An Improved Synthesis of 5,15-Diaryloctaalkylporphyrins

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The title compounds were prepared from an aromatic aldehyde and bis(3-ethyl-4-methyl-2-pyrrolyl)-methane in acetonitrile in the presence of catalytic amount of trichloroacetic acid, followed by *p*-chloranil oxidation. The reaction conditions employed here are milder than those previously reported, allowing efficient preparation of porphyrins with acid-labile groups such as cyclic acetals, for which the previous method provided no direct synthetic access. Using the new method, aromatic aldehydes with acid-labile groups, as well as sterically hindered aldehydes, gave the corresponding porphyrins in satisfactory yields (50-90%). This method therefore can be widely utilized for synthesis of 5,15-diaryloctaalkylporphyrins.

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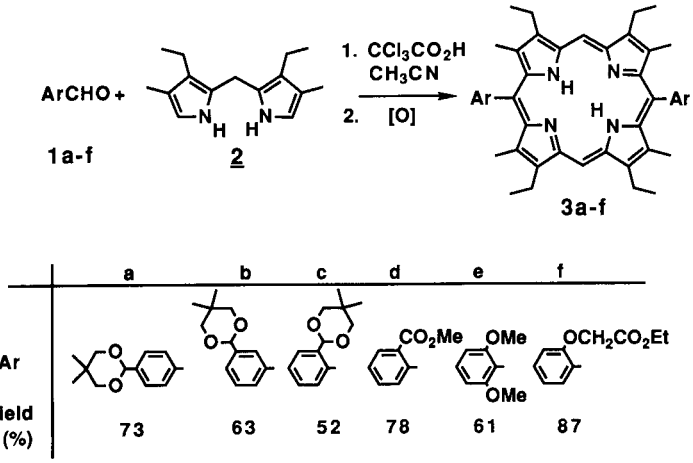
Many synthetic functionalized prophyrin systems are based on 5,15-diaryloctaalkylporphyrins, because of their ease of preparation, high symmetry, and thermal stability of atropisomers [1-3]. Synthesis of these porphyrins from 5,5'-unsubstituted dipyrromethane and aromatic aldehydes was first reported by Ogoshi *et al.* [2a] and later improved by Gunter and Mander [1a] and by Young and Chang [1c]. The procedure reported by Gunter and Mander has been widely used for preparation of 5,15-diaryloctaalkylporphyrins [4], while it gives rather poor results when the starting aldehydes have acid-labile groups such as acetals. We report herein a further improvement in the preparation of these porphyrins. Our synthesis is simple in practice, quite efficient in yields, and shows applicability to wider range of aromatic aldehydes than the standard method.

The aldehyde **1a** and bis(3-ethyl-4-methyl-2-pyrrolyl)-methane **2** [5] were allowed to react in acetonitrile in the presence of a catalytic amount of trichloroacetic acid for five hours at room temperature, followed by treatment with *p*-chloranil for three hours. After workup, the porphyrin **3a** was obtained in 70% yield. The thin-layer chromatography and ^{1}H nmr showed that no deprotection of cyclic acetal took place during porphyrin formation. The porphyrin **3a** was converted by acidic hydrolysis in high yield to diformyl porphyrin **4a**, which is a class of important precursors of oligomeric porphyrins [6]. On the other hand, when **1a** and **2** were treated in methanol in the presence of *p*-toluenesulfonic acid according to the standard procedure of Gunter and Mander [1a], a complex mixture was obtained from which only 7% of **4a** (complete deprotection took place) was separated by column chromatography. Our method therefore provides a convenient synthetic access to 5,15-bis(formylphenyl)porphyrins [7]. Formyl-substituted porphyrins were synthesized by oxidation of hydroxymethyl-substituted porphyrin [6a,b] or by *n*-butyllithium/*N*,*N*-dimethylformamide formylation from bromo-substituted porphyrin [6c]. However, the former method often suffers from undesirable oxidation of porphyrin ring and the latter gave the product only in low yield (15%).

