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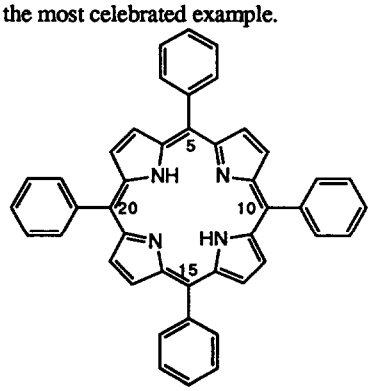
STEPWISE SYNTHESES OF UNSYMMETRICAL TETRA-ARYLPORPHYRINS. ADAPTATION OF THE MACDONALD DIPYRROLE SELF-CONDENSATION METHODOLOGY

David M. Wallace and Kevin M. Smith*
Department of Chemistry, University of California, Davis, CA 95616

Abstract: A new synthetic route to meso-tetraarylporphyrins [e.g. (12,13)] using a MacDonald-type 2+2 condensation is established. The method presented here shows wide applicability for the preparation of 5,10,15,20-tetra-aryl-substituted porphyrins with two-fold rotational symmetry. The 2+2 method is further extended to give a tetra-arylporphyrin (14) bearing four different aryl groups in a predesignated array.

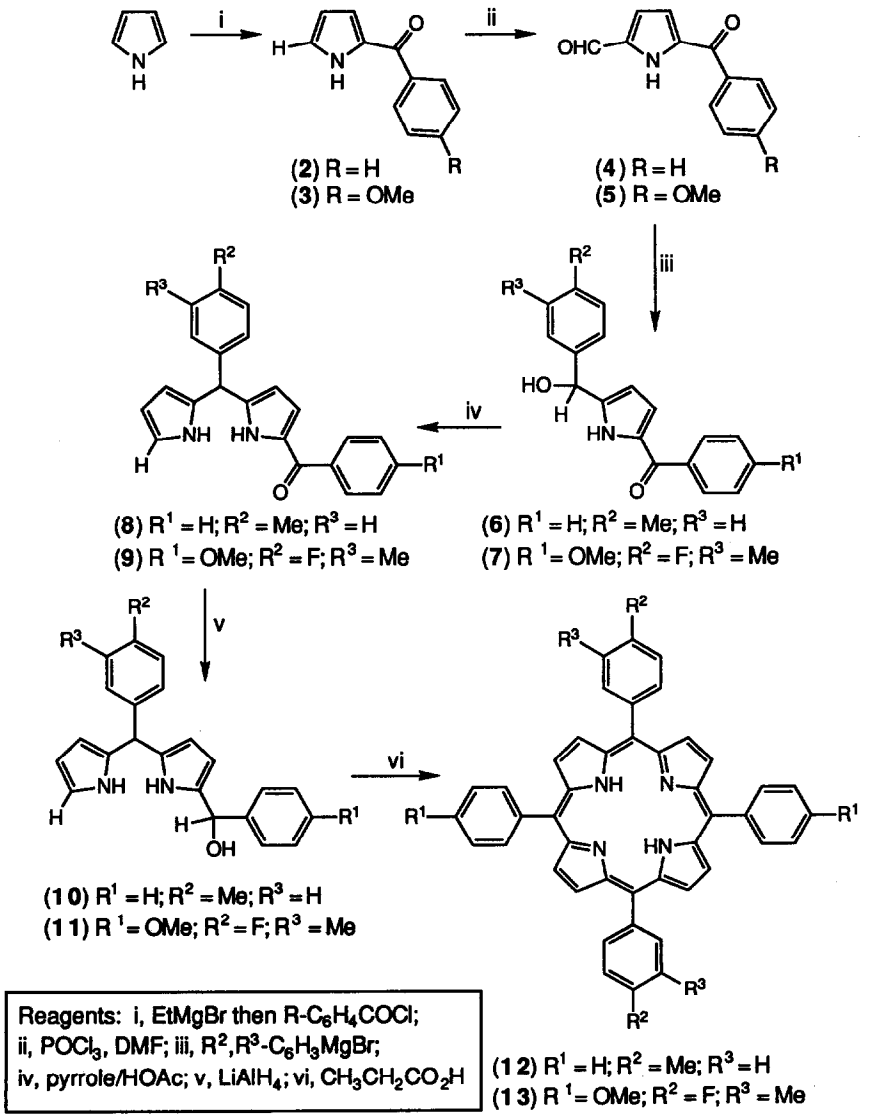
Synthetic approaches to octa-alkylporphyrins and natural porphyrins related to heme and chlorophyll have developed dramatically in the past fifty years, from monopyrrole tetramerizations, through Fischer's dipyrromethene self-condensations in organic acid melts,[1] through MacDonald's "2+2" methodology,[2] to the truly general approaches through unsymmetrically substituted b-bilenes and a,c-biladienes.[3,4] However, the most often used porphyrins for physical and spectroscopic studies are the *meso*-tetra-arylporphyrins, TPP (**1**) being the classical example,[5] and Collman's picket-fence porphyrin[6] being the most celebrated example.



