Studies of Porphyrin Synthesis through 3+1 Condensation

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Acid-catalyzed porphyrin formation from *meso*-aryltripyrromethanes and 2,5-bis(α-hydroxy-α-phenyl)methylfuran is studied. The condensation resulted in selective scrambling of tripyrromethanes when the condensation was carried out with catalytic amounts of BF_3 in methylene chloride. But the reaction carried out with *p*-TsOH or BEt_3 catalysts in the presence of NH_4Cl in acetonitrile, single porphyrin product was isolated without scrambling of starting tripyrromethane. The yields of porphyrin in these studies were somewhat lower than those of 2+2 condensations or aldehyde-pyrrole condensations.

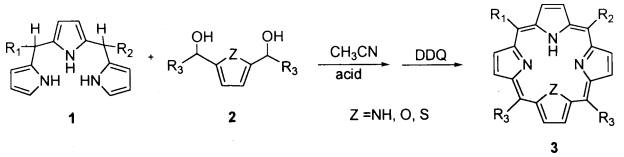
Introduction

We have been interested in synthesizing porphyrin building blocks for various model systems such as porphyrin-based molecular wire and molecular devices. The synthesis of *meso*-substituted porphyrins has traditionally been achieved by Rothemund method[1] or Adler method.[2-4] More recently, the new method has been developed by Lindsey.[5-7] The yields of porphyrins also have been significantly improved by applying various catalysts. Direct synthesis of porphyrins bearing different substituents at *meso* positions was only possible by Macdonalds type 2+2 condensation of two different dipyrromethanes. A *trans*-substituted porphyrins can be synthesized from mixed aldehydes condensations, but the separation of the desired isomers is usually difficult. The 3+1 approach on the other hand can be applied in the regioselective synthesis of *cis*-substituted porphyrins or $R_1R_2(R_3)_2$ type porphyrins as shown in Scheme 1. Regardless the position of linking (*meso*) carbon, it may be possible to synthsize the desired porphyrin as single isomer.

In order to broaden the scope and limitation of the synthesis of the model compounds, we have investigated several reaction parameters on the yields of porphyrins obtained in 3+1 condensation. The parameters studied include acid catalysts, acid concentration, reactant concentrations, the added inorganic salts and reaction times. These studies revealed that the 3+1 condensation generally gave lower yields of porphyrin compared to other methods.[8,9]

Experimenral Section

^{1}H NMR spectra (400 MHz, Bruker DPX-400, IFS48), IR spectra (JASCO IR100) and absorption spectra (Kontron 941) were collected routinely. Mass spectra were obtained by FAB. The formed porphyrins from crude reaction mixture were analyzed by laser desorption ionization mass spectrometry (LD-MS, Bruker Proflex II) without matrix. The progress of porphyrin forming reactions was monitored spectroscopically and extent of scrambling in the crude reaction mixture determined using LD-MS. The crude oxidized spectroscopic aliquats were spotted directly onto a LD-MS target with prior filtration through a pad of silica in a Pasteur pipette. The quantitative absorption spectral measurements were performed using Kontron 941 spectrometer. Pyrrole was distilled under low pressure and used prior to colorization. Acetonitrile used as reaction solvent as received (Aldrich). BF_3-etherate (Aldrich, redistilled grade), *p*-toluenesulfonic acid (*p*-TsOH), DDQ (aldrich) and TFA (Aldrich) were used as received. Column chromatography was routinely done using silica gel (Merck, 230-400 mesh). Compound **4** was obtained by reducing corresponding ketone.[8] Diols (**6a, 6b**) were synthesized as reported previously.[10] The 3+1 condensations were performed in small scale, with spectroscopic yield determination. The usual procedures are following; the diol (0.1 mmol) was dissolved in acetonitrile (10 mL) and tripyrromethane (0.1 mmol) was added. Then $BF_3 \cdot OEt_2$ (2 mM) was added to the stirred solution. The reaction was monitored at various time (min) by removing 50 μL of aliquats from the reaction mixture. The aliquat were added to 300 μL of 0.01 M solution of DDQ in toluene to oxidize any porphyrinogen formed. 25 μL of the aliquat of this solution was diluted again with appropriate amount of CH_2Cl_2/EtOH (3/1) to the total volume of 3.0 mL. The band at 416 nm was characteristic of a Soret band of N_3O-porphyrin. The spectroscopic yields then were determined assuming molar absorptivity of 160,000. The minimum change of the absorbance was taken in order to determine the relative yields of porphyrin in different time.



