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Solvent-Free Condensation of Pyrrole and Pentafluorobenzaldehyde: A Novel Synthetic Pathway to Corrole and Oligopyrromethenes

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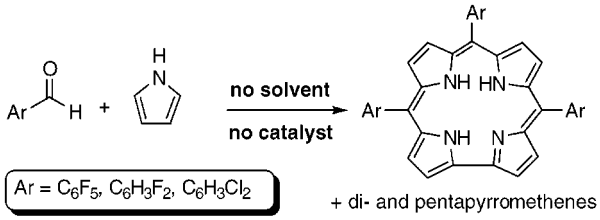
ABSTRACT



The solvent-free condensation of pyrrole and pentafluorobenzaldehyde (and to a lesser extent other electron-poor aldehydes as well) leads to a variety of products, of which three have been isolated and fully characterized. The two main products (11% each) are an open-chain pentapyrrole and corrole, a tetrapyrrolic macrocycle.

The most obvious synthetic pathway for the preparation of porphyrins is the cyclocondensation of an aldehyde and pyrrole (Scheme 1, left side). Landmarks in this aspect are the 1935 Rothmund procedure and the 1986 contribution by Lindsey and co-workers.[1] The Lindsey procedure currently allows the preparation of a large variety of porphyrins in reasonable yields.[2] It consists of mixing equimolar amounts of pyrrole and the appropiate aldehyde together with a catalytic amount of acid in a deaerated inert solvent for about 1 h, followed by treatment of the same solution by a substituted quinone. The intermediate formed prior to the oxidation step is a hexahydroporphyrin, more commonly known as porphyrinogen. Interestingly, the last common intermediate in the biosynthesis of all naturally occurring tetrapyrrolic macrocycles—porphyrin in hemes, chlorin in chlorophylls, and corrine in Vitamin B_{12}—is also a porphyrinogen (uroporphyrinogen III). Another class of cyclic tetrapyrroles are the corroles, which share with corrine an identical ring skeleton and with porphyrins their aromaticity. Porphyrins and corroles have also many other properties in common,[3,4] but corrole's research is much less developed because of problems in their synthesis. For example, the first *meso*-aryl-substituted corroles were reported as late as 1993,[5] more than 50 years after *meso*-tetraphenylporhyrin.[6] Also, all the procedures described up to 1998 require the preparation of at least one (usually many) nonobvious and unstable precursor.

Because of the increasing interest in expanded, contracted, and isomeric porphyrins,[3a] we have explored a new approach—

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(1) Lindsey, J. S. *Metalloporphyrins Catalyzed Oxidations*; Montanari, F., Casella, L., Eds.; Kluwer: Dordrecht, 1994; pp 49−86 and references therein.
(2) Li, F. R.; Yang, K. X.; Tyhonas, J. S.; MacCrum, K. A.; Lindsey, J. S. *Tetrahedron* **1997**, *53*, 12339. Wagner, R. W.; Johnson, T. E.; Lindsey, J. S. *Tetrahedron* **1997**, *53*, 6755.

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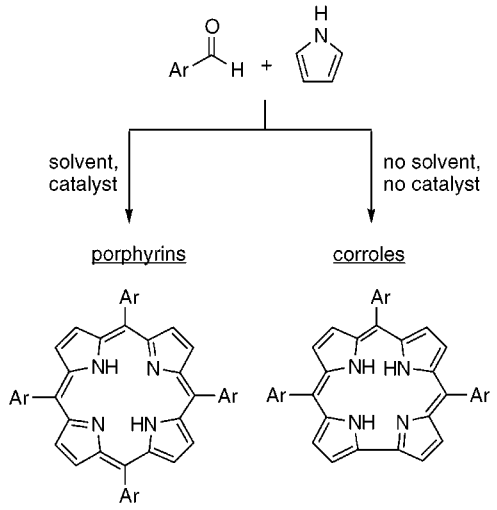
Scheme 1. Synthesis of Porphyrins and Corroles