Reactions of various aromatic aldehydes with **2** under the same conditions were examined. Representative results are shown in Scheme 1 together with the isolated yields [8]. Sterically hindered aromatic aldehydes such as **1c** or **1d** also gave the porphyrins in satisfactory yields. However, the reaction failed with 9-anthraldehyde where the steric hindrance is quite severe.

Scheme 1.



Synthesis of 5,15-diarylporphyrins (isolated yields are reported).

In summary, our method (trichloroacetic acid in acetonitrile) for preparation of 5,15-diarylporphyrins is a useful alternative to the standard one (*p*-toluenesulfonic acid in methanol), especially when acid-labile groups are present [9]. Moreover, the present method was successfully utilized for the synthesis of conformationally constrained trimeric and pentameric porphyrins [10].

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting

point apparatus and are uncorrected. The uv-visible spectra were recorded on a Shimadzu UV-3000 spectrometer. The ^{1}H nmr spectra were recorded on a JEOL GX-400 spectrometer, chemical shifts (in deuteriochloroform) being reported in the delta scale (ppm) relative to tetramethylsilane. Mass spectra of porphyrins were recorded on a JEOL DX-300 spectrometer, using the fast atom bombardment (FAB) method (*m*-nitrobenzyl alcohol matrix). Acetonitrile was stored over molecular sieves for several days, and used without further purification.

General Procedure for the Synthesis of 5,15-Diarylporphyrins from Dipyrromethane **2** and Aromatic Aldehydes **1a-f**.

The aromatic aldehyde (1.8 mmoles) and bis(3-ethyl-4-methyl-2-pyrrolyl)methane [5] (2, 1.8 mmoles) were dissolved in 20 ml of acetonitrile. Trichloroacetic acid (50 mg) was added, and the mixture was stirred for 5 hours (dark, under nitrogen, room temperature). *p*-Chloranil (720 mg) in 20 ml of tetrahydrofuran was added, and the mixture was stirred again for 3 hours. The solvent was evaporated, and the resulting solids were suspended in methanol, collected by filtration, and washed thoroughly with methanol. This crude product was dissolved in chloroform, washed with aqueous sodium bicarbonate solution and water, dried, evaporated, and recrystallized from dichloromethane/methanol to give the desired porphyrin. The filtrates were collected and separated by silica-gel column chromatography to give a minor second crop.

5,15-Bis(4-(5,5-dimethyl-1,3-dioxacyclohex-2-yl)phenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphine (**3a**).

Compound **3a** was obtained in 73% yield, mp >300°; uv (dichloromethane): λ max (dichloromethane): 406, 505, 539, 573 624 nm; ^{1}H nmr: δ 10.22 (2H, s, *meso*), 8.09 (4H, d, phenyl), 7.89 (4H, d, phenyl), 5.76 (2H, s, acetal), 3.99 (12H, q and d, Et and acetal-CH_2), 3.86 (4H, d, acetal-CH_2), 2.48 (12H, s, Me), 1.75 (12H, t, Et), 1.48 (6H, s, acetal-Me), 0.93 (6H, s, acetal-Me), -2.42 (2H, s, NH); ms: (m/e) 859 ($M+H^+$).

Anal. Calcd. for $C_{56}H_{66}N_4O_4$ (859.16): C, 78.29; H, 7.72; N, 6.52. Found: C, 77.82; H, 7.62; N, 6.46.

5,15-Bis(3-(5,5-dimethyl-1,3-dioxacyclohex-2-yl)phenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphine (**3b**).

Compound **3b** was obtained in 63% yield, mp >300°; uv (dichloromethane): λ max 407, 505, 539, 573, 624 nm; ^{1}H nmr: δ 10.23 (2H, s, *meso*), 8.21 (2H, s, phenyl), 8.07 (2H, d, phenyl), 7.97 (2H, d, phenyl), 7.77 (2H, t, phenyl), 5.64 (2H, s, acetal), 4.01 (8H, q, Et), 3.84 (4H, d, acetal-CH_2), 3.72 (4H, d, acetal-CH_2), 2.48 (12H, s, Me), 1.77 (12H, t, Et), 1.34 (6H, s, acetal-Me), 0.81 (6H, s, acetal-Me), -2.33 (2H, br, NH); ms: (m/e) 859 ($M+H^+$).