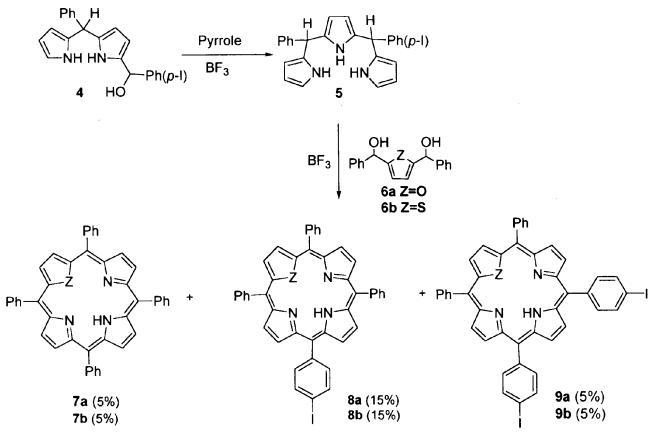
Scheme 1

5-(*p*-Iodophenyl)-10-phenyltripyrromethane (5). $BF_3 \cdot OEt_2$ (0.28 g, 1.98 mmol) was added dropwise to the stirring mixture of **4** (0.90 g, 1.98 mmol) and pyrrole (2.66 g, 39.6 mmol) under nitrogen. The mixture was stirred for 25 min at room temperature then CH_2Cl_2 (120 mL) was added. The whole mixture was combined with aqueous NaOH (0.1 N, 50 mL). Then the organic layer was washed with water and dried (Na_2SO_4). Excess pyrrole was removed under reduced pressure and remaining black solid was purified by

column chromatography on silica (chloroform/hexanes, 8/2). Fast moving dipyrromethanes (major) which were formed by cleavage of tripyrromethane were eluted first then desired product was eluted. Yield 0.19 g (29%), (Higher yield upto 80% was obtained when the reaction was carried out at 0 °C in the presence of 2 mM of BF_3). ^1H NMR ($CDCl_3$) δ 7.93 (bs, 2H, N-H), 7.76 (bs, 1H, N-H), 7.61 and 6.92 (two doublets, J = 8.3 Hz, 4H, Ar-H), 7.32-7.16 (m, 5H, Ar-H), 6.68 (dd, 2H, pyrrole-H), 6.13 (m, 2H, pyrrole-H), 5.87 (d, 1H, pyrrole-H), 5.83 (d, 1H, pyrrole-H), 5.76 (t, 1H, pyrrole-H), 5.73 (t, 1H, pyrrole-H), 5.37 (s, 1H, *meso*-H), 5.30 (s, 1H, *meso*-H). HRMS Calcd for $C_{22}H_{26}IN_3$ 503.0858, Found 503.0877.

