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Synthesis of *meso*-tetraaryl-21-oxa-22-thiaporphyrin from 2+2 condensation

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Abstract

The first synthesis of porphyrin containing oxygen and sulfur adjacent to each other is described. The synthesis utilizes the 2+2 condensation of dipyrromethane and (*meso*-aryl)furylthienylmethane. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: core-modified porphyrin; 2+2 condensation; dipyrromethanes.

The porphyrins have been recognized as one of the most important prosthetic groups in biological systems. The diverse chemistry performed by natural porphyrins has inspired works in various fields of chemistry.[1] Development of porphyrin macrocycles that mimic biological systems has focused on synthetic tailoring of the parent macrocycles. One approach for these involves replacement of one or more of the pyrrolic nitrogen with other heteroatoms such as oxygen, sulfur and selenium. These focus on the modification of the porphyrin core.[2] The replacement of one or more pyrroles in the porphyrin with other heterocycles changes the core size, the electrochemical properties and the spectral characteristics. These are important because controlled modification of the basic framework of porphyrins while keeping aromaticity intact will result in a systematic variation of the spectroscopic properties. This is also advantageous in building various model compounds because of the requirement of precise control of molecular energy. To date, the class of core-modified porphyrins has been expanded to the incorporation of benzene,[3] pyridine,[4] furan and thiophene.[5] Most of the modified porphyrinoids maintain their aromaticity in spite of the major modification of the original π-system.[6] At the same time, the synthesis of porphyrin isomers are another major concern with regard to the relationship between aromaticity and degree of distortion of the porphyrin plane.[7] Replacing nitrogen ligands in the core with other heteroatoms in a regiospecific manner could be accomplished by stepwise construction of building subunits. The symmetry of molecules changes by doing this and transition energy among the molecular orbitals accordingly changes.[8] Our current interests are development of a synthetic method for asymmetric porphyrins with different core-ligands. As a part of these efforts, we have recently

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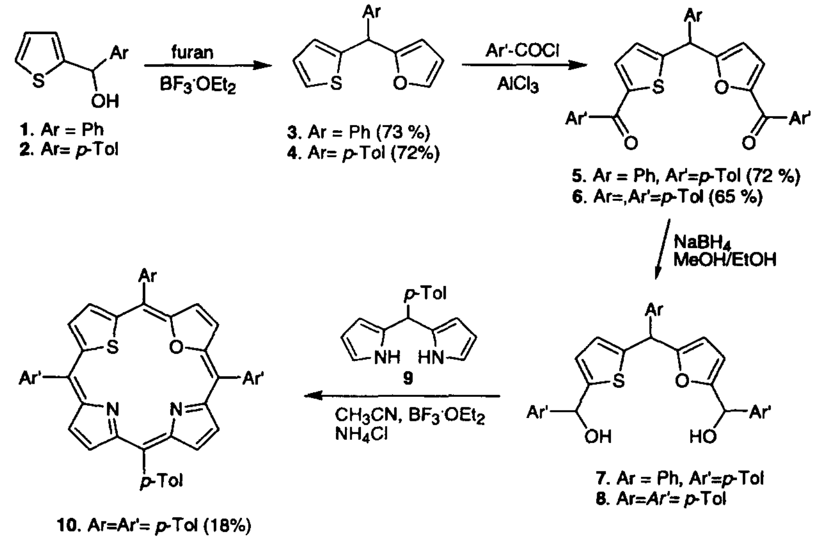
reported a synthesis of several core-modified porphyrins.[2] Since work by Ulman involving the synthesis and spectroscopic character of core-modified porphyrins has been published,[5] there have been several reports related with the synthesis and metal complexes of thiaporphyrins and oxaporphyrins. The reported compounds have two sulfur or oxygen atoms in *trans* (across) or *cis* (adjacent) fashions in the core. But there have been no successful reports for the selective synthesis of porphyrin (**10**) which have two heteroatoms in *cis* (adjacent) fashion in the core. Latos-Grazynski et al. recently reported some spectroscopic properties of nickel complexes of 5,10,15,20-tetraphenyl-21,23-dioxaporphyrin.[6] The attempted synthesis of 21,22-dioxaporphyrin analogs was first described by Broadhurst et al. in 1969.[9] But attempted condensation resulted in a complex mixture. Since we have successfully synthesized *meso*-phenyldifurylmethane or *meso*-phenyldithienylmethane with reasonable yields, we attempted to synthesize 21-oxa-22-thiaporphyrins (Scheme 1).



