flask. After about 10 min of blowing, a mixture of ether (2 mL) and cyclohexene (0.5 mL) was added to the mixture. The air blowing was continued for about 90 min to leave an essentially dry residue in the flask. The residue was triturated and stirred with more ether (4 mL), and the mixture was filtered. The red brick-colored powder was washed with ether and dried in air; yield was 940 mg (45%): ^1H NMR δ 12.77 (br, 2 H), 7.52–7.43 (m, 10 H), 7.04 (br, 1 H), 2.14 (s, 6 H), 1.50 (s, 3 H). MS, found *m/e* 418 and 420 for $(M - Br)^+$, $C_{24}H_{23}N_2$-Br requires *m/e* 418 and 420. Anal. Calcd: C, 57.74; H, 4.64; N, 5.61. Found: C, 57.85; H, 4.70; N, 5.67.

2,7,12,17-Tetramethyl-3,8,13,18-tetraphenylporphyrin (2). The bromodipyrrylmethene **7** (900 mg, 1.8 mmol), mixed with finely grounded malic acid (12 g), was placed in a small round-bottomed flask and heated in an oil bath maintained at 160 °C. The mixture was stirred magnetically during the heating in the open air. After about 2 h, the dark colored tar was cooled to 40 °C before being dissolved in water (100 mL) and CH_2Cl_2 (50 mL). This solution was partitioned in a separatory funnel and the organic phase was washed successively with 5% Na_2CO_3 solution and water before being evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2) and crystallized from CH_2Cl_2/MeOH to give 145 mg (24%): ^1H NMR δ 10.17 (s, 4 H), 8.21 (d, 8 H), 7.88 (t, 8 H), 7.74 (t, 4 H), 3.60 (s, 12 H), −3.39 (s, 2 H), UV-vis λ_{max} (ϵ_{max}) 409 nm (214 000), 504 (14 500), 540 (11 500), 570 (8 000), 624 (5 000). MS, found *m/e* 670 for M^+, $C_{48}H_{38}N_4$ requires *m/e* 670. Anal. Calcd: C, 85.94; H, 5.71; N, 8.35. Found: C, 85.86; H, 5.74; N, 8.29.

Ethyl 3,4-Diphenyl-5-methyl-2-pyrrolecarboxylate (9). This compound was prepared by following the same procedure as mentioned above for the preparation of **3**. Here **8**[16] (400 mg, 1.28 mmol) was reacted with phenylboronic acid (325 mg, 2.66 mmol) to afford **9** (370 mg, 95%): mp 165–167 °C (lit.[7] 168 °C).

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^{1}H NMR δ 8.95 (br, 1 H), 7.23–6.98 (m, 10 H), 4.16 (q, 2 H), 2.32 (s, 3 H), 1.13 (t, 3 H); MS, found m/e 305.2 for M^+, $C_{20}H_{19}NO_2$ requires 305.14.

Ethyl 4-Ethyl-3-methyl-5-phenyl-2-pyrrolecarboxylate (11). This compound was prepared by treating **10**[17] (730 mg, 2.37 mmol) with phenylboronic acid (300 mg, 2.46 mmol) to give **11** (575 mg, 94%) according to the procedure described previously for **3**: mp 93–95 °C; ^{1}H NMR δ 8.77 (br, 1 H), 7.45–7.29 (m, 5 H), 4.30 (q, 2 H), 2.55 (q, 2 H), 2.34 (s, 3 H), 1.34 (t, 3 H), 1.14 (t, 3 H); HRMS, found m/e 257.1422 for M^+, $C_{16}H_{19}NO_2$ requires 257.1415.

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Supporting Information Available: Proton NMR spectra for compounds **2**, **3**, **9**, and **11** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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