the solvent-free condensation of pyrrole and aldehydes (Scheme 1, right side). The rationale was that these unusual reaction conditions might lead to hitherto unobserved phenomena.[7] As described in our most recent communication, these expectations were fulfilled with electron-poor aldehydes.[8] Thus, the reactions of pentafluorobenzaldehyde with pyrrole resulted in the formation of the corresponding corrole (Scheme 1, Ar = C_6F_5, TpFPC-H_3) in 11% chemical yield. We now provide new details of this quite unusual reaction, including the structural data of TpFPC-H_3 and two other interesting products.

Our initial procedure consisted of heating an equimolar mixture of the aldehyde and pyrrole (2.5 mmol of each) on a solid support for 4 h at 100 °C, followed by dissolving the tarry product mixture in CH_2Cl_2 and oxidation by DDQ. Under these conditions, the isolation of the corroles requires two subsequent columns. Since then, we have found that both the heating and the solid support are not absolutely required. When pyrrole and the aldehyde are rapidly mixed at rt, a highly exothermic reaction takes place. Within seconds, the color changes to brown and the reaction mixture becomes very hot. After about 1 min, the reaction mixture solidifies and the reaction is complete. In addition to the simplicity and shortness of this procedure, the number of byproducts is also smaller (TLC, after DDQ oxidation). Still, because of the variation in the effectiveness of the stirring until solifidation occures, the reproducibilty in terms of isolated yields varies (8−11%) and the yield drops significantly upon attempted scaling up.

Better results in terms of upscaling were obtained if the reagents (15 mmol of each) were first dissolved in CH_2Cl_2, mixed with alumina, and heated in an open vessel to 60 °C. The reaction starts only after the solvent evaporates, and a 4 h reaction time is sufficient. The yield of TpFPC-H_3 remains reasonable, and much less tar is produced than at 100 °C. Because of that, 380 mg (12.7% yield) of the crude product can be obtained after only one column and 270 mg (9% yield) of analytical pure crystals is obtained after recrystallization. The whole synthetic procedure takes only about 10 h.

In both described procedures, several products with distinct colors can be separated by column chromatography (Figure 1). Advantageously, the corrole (Scheme 1, Ar = C_6F_5) is

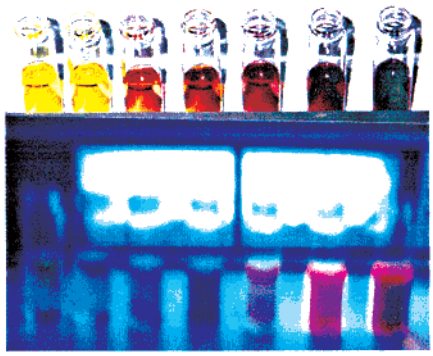


Figure 1. The three first eluting products under normal light and under a UV lamp.

easily identified due to its strong fluoresence, by shining a simple UV lamp on either the column or the isolated fractions. Still, to learn somewhat more about this surprising reaction, we have also isolated the two products which elute before the corrole.

The yellow fraction (<1% yield) was identified as the substituted dipyrromethene **1a** by MS and NMR, as well as by X-ray crystallography of the analogous 2,6-dichlorophenyl analogue (**1b**, Figure 2). Interestingly, **1b** crystallizes in a 1:1 ratio of two tautomers, which differ in the position of the NH proton and in the lengths of its hydrogen bond (2.083 and 2.230 Å in the two tautomers).