Anal. Calcd. for $C_{56}H_{66}N_4O_4$ (859.16): C, 78.29; H, 7.72; N, 6.52. Found: C, 78.09; H, 7.77; N, 6.47.

5,15-Bis(2-(5,5-dimethyl-1,3-dioxacyclohex-2-yl)phenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphine (**3c**).

Compound **3c** was obtained in 52% yield, mp >300°; ^{1}H nmr: δ 10.26 (2H, s, *meso*), 8.19 (2H, d, phenyl), 7.99 and 7.93 (2H, 2d, phenyl, *cis* and *trans*), 7.90 (2H, t, phenyl), 7.72 and 7.70 (2H, 2t, phenyl, *cis* and *trans*), 4.89 (2H, s, acetal), 4.02 (8H, q, Et), 3.28 and 3.26 (4H, 2d, acetal-CH_2, *cis* and *trans*), 2.47 (12H, s, Me), 2.42 (4H, d, acetal-CH_2), 1.76 (12H, t, Et), 1.23 and 1.21 (6H, 2s, acetal-Me, *cis* and *trans*), 0.11 (6H, s, acetal-Me), -2.39 (2H, s, NH); ms: (m/e) 859 ($M+H^+$).

Anal. Calcd. for $C_{56}H_{66}N_4O_4$ (859.16): C, 78.29; H, 7.72; N, 6.52. Found: C, 78.40; H, 7.76; N, 6.31.

5,15-Bis(2-(methoxycarbonyl)phenyl)-2,8,12,18-tetraethyl-3,7,13,-17-tetramethylporphine (**3d**).

Compound **3d** was obtained in 78% yield, mp >300°; uv λ max (dichloromethane): 409, 506, 541, 575, 627 nm; ^{1}H nmr: δ 10.18 (2H, s, *meso*), 8.35 (2H, dd, phenyl), 8.01 (2H, dd, phenyl), 7.89 (2H, m, phenyl), 7.84 (2H, m, phenyl), 4.00 (8H, m, Et), 2.75 (6H, s, CO_2Me), 2.43 (12H, s, Me), 1.76 (12H, t, Et), -2.24 (2H, br, NH); ms: (m/e) 747 ($M+H^+$).

Anal. Calcd. for $C_{48}H_{50}N_4O_4 \cdot ½\ H_2O$: C, 76.26; H, 6.80; N, 7.41. Found: C, 76.37; H, 6.70; N, 7.43.

5,15-Bis(2,6-dimethoxyphenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphine (**3e**).

Compound **3e** was obtained in 61% yield, mp >300°; uv (dichloromethane): λ max 407, 504, 539, 572, 625 nm; ^{1}H nmr: δ 10.11 (2H, s, *meso*), 7.74 (2H, t, phenyl), 7.00 (4H, d, phenyl), 4.01 (8H, q, Et), 3.55 (12H, s, OMe), 2.61 (12H, s, Me), 1.76 (12H, t, Et), -2.22 (2H, br, NH); ms: (m/e) 751 ($M+H^+$).

Anal. Calcd. for $C_{48}H_{54}N_4O_4$ (750.98): C, 76.77; H, 7.25; N, 7.46. Found: C, 76.62; H, 7.31; N, 7.20.

5,15-Bis(2-(ethoxycarbonylmethoxy)phenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphine (**3f**).

Compound **3f** was obtained in 87% yield, mp 277° dec; uv (dichloromethane): λ max 406, 504, 538, 571, 624 nm; ^{1}H nmr: δ 10.19 (2H, s, *meso*), 7.82 (2H, dd, phenyl), 7.74 (2H, m, phenyl), 7.39 (2H, m, phenyl), 7.13 (2H, dd, phenyl), 4.50 and 4.45 (4H, 2s, OCH_2CO_2, *cis* and *trans*), 4.10 (4H, m, OEt), 4.02 (8H, m, Et), 2.61 (12H, s, Me), 1.78 (12H, t, Et), 1.10 (6H, m, OEt), -2.34 (2H, br, NH); ms: (m/e) 835 ($M+H^+$).

