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A New Synthesis of Porphyrins via Tetramerization of 2-(Hydroxymethyl)pyrroles

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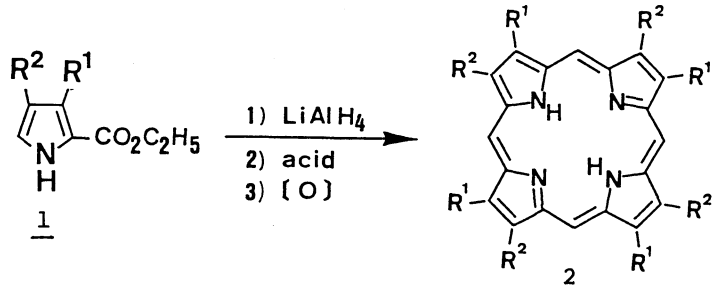
Acid catalyzed cyclization of 2-(hydroxymethyl)pyrroles with electron-donating substituents at the β-position gives a mixture of four isomers of porphyrins (type I-IV) in the homogeneous reaction. The isomerization during cyclization can be minimized in the heterogeneous reaction using silica gel as an acid catalyst to give type I porphyrins selectively.

One of the most successful synthesis of porphyrins from pyrroles involves the tetramerization of 2-(aminomethyl)- or 2-(hydroxymethyl)pyrroles, which is the biosynthetic route to natural porphyrins.[1] A variety of porphyrins have been prepared by this approach.[2] However, acid-induced tetramerization of monopyrroles generally accompanies the isomerization of intermediates to give a mixture of all four possible isomers of porphyrins. The isomerization proceeds very fast when the β-substituents are electron-donating groups such as alkyl or aryl groups.[3] Now we have found that it is very difficult to bring about the tetramerization of monopyrroles without isomerization under homogeneous conditions but type I porphyrins are selectively formed from the heterogeneous reaction using silica gel as an acid catalyst.[4]

In the scheme is shown the preparation of porphyrins. The requisite esters (1) are prepared in one step by the reaction of nitroalkenes with ethyl isocyanoacetate.[5] 2-(Hydroxymethyl)pyrroles, formed by the reduction of 1 with $LiAlH_4$ at 0 °C,[6] are readily tetramerized to porphyrins on treatment with an acid and an oxidizing agent.



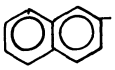
1

2

Type I

The results are summarized in the table. Four possible isomers (type I-IV) were formed. The ratio of these isomers depends on the reaction conditions and substituents (R^1-R^2). For example, complete scramble of isomers occurred when the reaction was carried out in refluxing acetic acid. The amount of type I was increased under milder reaction conditions. However, homogeneous conditions using acetic acid or p-toluenesulfonic acid in CH_2Cl_2 always caused some isomerization even when the reaction was carried out at 0 °C for a short reaction time such as 5 min. On the other hand, the heterogeneous reaction using silica gel in CH_2Cl_2 did not cause such isomerization to give type I porphyrins selectively. The ratio of isomers can be determined by NMR signals of the protons at the meso positions or the methyl protons as shown in Fig. 1. When β-substituents are electron-withdrawing groups such as C_6F_5, the isomerization proceeds very slowly. In such cases type I porphyrins were obtained in good yield on treatment of 2-(hydroxymethyl)pyrroles with p-toluenesulfonic acid in CH_2Cl_2 followed by oxidation with chloranil.[7)]

Table 1. Preparation of Porphyrins by Tetramerization of 2-(Hydroxymethyl)pyrroles

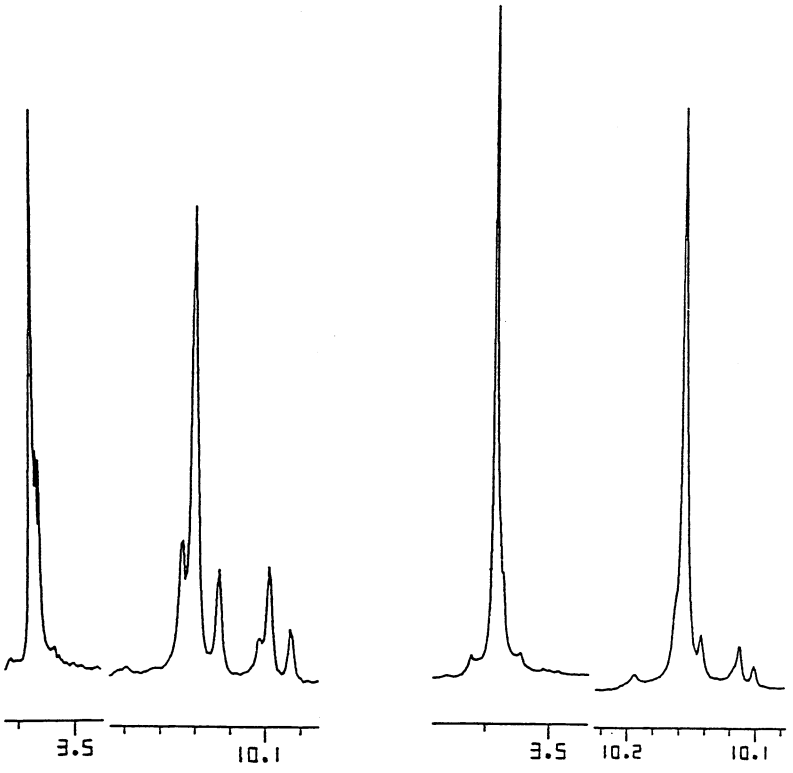
R^1	R^2	Conditions[a)]	Yield/%	Type I[b)]
C_2H_5	CH_3	AcOH, 100 °C, 1 h	40	ca 10-20%
C_2H_5	CH_3	Silica gel-CH_2Cl_2, 25 °C, 24 h	30	ca 95%
n-C_6H_{13}	CH_3	AcOH, 100 °C, 1 h	40	ca 10-20%
n-C_6H_{13}	CH_3	Silica gel-CH_2Cl_2, 25 °C, 24 h	25	ca 95%
C_6H_5	CH_3	AcOH, 100 °C, 1 h	50	ca 20%
C_6H_5	CH_3	Silica gel-CH_2Cl_2, 25 °C, 24 h	35	ca 95%
p-$CH_3C_6H_4$	CH_3	p-TsOH-CH_2Cl_2, 0 °C, 5 min	35	ca 40%
p-$CH_3C_6H_4$	CH_3	Silica gel-CH_2Cl_2, 25 °C, 24 h	35	ca 90%
p-$CH_3OC_6H_4$	CH_3	Silica gel-CH_2Cl_2, 25 °C, 24 h	40	ca 75%
	CH_3	Silica gel-CH_2Cl_2, 25 °C, 24 h	45	ca 90%
C_6F_5	CH_3	p-TsOH-CH_2Cl_2, 25 °C, 24 h	55	100%