Porphyrin (7a), (8a) and (9a). Tripyrromethane (**5**) (0.30 g, 0.60 mmol) and (**6a**) (0.17 g, 0.60 mmol) were dissolved in chloroform (60 mL), then $BF_3 \cdot OEt_2$ (147 μL, 1.20 mmol) was added. The mixture was stirred at room temperature for 25 min then triethylamine (1.5 mL) and DDQ (0.40 g, 1.80 mmol) were added at once. The mixture was stirred for 1hr at room temperature. The remaining solid material was removed by filtration. Evaporation of the solvent under reduced pressure and vaccum drying afforded the black solid which was purified by column chromatography on silica ($CHCl_3$/THF, 9/1). The fast moving fraction was porphyrin (**9a)** (22 mg, 5%). Second moving band was identified as porphyrin (**8a)** (67 mg, 15%). The last moving band was porphyrin (**7a)** (25 mg, 5%). ^1H NMR ($CDCl_3$); For (**7a**): δ 9.17 (s, 2H, furan-H), 8.87 (s, 2H, pyrrole-H), 8.57 (q, 4H, pyrrole-H), 8.19-8.17 (m, 8H, Ar(o)-H), 7.77-7.73 (m, 12H, Ar-H). HRMS Calcd for $C_{44}H_{29}N_3O$ 616.2389, Found 616.2413. For (**8a)**: δ 9.18 (s, 2H, furan-H), 8.89 and 8.86 (two doublets, 2H, pyrrole-H), 8.60 (dd, 2H, pyrrole-H), 8.54 (dd, 2H, pyrrole-H), 8.19-8.16 (m, 6H, Ar(o)-H), 8.08-7.91 (two doublets, 4H, Ar-H), 7.81-7.72 (m, 9H, Ar-H), -1.58 (bs, 1H, N-H). HRMS Calcd for $C_{44}H_{28}IN_3O$ 742.1355, Found 742.1393. For (**9a**): δ 9.19 (s, 2H, furan-H), 8.87 (s, 2H, pyrrole-H), 8.59 and 8.55 (two doublets, 4H, pyrrole-H), 8.18-8.16 (m, 4H, Ar(o)-H), 8.09-7.90 (two doublets, 8H, Ar-H), 7.80-7.73 (m, 6H, Ar-H), -1.62 (bs, 1H, N-H). HRMS Calcd for $C_{44}H_{27}I_2N_3O$ 868.0322, Found 868.0364.

Porphyrin (7b), (8b) and (9b). Tripyrromethane (**5**) (0.30 g, 0.60 mmol), diol (**6b)** (0.18 g, 0.60 mmol) and $BF_3 \cdot OEt_2$ (147 μL, 1.20 mmol) were treated identically as for the synthesis of **7a**. Column chromatography on silica (chloroform/hexanes, 7/3) gave good separation of three porphyrins; The fast moving fraction was porphyrin (**9b)** (22 mg, 5%). Second moving band was identified as porphyrin (**8b)** (68 mg, 15%). The last moving band was porphyrin (**7b)** (22 mg, 5%). ^1H NMR ($CDCl_3$) for (**8b)**; δ 9.76 (s, 2H, thiophene-H), 8.95 (dd, 1H, pyrrole-H), 8.91 (dd, 1H, pyrrole-H), 8.69 (dd, 2H, J = 4.7 Hz, pyrrole-H), 8.60 (dd, 2H, J = 4.7 Hz, pyrrole-H), 8.26-8.24 (m, 4H, Ar(o)-H), 8.21-8.18 (m, 2H, Ar-H), 8.09 and 7.94 (two doublets, 4H, J = 5.0 Hz, Ar-H), 7.84-7.75 (m, 9H, Ar-H), -2.73 (bs, 1H, N-H). HRMS Calcd for $C_{44}H_{28}IN_3S$ 757.1049, Found 757.1070. For (**9b**) δ 9.76 (s, 2H, thiophene-H), 8.93 (d, 2H, pyrrole-H), 8.70 and 8.59 (two doublets, 4H, pyrrole-H), 8.25-8.23 (m, 4H, Ar-H), 8.10 and 7.93 (two doublets, 8H, Ar-H), 7.85-7.76 (m, 6H, Ar-H), -2.77 (bs, 1H, N-H). HRMS Calcd for $C_{44}H_{27}I_2N_3S$ 883.0015, Found 883.0068. For (**7b**) d 9.80 (s, 2H, thiophene-H), 8.93 (s, 2H, pyrrole-H), 8.71-8.60 (dd, 4H, pyrrole-H), 8.29-8.19 (m, 8H, Ar-H), 7.90-7.73 (m, 12H, Ar-H), -2.70 (bs, 1H, N-H). HRMS Calcd for $C_{44}H_{29}N_3S$ 631.2082, Found 631.2083.