Scheme 1.

The (*meso*-phenyl)furylthienylmethane (**3**) and (*meso*-tolyl)furylthienylmethane (**4**) were obtained by acid catalyzed condensation of 2-(α-hydroxy-α-aryl)thiophene (**1**), (**2**) with excess furan. Furan was used as a reactant and the solvent. Acid-catalyzed room temperature condensation gave high yields of desired products. Attempted condensation of 2-(α-hydroxy-α-phenyl)methylfuran with excess thiophene under the same condition did not give the desired product. This is due to higher reactivity of furan than thiophene toward electrophile. The gas chromatographic analysis of the crude reaction mixture of **3** and **4** did not contain any *meso*-phenyl-(thien-2-yl)-(furan-3-yl)methane or *meso*-tolyl-(thien-2-yl)-(furan-3-yl)methane indicating large reactivity differences between C-2 and C-3 of furan compare to that of pyrrole. The acylation of **3** and **4** proceeds exclusively to bisacylated compounds under the Friedel–Craft acylation conditions. The acylation of **3** or **4** with aroyl chloride was carried out in the presence of $AlCl_3$. Optimal ratio for the bisacylation was found to be 1:2.5:3.8 (**3**:aroyl chlorides:$AlCl_3$). No mono-acylated products were observed under this condition.

Since the reduction of 1,9-bisacyldipyrromethanes proceeded smoothly with a large excess of reducing agents,[11] we attempted the carbonyl reduction of **5** or **6** using 30 molar equivalents of $NaBH_4$ in MeOH:EtOH (2:1) at room temperature. The progress of reduction can be easily followed by IR spectrometer. The carbonyl stretching had disappeared while O–H stretching appeared in 10 min of the reaction. The basic workup is crucial in order to prevent decomposition of rather unstable diols

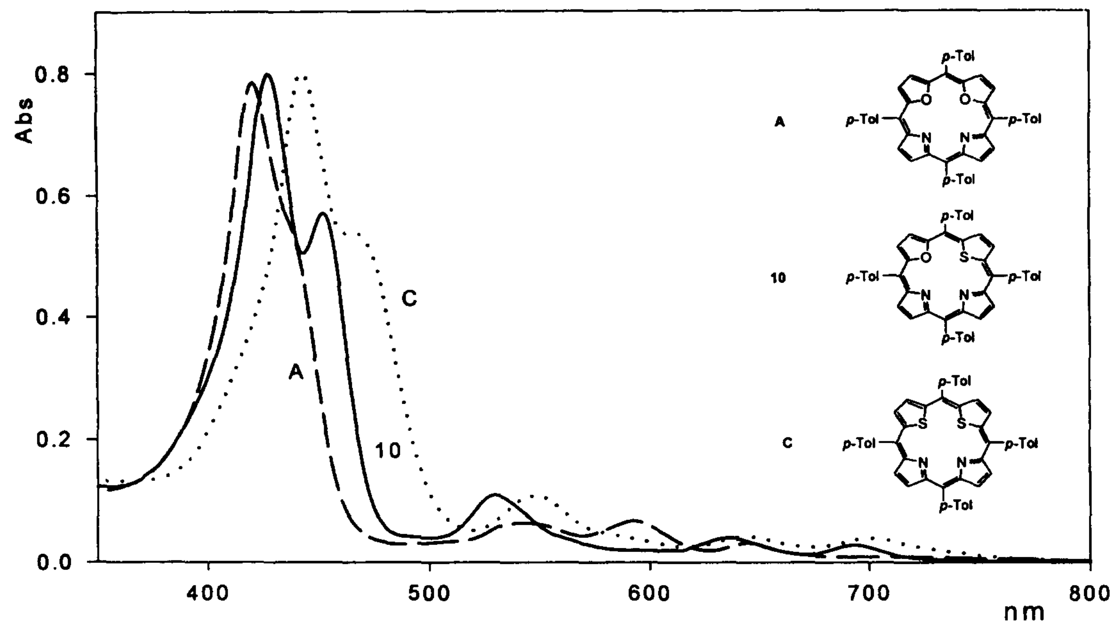


Figure 1. UV–vis spectra of three core-modified porphyrins, **A** (8.99×10^{-6} M), **10** (5.90×10^{-6} M) and **C** (6.74×10^{-6} M). Each spectra was obtained in CH_2Cl_2:EtOH (3:1)