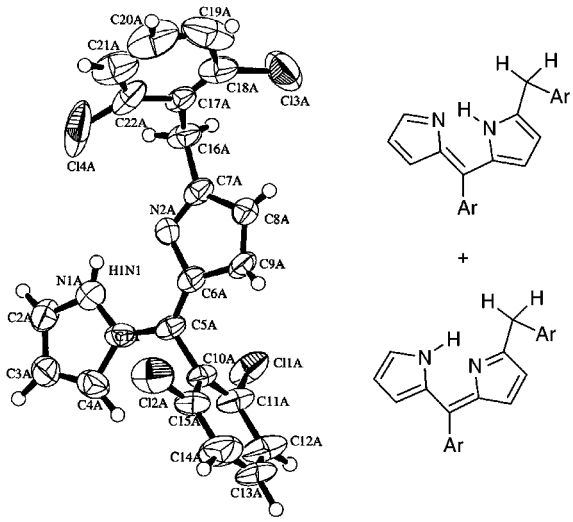
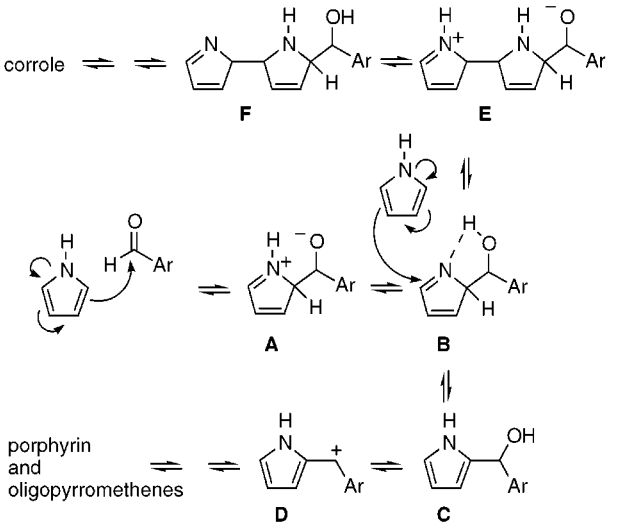


Figure 2. The structure of one of the two tautomers of **1b** (**1a**, Ar = C_6F_5; **1b**, Ar = 2,6-dichlorophenyl).

From a chemical point of view, the presence of **1a** in the reaction mixtures indicates that the present reaction scenario is similar to that of porphyrin synthesis (Scheme 2, lower part),[9] in which dipyrromethenes are dead end products.[10]

Scheme 2



However, in the present case **1a** might actually be a precursor of the corrole by providing an H-bound imine (C_{7A}−N_{2A} in Figure 2) as an electrophilic site for attack by pyrrole and the C_6F_6-CH_2 as an anionic leaving group. Although this proposal provides an explanation for the fact that corroles are formed only with electron-poor aldehydes, it must be considered as only one of many other possibilities. For example, different imine intermediates such as **B** are certainly formed during reaction (Scheme 1). In the presence of acid catalysts, the reaction proceeds toward intermediate **D**, which leads to oligopyrromethanes and porphyrinogen. Under the current reaction conditions—no acid catalyst and the plausible H-bonding interaction of the imine nitrogen with the acidic OH (for Ar = C_6F_5)—intermediate **B** could accumulate to an extent that allows its attack by pyrrole, eventually leading to corrole as shown in the upper part of Scheme 2.

That the "normal" pathway is still operative is indicated by the next-eluting product (the orange-red fraction in Figure 1), which is a major constituent of the reaction mixture. It is formed in 11% yield and is easily purified because of its large tendency to crystallize. This product was identified as the novel pentapyrrotetramethene **2** by MS, NMR, and X-ray crystallography (Figure 3).