Scheme 2

Results and Discussion

Tripyrromethane **5** was synthesized from the condensation of alcohol **4** with pyrrole in the presence of $BF_3 \cdot OEt_2$ as shown in Scheme 2. GC-Mass analysis of the crude product indicated the formation of small amount of *N*-confused tripyrromethane. But the fraction of the *N*-confused tripyrromethane is quite small. Proton and carbon NMR spectra indicated that no diastereomeric mixture of **5** was formed in the reaction. But dipyrromethanes were isolated when the reaction ran with extended time. The formation of dipyrromethanes indicates the cleavage of tripyrromethanes under high acid concentration with longer reaction time.

The tripyrromethane **5** also could be obtained as a minor product from dipyrromethane synthesis developed previously.[11] The tripyrromethane was isolated by column chromatography of the residual black material after isolating dipyrromethane by vacuum distillation. The traditional condensation of **5** with **6a** in CH_2Cl_2 in the presence of BF_3-etherate resulted in the formation of three porphyrins **7a**, **8a** and **9a**. The formation of **7a** and **9a** indicates that the reversible cleavage of the tripyrromethane **5** occur during the condensation. These results also indicate that nucleophilic attack of the pyrrole to the cationic center of furanyl α-position (after dehydration) is possibly faster than acid-catalyzed cleavage of tripyrromethane. Similar condensation of **5** with **6b** also afforded three porphyrins **7b**, **8b** and **9b**. The identity of the three porphyrins isolated form each reactions was easily determined by proton NMR and high resolution mass spectrometry (HRMS) due to large difference in molecular weight and their different symmetric character. The proton NMR spectra were shown in Figure 1. The integration and

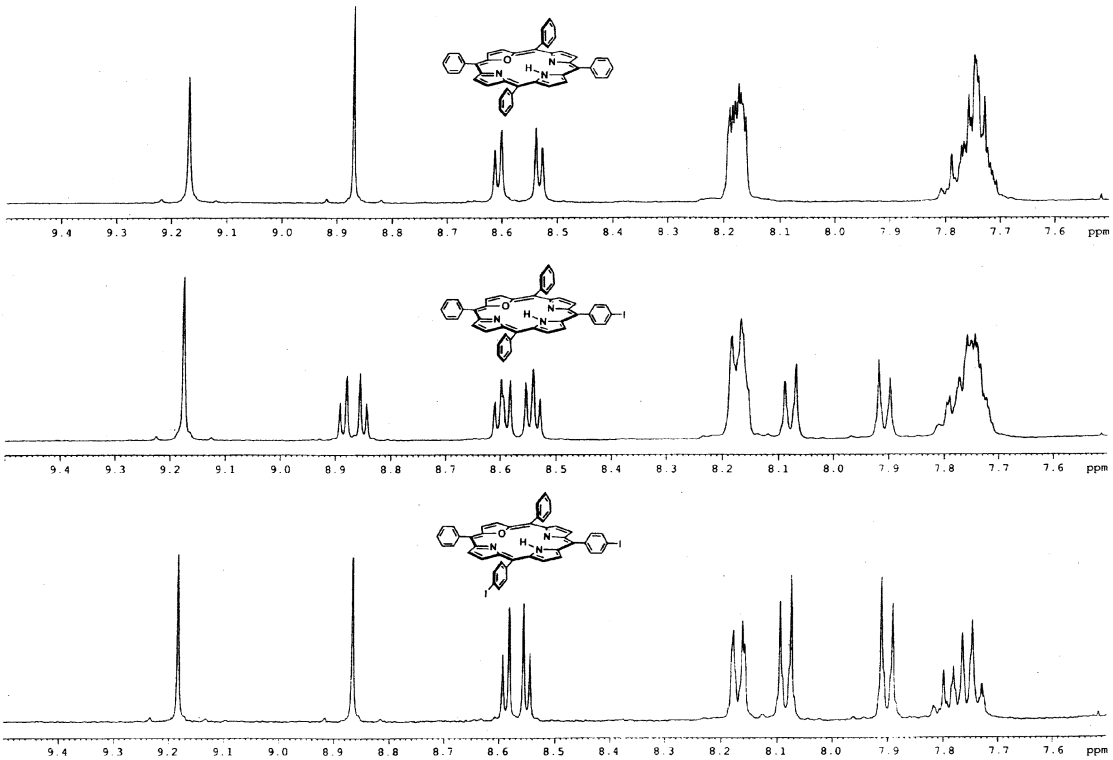
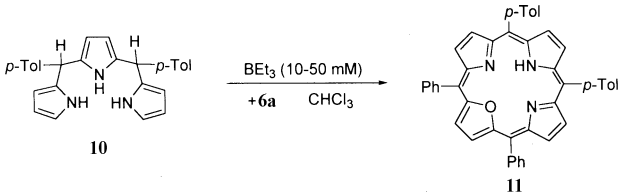