a) Oxidation was carried out with chloranil.

b) The exact ratio could not be determined due to the complicated signals of type IV porphyrins. However, the sharp singlet shown in Fig. 1 should be that of type I porphyrins. Type II porphyrins give a single peak of CH_3, but two peaks of meso-H.

As β-substituents of porphyrins are derived from nitroalkenes and aldehydes, various alkyl and aryl groups are readily introduced by the present method. It should be emphasized that porphyrins having four β-aryls are now readily prepared. Porphyrins having four meso aryls, which are prepared from aromatic aldehyde and pyrrole, have been used extensively in physicochemical studies of biomimetic transformations as well as being model in a host of biologically related problems.

Newly prepared porphyrins having four β-aryls may be also useful in the related studies.[8)]



(a) (b)

Fig. 1. Partial NMR spectra of porphyrins (R^1 = p-$CH_3C_6H_4$, R^2 = CH_3)
(a) Cyclization conditions: p-TsOH in CH_2Cl_2, 0 °C, 5 min
(b) Cyclization conditions: Silica gel in CH_2Cl_2, 25 °C, 24 h
Protons at the meso position are enlarged.

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4) The rearrangement of the intermediates of porphyrins has been studied extensively, see, D. Mauzerall, J. Am. Chem. Soc., 82, 2601, 2605 (1960); A. R. Battersby and E. McDonald, Acc. Chem. Res., 12, 14 (1979); A. H. Jackson, W. Lertwanawatana, R. K. Pandey, and K. R. N. Rao, J. Chem. Soc.,

Perkin Trans. 1, 1989, 374. Unsymmetrical pyrromethanes are prepared by using a montmorillonite clay as catalyst, see, A. H. Jackson, R. K. Pandey, K. R. N. Rao, and E. Roberts, Tetrahedron Lett., 26, 793 (1985). Heterogeneous reactions prohibit the formation of symmetrical pyrromethanes.

5) D. H. R. Barton and S. Z. Zard, J. Chem. Soc., Chem. Commun., 1985, 1098.

6) N. Ono and K. Maruyama, Chem. Lett., 1988, 1511.

7) 2-(Hydroxymethyl)pyrroles with a trifluromethyl group at the 4-position gives type I porphyrins without accompanying other type of porphyrins, see, K. Aoyagi, H. Toi, Y. Aoyama, H. Ogoshi, Chem. Lett., 1988, 1881.

8) Spectral data of new porphyrins are shown here. Mass spectra were measured by FAB method, where M+1 peaks appeared as parent ones.
2 (R^1 = C_6H_5): NMR ($CDCl_3$) δ -3.45 (s, 2 H), 3.65 (s, 12 H), 7.6-8.2 (m, 20 H), 10.25 (s, 4 H). Vis (CH_2Cl_2) 408, 506, 539, 571. Ms 663 (M+1).
2 (R^1 = p-$CH_3C_6H_4$): NMR ($CDCl_3$) δ -3.41 (s, 2 H), 2.68 (s, 12 H), 3.60 (s, 12 H), 7.66 (d, 8 H), 8.06 (d, 8 H), 10.15 (s, 4 H). Vis (CH_2Cl_2) 408, 506, 539, 571, 626. Ms 727 (M+1).
2 (R^1 = p-$CH_3OC_6H_4$): NMR ($CDCl_3$) δ -3.35 (s, 2 H), 3.70 (s, 12 H), 3.89 (s, 12 H), 7.27 (d, 8 H), 7.90 (d, 8 H), 9.90 (s, 4 H). Ms 791 (M+1).
2 (R^1 = ): NMR ($CDCl_3$) δ -3.27 (s, 2 H), 3.50 (s, 12 H), 7.7-8.3 (m, 28 H), 10.23 (s, 4 H). Vis (CH_2Cl_2) 411, 507, 542, 573, 627. Ms 863 (M+1).
2 (R^1 = C_6F_5): NMR ($CDCl_3$) δ -3.30 (s, 2 H), 3.53 (s, 12 H), 9.82 (s, 4 H). Vis (CH_2Cl_2) 408, 504, 575, 629. Ms 1031 (M+1).
Replacement of alkyl groups in 2 by aryl groups causes about 10 nm red shift in visible spectrum.

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