7 and **8**. The diol was very unstable and should be used immediately after workup. The porphyrin synthesis from the condensation of **8** with *meso*-tolyldipyrromethane (**9**) using the previously known conditions[10,12] (10 mM **8** in acetonitrile at 0°C catalyzed by BF_3OEt_2 in the presence of 10 mM NH_4Cl) afforded 18.4% of the desired porphyrin (**10**).[13] The LD-MS analysis indicates that the condensation did not result in scrambling of dipyrromethanes and no other porphyrin components were observed. The porphyrin (**10**) was quite basic compared to the mono-heteroatom analogues.[5] The porphyrin component was bound to silica and elution of the porphyrin was not possible under normal solvent conditions. The elution was only possible by adding TFA in the eluent. This observation indicates that the porphyrin (**10**) possibly has good affinity to the cationic species. The basicity of heteroatom porphyrins have the order of $OSN_2>ON_3>SN_3>N_4$-porphyrin. The absorption spectrum of **10** in CH_2Cl_2:EtOH (3:1) showed a partial overlap of the Q_{IV} band with the Soret band (Fig. 1). The absorption spectra of O_2N_2 (**A**), S_2N_2 (**C**)[14] and OSN_2 porphyrin indicate that there is good correlation between the presence of heteroatoms and degree of distortion. The UV–vis spectrum for porphyrin (**10**) shows a typical Soret band at 427 nm. The observed Soret band was lying half way between S_2N_2-porphyrin (441 nm) and O_2N_2-porphyrin (420 nm) as shown in Fig. 1.

Introduction of two oxygen atoms adjacent to each other in the core causes strong hypsochromic shift of all Q bands compared to $TPPH_2$.[1] Because the steric effects in the core are predominant on the flexibility of porphyrin plane, the degree of distortion must be in between S_2N_2-porphyrin and O_2N_2-porphyrin. So far, the results obtained indicate that the 2+2 approach is one of the best ways to obtain various core-modified porphyrins bearing heteroatoms adjacent each other. In order to establish synthetic generality for the preparation of porphyrin building blocks, extensive adjustment is under investigation.

Acknowledgements

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13. The spectroscopic properties for porphyrin (**10**): ^{1}H NMR ($CDCl_3$, TFA-*d*): δ 10.18 and 9.94 (two doublets, 2H, *J*=5.0 Hz), 9.91 and 9.81 (two doublet, 2H, *J*=5.0 Hz), 9.10 and 8.88 (two doublets, 2H, *J*=5.0 Hz), 8.85 and 8.64 (two doublets, 2H, *J*=4.6 Hz), 8.55 and 7.95 (two doublets, 4H, *J*=7.9 Hz, Ar-H), 8.43 and 7.89 (two doublets, 4H, *J*=7.8 Hz, Ar-H), 8.33 and 7.85 (two doublets, 4H, *J*=7.8 Hz, Ar-H), 8.24 and 7.79 (two doublets, 4H, *J*=7.8 Hz, Ar-H), 2.83 (s, 3H, Ar-CH_3), 2.81 (s, 3H, Ar-CH_3), 2.80 (s, 6H, Ar-CH_3). UV–vis (CH_2Cl_2:EtOH, 3:1) λ_{max} ($\varepsilon \times 10^3$) 427 (139), 452 (100), 529 (18), 635 (6.5), 692 (4.5); FABMS calcd for $C_{48}H_{36}N_2OS$: 689.88. Found: 689.48.
14. The synthesis and characterization of porphyrin (**A**) and (**C**) have been reported in Ref. 2f.