Figure 1. 400 MHz ^{1}H NMR spectra of the three porphyrins **7a** (top), **8a** (mid) and **9a** (bottom) formed from the condensation of **5** and **6a**.

symmetry of each porphyrins clearly indicated the presence of the number of the *p*-iodophenyl group.

In order to avoid reversible cleavage of tripyrromethane during the condensation, we decided to adapt the low scrambling conditions developed by Lindsey *et al.*[9] in the condensations. The rapid small scale assay of the products using LD-MS enables to identify the degree of scrambling. Thus, we applied the same method in this study to survey conditions and suitable catalysts in the 3+1 condensations. The first condensation we atempted was use of BEt_3 as alternative catalyst. As shown in Scheme 3, the attempted condensation of in $CHCl_3$ gave clean reaction without any evidence of scrambling. Although the yields were somewhat lower (5-15%) than other condensations (data not shown), higher concentration of acid up to 30 mM didnt result in the cleavage of tripyrromethane.

These results indicate that the reaction catalyzed by triethylborane can be used in the synthesis of porphyrins without scrambling. Acid concentration giving unscrambled porphyrin product was as high as 50 mM. This remarkable stability of tripyrromethanes under such a large amount of acid present indicates that the triethylborane is an excellent catalyst for the porphyrin forming reaction.



10 **11**

Scheme 3

The yields of porphyrin over variation of reactant concentration (1, 10 and 50 mM) were monitored from 1 min to 90 min as shown in Figure 1. The yield of porphyrin reached a maximum within 5 min at 10 mM reactant concentration. There was no catalytic activity of acid when 1 mM of $BF_3 \cdot OEt_2$ was applied. Higher concentration of acid also gave adversary effect on the yield of porphyin. Figure 2 showed the dependence on yield when *p*-TsOH was applied

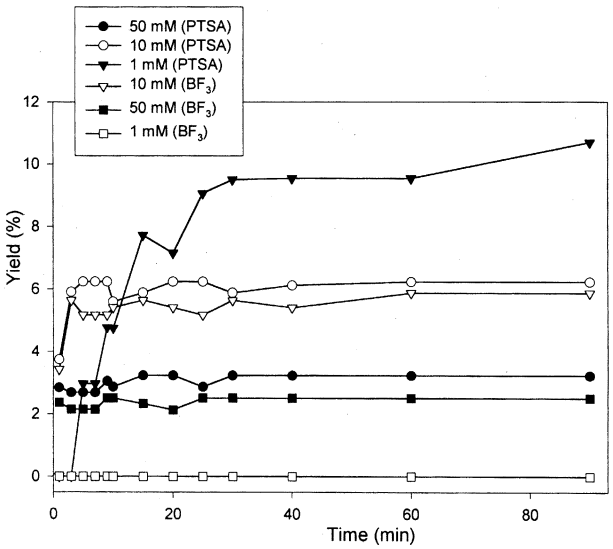


Figure 2. Dependence of the spectroscopic yields on the concentration of reactants (tolyl-TPM and diol) in acetonitrile catalyzed by $BF_3 \cdot OEt_2$ and PTSA. No scrambling was detected by LD-MS for the conditions applied.

