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Microwave-assisted synthesis of non-substituted tripyrrane, tetrapyrrane and pentapyrrane

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Abstract—The microwave-assisted one-step condensation of aqueous formaldehyde with pyrrole was successfully applied for the preparation of non-substituted tri-, tetra- and pentapyrranes with reasonable yields. All three compounds are important precursors to advanced porphyrins and porphyrin analogs. The advantages of this method are short reaction times, clean reaction mixtures and work in the non-toxic and environment friendly solvent—water.

The most straightforward synthesis of symmetrically-substituted porphyrinoids, such as triarylcorroles, tetrarylporphyrins and expanded porphyrins, relies on cyclocondensation of pyrrole and aldehydes. However, there is also large demand for derivatives where non-identical substituents occupy the methine bridges between the pyrrole rings (called *meso*-carbon atoms), as well as for porphyrinoids that are not *meso*-substituted. Efficient methods for the preparation of methylene-bridged oligopyrroles (called dipyrromethanes for the simplest molecule, but tripyrrane, tetrapyrrane, etc. for the other cases) are hence desirable, as these compounds can be applied as precursors for the synthesis of many new derivatives.[1–4] Previous reports have mainly focused on one-flask methods for the synthesis of *meso*-substituted oligopyrranes.[5–8] The procedures usually involve acid-catalyzed condensation of an aldehyde with pyrrole, where the polymerization process is suppressed by using a very large excess of pyrrole. Unsubstituted dipyrromethane and tripyrrane (**3**) were also reported and applied, but not any of the larger oligomers.[9,10] One interesting outcome is that water was found to be the best solvent for the preparation of tripyrrane **3**, as well as of its synthetic precursor 2,5-bis(hydroxymethyl)pyrrole. Since water is also an ideal solvent for microwave-assisted synthesis,[11] we decided to examine the utility of microwave irradiation with regard to affecting the reaction between aqueous formaldehyde and pyrrole.

We here report the microwave-assisted condensation of aqueous formaldehyde with pyrrole as a very convenient approach for the synthesis of non-substituted tri-, tetra- and penta-pyrranes (Scheme 1).[12] An open to air mixture consisting of 5 mL of 1.4 M formalin (**1**) (6.2 mmol) and 1.7 mL of (24.6 mmol) pyrrole (**2**) was heated in a microwave oven (240 W power) for 40 s.[13] The brownish oil obtained from extraction of the reaction mixture by dichloromethane was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 17/3). Single column chromatography was sufficient for separating the desired components of the reaction in reasonable yields: tripyrrane (**3**)—11%, tetrapyrrane (**4**)—17% and pentapyrrane (**5**)—19%. The compounds were found to be sensitive to light and air, but were stable for extended periods when stored in a freezer under an inert atmosphere.

Tetrapyrrane **4** is a potential precursor to the parent (and still unknown) macrocyclic and aromatic corrole **6** (Scheme 2). Large efforts devoted to preparing **6** from **4** were not met with any real success: small amounts of porphine (the parent porphyrin) and biliverdin-like compounds were obtained instead. On the other hand, oxidation of pentapyrrane **5** using *p*-chloranil resulted in the formation of the *meso*-pyrrole-substituted porphine **7** (Scheme 3) as a single product in a respectable 47% yield. Compound **7** was recently obtained (and fully characterized) in 7% yield from the condensation of **3** with 2-formyl-pyrrole.[14]

Microwave-assisted condensation of formalin and pyrrole in aqueous solution is a very convenient