(1)

Tetraphenylporphyrin was first synthesized fifty years ago by Rothemund,[5] who caused benzaldehyde and pyrrole in pyridine to react in a sealed bomb at 150°C for 24 hours. The yields were low and very few substituted benzaldehydes could be used due to the severe conditions. Adler and coworkers modified the Rothemund reaction by allowing benzaldehyde and pyrrole to react for 30 minutes in refluxing propionic acid open to the air.[7] The yields were above 20% and the milder reaction conditions allowed a wider selection of substituted benzaldehydes to be used. Lindsey[8] improved tetra-arylporphyrin synthesis further by reacting benzaldehyde and pyrrole in methylene chloride under N_2 in the presence of boron trifluoride etherate at room temperature (to give a porphyrinogen), and then oxidizing with p-chloranil to produce yields of 30-40%. Synthetic developments in the area of unsymmetrically functionalized tetra-arylporphyrins have lagged far behind. These porphyrins are usually synthesized by the condensation of pyrrole with a mixture of aryl-aldehydes;[9] this results in poor yields after intensive chromatographic separation and purification.

We have embarked upon a program to bring tetra-arylporphyrin rational synthesis to the same level of sophistication as for "regular" (usually *meso*-unsubstituted) porphyrins of the heme and chlorophyll series. Future papers will describe completely unsymmetrical examples and approaches which we are currently investigating. In this first paper we raise the art of tetra-arylporphyrin synthesis to the "MacDonald-type" 2+2 level, which involves condensation of two dipyrroles. Even though the MacDonald route has some symmetry limitations associated with it, it still has served a very important role in the history of porphyrin synthesis, and we anticipate that our tetra-aryl modification of this approach will be equally serviceable when porphyrins of the appropriate symmetry are needed.



Pyrrole was first reacted with ethyl magnesium bromide to form the 2-pyrrole magnesium bromide. This was then added to the corresponding acid chloride to yield the 2-acylpyrrole (**2**,**3**).[10] Vilsmeier formylation [to give (**4**,**5**)]

followed by Grignard reaction with the analogous substituted phenyl magnesium bromide produced the desired 5-(arylhydroxymethyl)pyrrole (**6,7**) in 45% yield. An alternative synthesis of the hydroxymethyl-pyrrole was a Friedel-Crafts acylation and subsequent borohydride reduction to the alcohol. In this case the overall yield was only 18.5% due to competitive acylation at the 4-position of the pyrrole; however this method will be useful when using aryl-substituents which are sensitive to Grignard reagents. The alcohol was then condensed with pyrrole in glacial acetic acid to produce the dipyrromethane (**8,9**). Reduction with $LiAlH_4$ gave the acid-sensitive alcohol (**10,11**) which was directly used for the porphyrin formation reaction in propionic acid.[11]

The porphyrins were obtained in yields of 31% (**12**) and 24% (**13**), and are comparable with those of the tetra-arylporphyrins synthesized by the Adler methodology.[7,12]

