A Facile Route to Tripyrrane from 2,5-Bis(hydroxymethyl)pyrrole and the Improved Synthesis of Porphine by the "3+1" Approach

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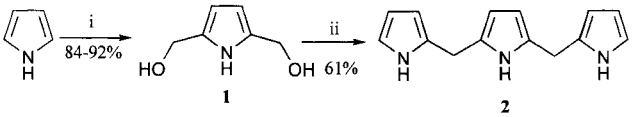
Abstract: The treatment of 2,5-bis(hydroxymethyl)pyrrole with pyrrole in the presence of hydrochloric acid gave tripyrrane in 61% yield, which afforded porphine in an improved 31% yield by the "3+1" approach.

Keywords: tripyrrane, porphine, 2,5-bis(hydroxymethyl)pyrrole, "3+1" type condensation, β-substituted porphyrin

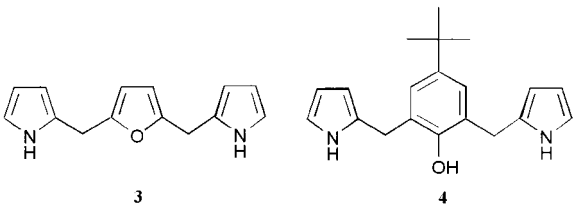
β-Substituted porphyrins are usually synthesized by the '3+1' technique known as MacDonald condensation.[1] Moreover, this procedure affords new aromatic porphyrinoid systems, including benzene- and pyridine-containing macrocycles and carbaporphyrins, by utilizing other aromatic aldehydes.[2] During this condensation, tripyrranes, which are the methylene bridged linear trimers of pyrrole, are the key compounds as the "3" component. However, their synthesis is sometimes cumbersome with low yields because of having two ester or carboxyl groups at the C-2 and C-14 positions of the tripyrranes. In particular, unsubstituted tripyrrane (**2**)[3], to the best of our knowledge, has not yet been isolated.[4] Therefore, our strategy to develop a facile route to **2** would provide a new way to porphine and β-substituted porphyrins by the "3+1" type procedure as well as macrocycles such as homoporphyrins,[5] *N*-confused porphyrins[6] and expanded porphyrins.[7]

Porphyrins are known to be easily obtained by treatment of the precursor 'porphyrinogen' with oxidizing agents such as chloranil. Therefore, the preparation of porphyrinogen by the '3+1' condensation is the important step in our synthesis. The synthesis of calix[4]arenes from phenolic trimers by Kämmerer and his co-workers[8] suggested to us an approach to tripyrrane and porphyrinogen, whose structures resemble that of calix[4]arene; in 1979 they reported a route to the methylene bridged trimer of phenols by the condensation of 2,6-bis(hydroxymethyl)-4-substituted phenols with excess 4-substituted phenols in the presence of hydrochloric acid. The trimers were then converted to calix[4]arenes using the acid-catalyzed '3+1′ condensation with 2,6-bis(halogenomethyl)-4-substituted phenols. We applied this methodology to the synthesis of tripyrrane (**2**) (Scheme 1). The starting 2,5-bis(hydroxymethyl)pyrrole (**1**)[9] was obtained in good yield (84-92%) from pyrrole and formalin according to a modification of the literature method.[10] We then examined preparing **2** from **1** under various reaction conditions. Due to the lability and high reactivity of **1**, it afforded only intractable tar above room temperature in the presence of acid. In alcoholic solution, the condensation products were a mixture of the dimer and trimer. The trifluoroacetic acid-catalyzed condensation of **1** with excess pyrrole was found to be quite effective, but always accompanied by a small amount of the dimer. Finally, the hydrochloric acid-catalyzed condensation in water at low temperature gave **2** in the best yield (61%).



Scheme 1. *Reagents and conditions:* i, 2 equiv. formalin, K_2CO_3 aq. soln., 5°C,7 d. ii, excess pyrrole, 0.15 equiv. HCl, below 5°C, 30min

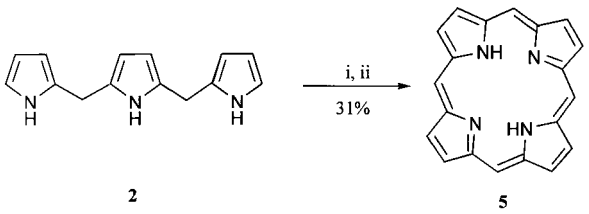
In a typical experiment, pyrrole (26.4 g, 394 mmol) was added to a stirred solution of **1** (5.0 g, 39 mmol) in water (700 cm^3) below 5 °C under argon with shielding from light. After 30 min, concentrated hydrochloric acid (0.5 cm^3, 6 mmol) was added to the efficiently stirred solution. The solution immediately changed to a white emulsion. After 30 min, the mixture was neutralized with aqueous $NaHCO_3$, water and excess pyrrole were removed *in vacuo* (3-4 Torr) with a rotary evaporator, the residue was extracted with Et_2O or CH_2Cl_2, and the extract was subjected to distillation to give **2** (5.4 g, 61%).[11] Instead of the distillation, the separation by column chromatography on silica gel using CH_2Cl_2 as an eluent afforded **2** in 41% yield.