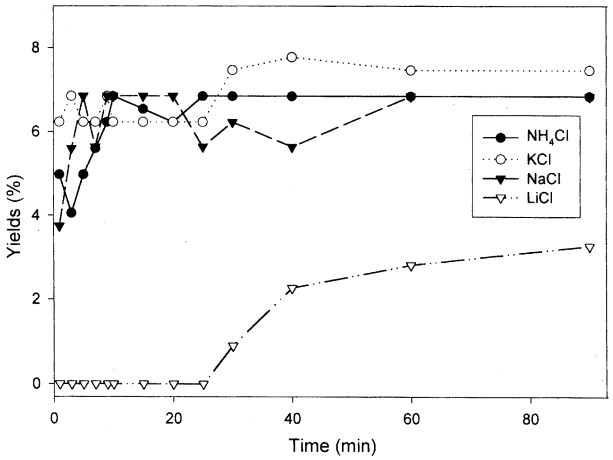


Figure 3. Effect of inorganic salts on the condensation of tolyl-TPM (10 mM) and diol (10 mM) in acetonitrile catalyzed by BF_3 (2 mM).

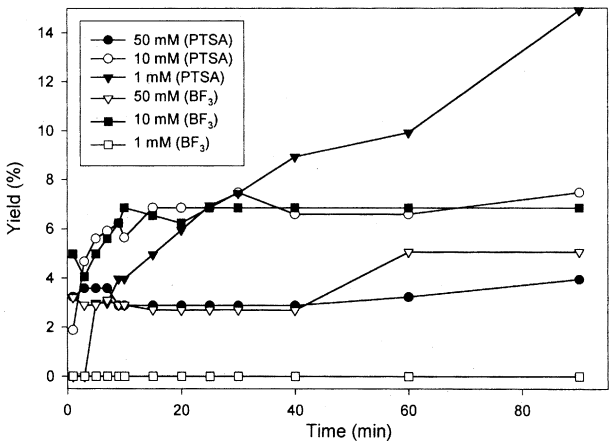


Figure 4. Dependence of the spectroscopic yield on the concentration of reactant in the presence of NH_4Cl (100 mM) catalyzed by acids.

for catalyst. Application of *p*-TsOH gave higher yield of porphyrin at low acid concentration (1 mM) as shown in Figure 2. The beneficial effects of the added inorganic salts on the yield of porphyrin were reported in the pyrrole-aldehydes and 2+2 condensation.[8] Since the best result of salt effect has been reported when combined with BF_3, we examined the salt effect by performing reactions at 10 mM of reactants in the presence of various salts (Figure 3 and Figure 4). The yields were almost independent of added salts and LiCl and Cs_2CO_3 seemed to somewhat deactivate the catalyst. Best yield was obtained when 100 mM of KCl or NH_4Cl were applied. Thus, the low scrambling conditions identified in the 2+2 condensation can be generally applied for the synthesis of porphyrins with little scrambling: for example 10 mM of reactants in acetonitrile at 0 °C in the presence of NH_4Cl (100 mM) catalyzed by $BF_3{\cdot}OEt_2$ (1 mM).

The spectroscopic yields and extent of scrambling were not changing with reaction time. Optimized reaction showed an initial burst of porphyrin formation within a few minutes of the reaction. The reaction was faster when heteroatoms (O,S) were present in the reactants. The oxaporphyrins are significantly more basic than regular porphyrins.[9] In conclusion, we have shown that the 3+1 condensation of tripyrromethane with diol also a good methods for the synthesis of *cis*-substituted porphyrins. The low scambling conditions can be applied in 3+1 condensation even if the yields were somewhat lower than 2+2 condensation.

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