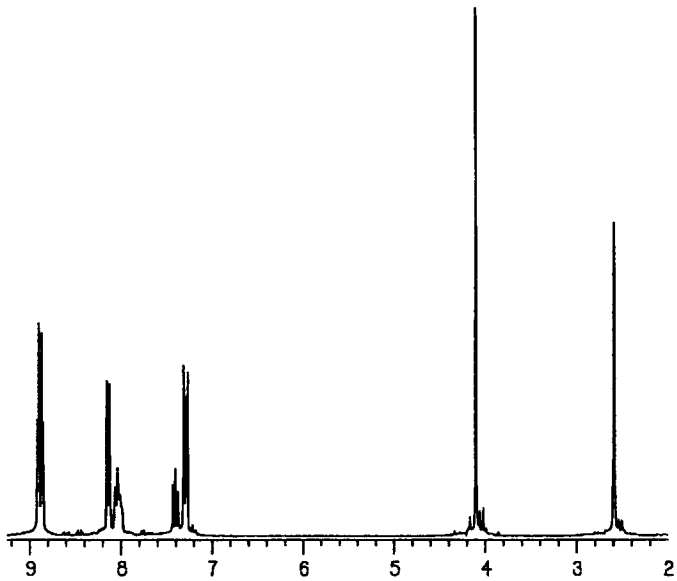
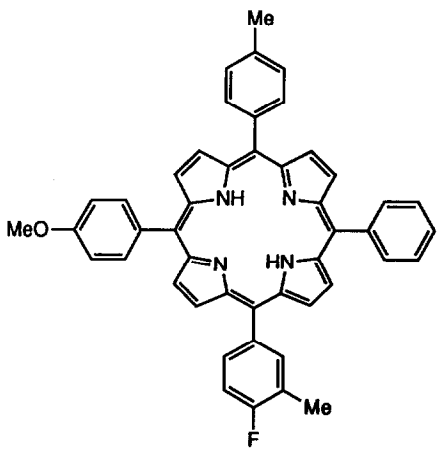


Figure 1: Proton NMR spectrum, in $CDCl_3$, of tetra-arylporphyrin (**13**). Chemical shifts are in ppm.



(**14**)

The proton NMR spectrum of compound (**13**) is shown in Figure 1. Two singlets at 2.59 and 4.09 ppm correspond to the R^3 methyl and methoxy protons respectively, with each integrating to six protons. The meta and ortho protons of the p-methoxyphenyl ring appear as doublets at 7.29 and 8.13 ppm. The meta proton adjacent to the fluorine appears as a doublet of doublets (J = 8.9 Hz) at 7.40 ppm and the two ortho protons appear as a multiplet at ~ 8.03 ppm. Finally, the pyrrole-β protons appear as two doublets showing an AB pattern (J = 4.6 Hz) at 8.85 and 8.90 ppm.

The above results point to a tetraphenylporphyrin with two-fold rotational symmetry. The high resolution mass spectra for compounds (**12**) and (**13**) also confirm their structure: (**12**) Calcd for $C_{46}H_{34}N_4$: 642.2783; Found: 642.2762. (**13**) Calcd for $C_{48}H_{36}F_2N_4O_2$: 738.2806;

Found: 738.2830.

Cross condensation of the two dipyrromethanes (**10**) and (**11**) in propionic acid gave a mixture of three porphyrins, (**12**), (**13**), and (**14**) from which (**14**) was readily separated in 7.5% yield (unoptimized). This represents the first example of a tetra-arylporphyrin synthesis in which all four aryl rings are differentially substituted, and in which the regiochemistry of the substituent array is definitively known. Having demonstrated the feasibility of the 2+2 method for tetra-arylporphyrin synthesis, and shown that it can be used to obtain predetermined and uniquely substituted tetra-arylporphyrins, we are currently embarking upon methodology which employs open-chain tetrapyrrolic intermediates in the hope of developing a truly general synthesis of tetra-arylporphyrins which will provide pure products without the need for chromatographic separation of isomers and other porphyrinic byproducts. This work will be reported elsewhere in due course.

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