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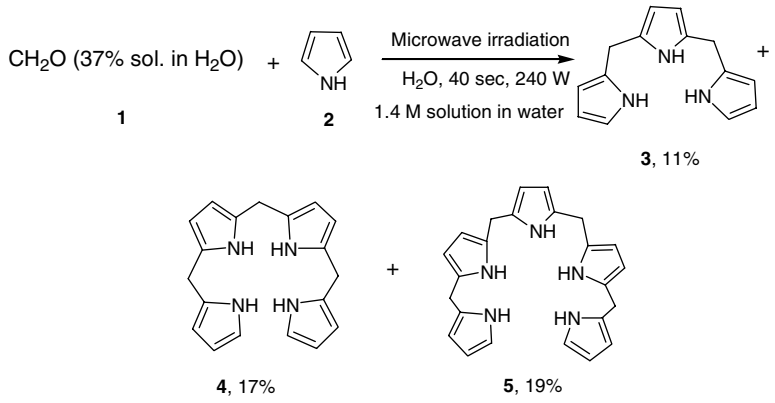
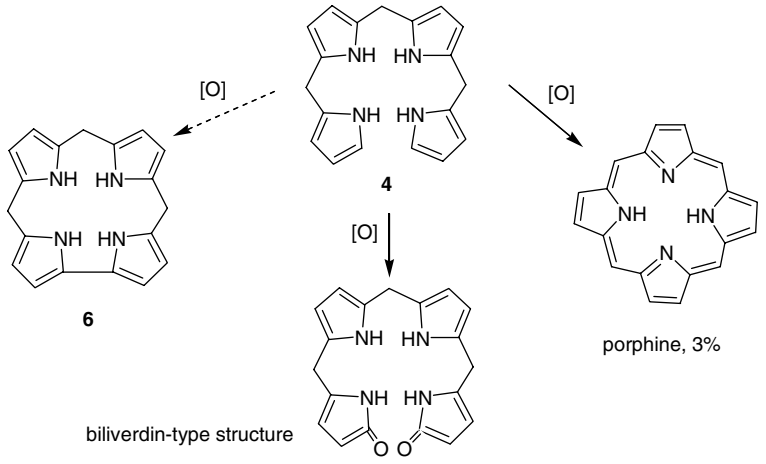
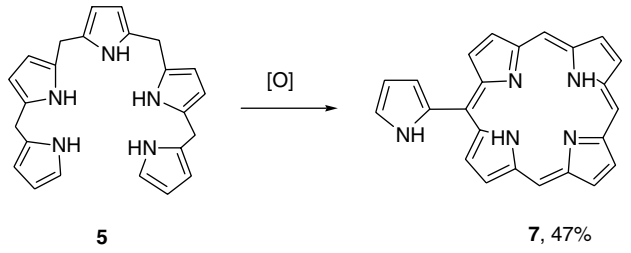


Scheme 1.



Scheme 2.



Scheme 3.

approach to the synthesis of oligopyrranes. The tetrapyrrane and pentapyrrane could not be oxidized to the expected macrocyclic compounds, corrole and sapphyrin, respectively, but rather to porphine and pyrrole-substituted porphine. This apparently reflects the much larger stability of (metal-free) porphyrins relative to both the contracted and expanded analogs.

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12. For microwave-assisted syntheses of metallophthalocyanines, see: Bahadoran, F.; Dialameh, S. *J. Porphyrins Phthalocyanines* **2005**, *9*, 163–169.
13. A domestic microwave oven, model R-240F of the Sharp company, was used for these experiments. The physical data for the reaction products are as follows. Compound **3**: The tripyrrane was obtained as a colourless solid (0.15 g, 11%). All physicochemical properties coincided with literature data.[9] R_f (silica, *n*-hexane:ethyl acetate, 2:1) = 0.55. Compound **4**: The tetrapyrrane was obtained as an amorphous solid (0.32 g, 17%). R_f (silica, *n*-hexane:ethyl acetate, 2:1) = 0.53; 300 MHz ^{1}H NMR ($CDCl_3$): $\delta = 7.74$ (br s, 2H, NH), 7.49 (br s, 2H, NH), 6.55 (m, 2H, α-pyrrole-H), 6.10 (dd, ^3J (H, H) = 3.0 Hz, ^3J (H, H) = 2.7 Hz, 2H, β-pyrrole-H), 5.94 (m, 2H, β-pyrrole-H), 5.84 (m, 4H, β-pyrrole-H), 3.77 (s, 4H, *meso*-H), 3.63 (m, 2H, *meso*-H); MS (MALDI-TOF): *m*/*z* (%): 303.26 [M$^-$, 100%]. Compound **5**: The pentapyrrane was obtained as a yellowish oil (0.45 g, 19%). R_f (silica, *n*-hexane:ethyl acetate, 2:1) = 0.51; 300 MHz ^{1}H NMR ($CDCl_3$): $\delta = 7.68$ (br s, 2H, NH), 7.48 (br s, 1H, NH), 7.43 (br s, 2H, NH), 6.55 (m, 2H, α-pyrrole-H), 6.08 (dd, ^3J (H, H) = 2.7 Hz, ^3J (H, H) = 3.3 Hz, 2H, β-pyrrole-H), 5.92 (m, 2H, β-pyrrole-H), 5.83 (t, ^3J (H, H) = 3.0 Hz, 2H, β-pyrrole-H), 5.80 (d, ^3J (H, H) = 2.7 Hz, 2H, β-pyrrole-H), 5.78 (d, ^3J (H, H) = 2.7 Hz, 2H, β-pyrrole-H), 3.74 (s, 4H, *meso*-H), 3.59 (s, 4H, *meso*-H); MS (MALDI-TOF): *m*/*z* (%): 382.19 [M$^-$, 100%]. Compounds **3**, **4** and **5** were obtained in 9, 11 and 10% yields, respectively, when a Biotage microwave synthesizer (Biotage Initiator^{TM}) was used under the same conditions (40 s and 240 W) used for the domestic microwave oven. The temperature reached 60 °C and no significant pressure developed.
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