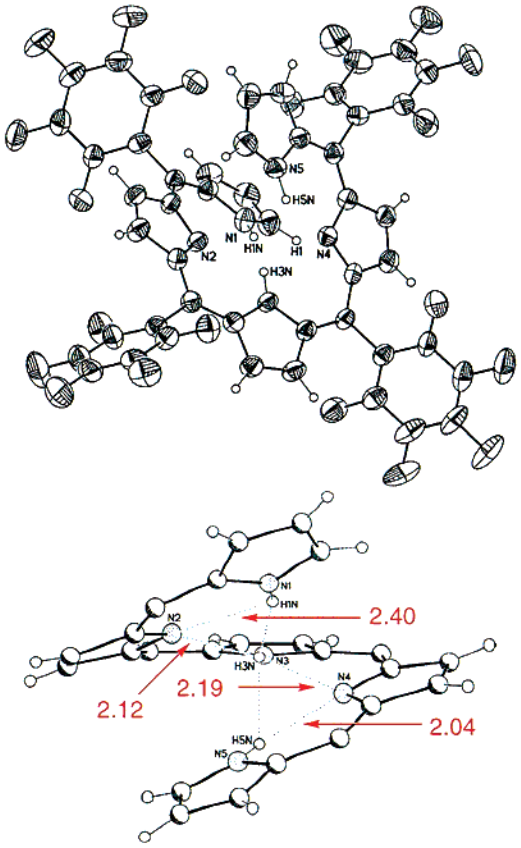


Figure 3. The full (top) and partial (bottom) X-ray structure of the pentapyrrotetramethene **2**.

To our knowledge, **2** is the largest structurally characterized acyclic oligopyrromethene, i.e., an oligomer composed only of pyrroles bridged by one unsaturated carbon.[11] Its crystal structure is very important, since it serves to demonstrate that although **2** is an open chain polypyrrole, it is clearly helical in the solid state. Also, several hydrogen bonds between the pyrrolic NH protons and the imine-like pyrrole nitrogens can be identified (Figure 3, bottom). Now,

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(7) (a) For a recent review on solvent-free reactions, see: Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480. (b) For trace amounts of corroles in the Rothmund and Lindsey procedures, see: Rose, E.; Kossanyi, A.; Quelquejeu, M.; Soleilhavoup, M.; Duwavran, F.; Bernard, N.; Lecas, A. *J. Am. Chem. Soc.* **1996**, *118*, 1567. Latos-Grazynsky, L.; Chmielewski, P. J. *New J. Chem.* **1997**, *21*, 691.

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(9) (a) For isolation of the zinc(II) complex of **1b** in a modified Rothmund procedure, see: Hill, C. L.; Williamson, M. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1228. (b) For synthesis of the somewhat related dipyrromethanes (the bridging carbon is saturated and there is only one aryl) under a modified Lindsey procedure, see: Littler, B. J.; Miller, M. A.; Hung, C. H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391.

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(11) (a) For the structural characterization of larger oligomers with direct pyrrole−pyrrole linkages (up to nine pyrroles), see: Morisini, P.; Schere, M.; Meyer, S.; Lynch, V.; Sessler, J. L. *J. Org. Chem.* **1997**, *62*, 8848. (b) For a not well resolved structure of a methene-only bridged pentamer with three pyrroles and two pyrrolidones, see: Wagner, U. G.; Kratsky, C.; Falk, H.; Flodl, H. *Monatsh. Chem.* **1987**, *118*, 1185.

both helicity and hydrogen bonding are considered crucial factors in biological systems (bile pigments and extended derivatives thereof) and in the synthesis of both linear and cyclic oligopyrroles.[12,13] There are however two major differences between those systems and the current structure. First, in all other motifs there is at least either one saturated bridging carbon or a direct pyrrole−pyrrole linkage (usually many). Second, oxygen-containg substituents participate in the H-bonding therein, while in **2** these interactions rely solely on the pyrroles. Most important, we note that the overall shape of **2** resembles the twisting of the octa- and decaphyrins described by Vogel and Sessler,[13] which all adopt a "figure-eight" conformation. Accordingly, compound **2** might be an excellent precursor for additional members of the higher order oligocyclopyrroles, in addition to the cyclic pentapyrroles sapphyrin (one direct pyrrole−pyrrole linkage) and pentaphyrin (no direct pyrrole−pyrrole linkages). These opportunities will be investigated soon.