Although the acid-catalyzed condensation of 1,3-bis(hydroxymethyl)benzene or 2,6-bis(hydroxymethyl)pyridine with excess pyrrole was not successful, 2,5-bis(2-pyrrolylmethyl)furan (**3**)[12] (53%) and 2,6-bis(2-pyrrolylmethyl)-4-*tert*-butylphenol (**4**)[13] (32%) were obtained upon

refluxing for 1 h from the corresponding bis(hydroxymethyl)arenes and pyrrole in a similar manner.

In order to demonstrate the usefulness of the newly-acquired **2**, the synthesis of porphyrins by the "3+1" method was carried out; the condensation of **2** (1 mmol dm^{-3}) with an equimolar amount of **1** in chloroform in the presence of BF_3·MeOH according to the Lindsey method[14] gave porphyrinogen *in situ*, which was then oxidized by chloranil to afford porphine **5** in 31% yield (Scheme 2).[15] As an example of the β-substituted porphyrins, 2,3-diethylporphyrin (26%) was similarly prepared from **2** and 2,5-bis(hydroxymethyl)-3,4-diethylpyrrole. Despite using a high-dilution technique, our method is very easy to perform. Although porphine is the most basic compound in the porphyrin chemistry and it has been more than sixty years since its first synthesis,[16] its preparation is still one of the most difficult processes in organic synthesis.[17] The highest yield during porphine synthesis hitherto has been 8-10% which was accomplished by Longo and his coworkers in the reaction of 2-(hydroxymethyl)pyrrole over a period of 10 days in chromatographed ethylbenzene at 100°C.[18] Our "3+1" type condensation using **2** would be a superior method for the porphyrin synthesis.



2 5

Scheme 2. *Reagents and conditions*: i, 1 equiv. **1**, BF_3·MeOH, $CHCl_3$,30 min, r.t. ii, chloranil, 30 min, reflux

In conclusion, tripyrrane (**2**) was first isolated in good yield by a simple operation from the readily available 2,5-bis(hydroxymethyl)pyrrole and excess pyrrole and successfully applied to the synthesis of porphine in an improved yield. This new synthesis of tripyrrane would also serve the chemistry of porphyrin and homoporphyrin.

Acknowledgement

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(10) Compound **1**: Can be stored for over 5 years at -20C° in a freezer. Colorless needle crystals, mp 115-116 °C (dec., acetone, lit.[9] 117-118 °C). ^{1}H NMR (90MHz, acetone-d_6): δ=3.79 (br, 2H, OH), 4.48 (s, 4H, CH_2), 5.84 (s, 2H, 3-H), 9.70 (br, 1H, NH). Ms: m/z 127(M^+, 54), 110(46), 96(14), 80(100), 53(14). FTIR (KBr, cm^{-1}) 3304, 3250, 2938, 2869, 1425, 1203, 1027, 775.
(11) Compound **2**: Must be stored in a freezer. A colorless solid. mp 97-98 °C (bp 186-194 °C/ 0.1 Torr). Tlc: R_f 0.90 (silica gel, CH_2Cl_2). ^{1}H NMR (90MHz, $CDCl_3$): δ=3.74 (s, 4H, 5,10-H), 5.86 (d, 2H, *J*=2.4, 7-,8-H), 5.93 (m, 2H, 3-,12-H), 6.07 (m, 2H, 2-,13-H), 6.50 (m, 2H, 1-,14-H), 7.36 (br, 1H, 16-NH), 7.64 (br, 2H, 15-,17-NH). Ms: m/z 225(M^+, 100), 158(52), 145(71), 80(74). FTIR (KBr, cm^{-1}): 3415, 3338, 3085, 2898, 1097, 1026, 808, 800, 733, 725. Anal. for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.69; H, 6.52; N, 18.82.
(12) Compound **3**: A pale yellow solid, mp 82-83 °C (bp 158-160 °C/ 0.1 Torr). Tlc: R_f 0.95 (silica gel, CH_2Cl_2). ^{1}H NMR (90MHz, $CDCl_3$): δ=3.95 (s, 4H, CH_2), 5.95 (s, 2H, 3-,4-H), 6.00 (m, 2H, 3'-H), 6.13 (m, 2H, 4'-H), 6.65 (m, 2H, 5'-H), 8.00 (br, 2H, NH). Ms: m/z 226(M^+, 100), 159(49), 146(78), 80(47). FTIR (KBr, cm^{-1}): 3376, 3351,3336, 3129, 3105, 2886, 2830, 1563, 1182, 1113, 1013, 802, 719, 708. Anal. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.03; H, 6.31; N, 12.40.
(13) Compound **4**: Must be separated by silica gel column (CH_2Cl_2) before the distillation. A colorless viscous oil, bp 198-203 °C/ 0.1 Torr. Tlc: R_f 0.83 (silica gel, CH_2Cl_2). ^{1}H NMR (90MHz, $CDCl_3$): δ=1.27 (s, 9H, CH_3), 3.87 (s, 4H, CH_2), 5.38 (br, 1H, OH), 6.02 (m, 2H, 3'-H), 6.08 (m, 2H, 4'-H), 6.53 (m, 2H, 5'-H), 7.04 (s, 2H, 3-,5-H), 8.09 (br, 2H, NH). Ms: m/z 308(M^+, 40), 242(45), 226(100), 80(21). FTIR (neat): 3391, 3098, 2961, 2905, 2868, 1485, 1203, 1025, 719 cm^{-1}. Anal. for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.52; H, 7.93; N, 8.79.
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