Anal. Calcd. for $C_{52}H_{58}N_4O_6$ (835.05): C, 74.79; H, 7.00; N, 6.71. Found: C, 74.63; H, 7.07; N, 6.83.

5,15-Bis(4-formylphenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphine (**4a**).

The porphyrin **1a** (145 mg, 0.17 mmole) was dissolved in a mixture of trifluoroacetic acid (8 ml) and 10% aqueous sulfuric acid (3 ml), and the solution was stirred for 1 hour at room temperature, poured into water, extracted with chloroform, washed with aqueous sodium bicarbonate solution and water, dried over sodium sulfate and evaporated. The compound **4a** was precipitated from dichloromethane-methanol (223 mg, 0.16 mmole, 96%), mp >300°; uv: (dichloromethane): λ max 410, 507, 540, 575, 626 nm; ^{1}H nmr: δ 10.40 (2H, s, CHO), 10.26 (2H, s, *meso*), 8.29 (8H, phenyl), 4.02 (8H, q, Et), 2.46 (12H, s, Me), 1.77 (12H, t, Et), -2.41 (2H, br, NH); ms: (m/e) 687 ($M+H^+$).

Anal. Calcd. for $C_{46}H_{46}N_4O_2$ (686.90): C, 80.44; H, 6.75; N, 8.16. Found: C, 80.34; H, 6.66; N, 7.92.

5,15-Bis(3-formylphenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphine (**4b**).

The compound **4b** was prepared in a similar manner with **4a** in 97% yield, mp >300°; uv (dichloromethane): λ max 408, 506, 540, 574, 626 nm; ^{1}H nmr: δ 10.31 and 10.26 (2H and 2H, 2s, *meso* and CHO), 8.62 (2H, s, phenyl), 8.37 (4H, 2d, phenyl), 7.95 (2H, t, phenyl), 4.02 (8H, q, Et), 2.45 (12H, s, Me), 1.78 (12H, t, Et), -2.39 (2H, br, NH); ms: (m/e) 687 ($M+H^+$).

Anal. Calcd. for $C_{46}H_{46}N_4O_2$ (686.90): C, 80.44; H, 6.75; N, 8.16.

Found: C, 80.47; H, 6.68; N, 7.95.

5,15-Bis(2-formylphenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphine (**4c**).

The compound **4c** was prepared in a similar manner with **4a** in 85% yield, mp >300°; uv (dichloromethane): λ max 413, 508, 543, 576, 628 nm; ^{1}H nmr: δ 10.27 (2H, s, *meso*), 9.61 and 9.56 (2H, 2s, CHO, *cis* and *trans* = 1:1), 8.41 (2H, d, phenyl), 8.14 (2H, d, phenyl), 7.96 (4H, m, phenyl), 4.01 (8H, q, Et), 2.41 (12H, s, Me), 1.77 (12H, t, Et), -2.30 (2H, br, NH); ms: (m/e) 687 ($M+H^+$).

Anal. Calcd. for $C_{46}H_{46}N_4O_2$ (686.90): C, 80.44; H, 6.75; N, 8.16. Found: C, 80.24; H, 6.68; N, 7.88.

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[8] Mixtures of atropisomeric porphyrins (*cis* and *trans*) were obtained from unsymmetrically substituted benzaldehydes **1b-d** and **1f**. The formyl-substituted porphyrins **4b** and **4c** were also obtained as mixtures of atropisomers.

[9] A Chinese group reported synthesis of 5,15-diaryloctaalkylporphyrins from dipyrromethanes and aromatic aldehydes in the presence of trifluoro- or trichloroacetic acid, although they used only *para*-substituted benzaldehydes and no acid-labile substituents were investigated. See: G. Li, S. Wu and Y. Ten, *Youji Huaxue*, 300 (1985); *Chem. Abstr.*, **104**, 148603k (1986).

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