Finally, growing X-ray quality crystals of the corrole appeared to be a very difficult task because of its very high solubility in all common organic solvents. After many attempts we were able to collect data on crystals formed in a highly concentrated *m*-xylene solution and from EtOH, still with relatively low resolution because of their small sizes, as well as the following problems. The crystal grown from EtOH contained four molecules of solvent per corrole, with some of the EtOH molecules in H-bonding interactions with the imine-like nitrogens. However, the hydrogens could not be precisely located. The crystals grown from *m*-xylene were found to contain solvent as well but were of better quality. Their analysis was carried out at low temperature (116 K), which allowed the precise location of all the hydrogen atoms. Still, due to loose crystal packing, the central C_6F_5 ring was found to be orientationally disordered with respect to the core fragment (its two major orientations are 32.5° apart). The basic molecular structure of TpFPC-H_3 is demonstrated in Figure 4 (for clarity only one of the two possible orientations of the central aryl ring is shown). Noteworthy is the significant distortion from planarity of the corrole macrocycle as to minimize the steric hindrance between the inner protons. This is achieved by adopting a puckered conformation in which the pyrrole rings turn slightly either up or down. The twist angles between the rings increase in moving clockwise from B around the macrocycle in the order of 4.4, 9.4, 19.1, and 19.5°, respectively. In the resulting structure, the NH protons of rings A and D are out of the mean plane of the four nitrogen atoms by 0.89 and −0.46 Å, respectively, while that of ring B is almost in-plane (+0.1 Å only). These distortions position the hydrogens at the shortest possible van der Waals distances of 2.0−2.2 Å.

To our knowledge, despite the 35 years of corrole research, there is only one previously reported X-ray structure of any metal-free corrole.[14] The importance of the structure of TpFPC-H_3 is that it serves as a reference point for its metal

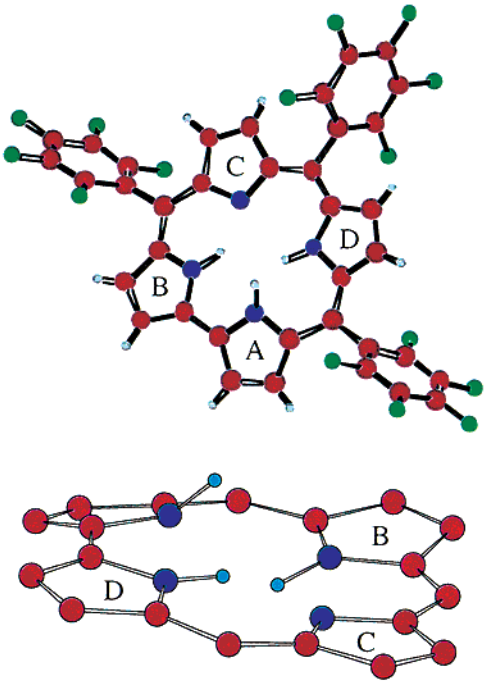

Figure 4. Top and side view models of the X-ray structure of corrole TpFPC-H_3.

complexes, of which we have already prepared a large variety. Furthermore, we have recently demonstrated for the first time that these complexes are potent catalysts for functionalization of hydrocarbons.[15] The understanding of selectivity in these processes really relies on structural data of the complexes.

In conclusion, with the new procedures in hand, aliquots of 270 mg of pure TpFPC-H_3 are now routinely obtained in our laboratory in the matter of a day or two, starting from readily available starting materials.[16] This is in sharp contrast to all previous synthetic methodologies for the preparation of corroles, which require many separate synthetic steps and are accordingly much more time-consuming. Also, the instability of many of the synthetic intermediates limits those methods to experts in the field. Another adavantage of our procedures is that the isolation of other products with high potential becomes feasable.

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(16) (a) TpFPC-H_3 has recently become commercially available, by Strem Chemicals. (b) Gross, Z. (Technion) IL-A 126426.