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The First Synthesis of Monoazaporphyrins Bearing a Nitrogen Atom at the Peripheral Position

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Abstract : 2-Aza-3,7,8,12,13,17,18-heptaalkylporphyrins were synthesized by use of improved '3+1' condensation under non-acidic conditions.

Representative natural porphyrins such as heme and chlorophyll are well known to play important roles in organisms. In view of clarification of biological activities of porphyrins and development to drugs such as sensitizers of photodynamic therapy (PDT)[1] and agents for magnetic resonance imaging (MRI),[2] structurally modified and simplified porphyrins are of particular interests. In the context, recently many kinds of 'expanded porphyrins' such as texaphyrins, cumulene porphycenes, sapphyrins, and vinylogous porphyrins which have extended conjugated systems,[3] and 'heteroporphyrins' which contain heteroaromatic units such as furan and thiophene have been synthesized.[4] Montforts reported that monoazaporphyrins having an extra nitrogen atom at the meso position, i.e. the methine bridge of the porphyrin skeleton, had a stronger absorption than that of the original porphyrin in the wavelength (nearby 630 nm) of the light applied to PDT, and that the corresponding monoazachlorins showed a strong absorption in the efficient wavelength (650 nm) for PDT,[5] in which the light of region 650-900 nm is desirable because of effective penetration into human cells. Aiming at search for the new candidates for PDT agents, we intended to synthesize novel porphyrin analogues having extra nitrogen atoms at the peripheral positions that are the β positions of pyrrole ring in porphyrin skeleton. A variety of approaches for synthesis of porphyrins have been developed: stepwise condensation of monopyrroles,[6] '2+2' MacDonald dipyrrylmethane synthesis,[7] and '3+1' condensation of a tripyrrane and a diformylpyrrole.[8] These methods, however, are usually adopted under acidic conditions upon cyclization, and appear not to be applied to the synthesis of porphyrins containing basic nitrogen aromatics such as imidazole unit. Here we report on the first synthesis of new azaporphyrins containing an imidazole unit by use of '3+1' condensation under non-acidic conditions.

Recently, Smith reported one-pot synthesis of regiochemically pure porphyrins under non-acidic conditions.[9] By the use of this method we attempted synthesis of diazaporphyrins **3** and **4** by condensation of 3,4-diethylpyrrole **1** and 2,5-bis[(N,N,N-trimethylammonio)methyl]-4-methylimidazole diiodide **2a**, which was

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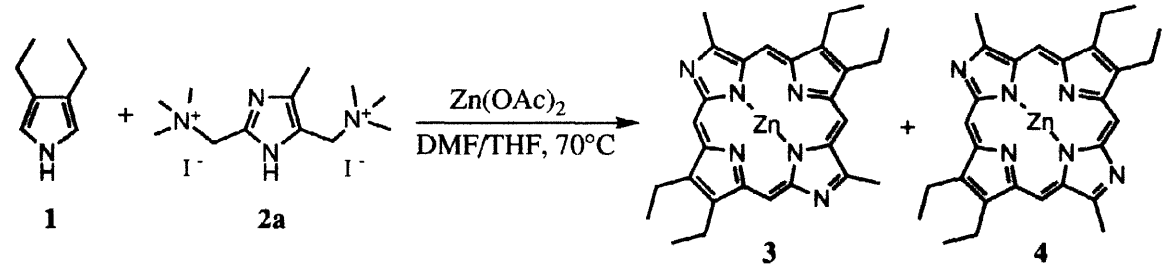
prepared by Mannich reaction of 4-methylimidazole, 40% aqueous dimetylamine solution, and 37% aqueous formaldehyde solution, followed by treating with methyl iodide in DMF. Unfortunately we couldn't find formation of the desired diazaporphyrins **3** and **4** on TLC monitor. After extensive investigation of reaction conditions, we obtained them by condensation of **1** (1.0 mmol) and **2a** (1.5 mmol) in a solvent mixture (125 ml) of DMF and THF (1/20) in the presence of $Zn(OAc)_2$ (3.0 mmol) at 70 ℃ for 6 h, while the yields were extremely low (< 1%). These porphyrins **3** and **4** were so unstable that we could not perform detailed spectroscopic analysis.[10] (scheme 1)



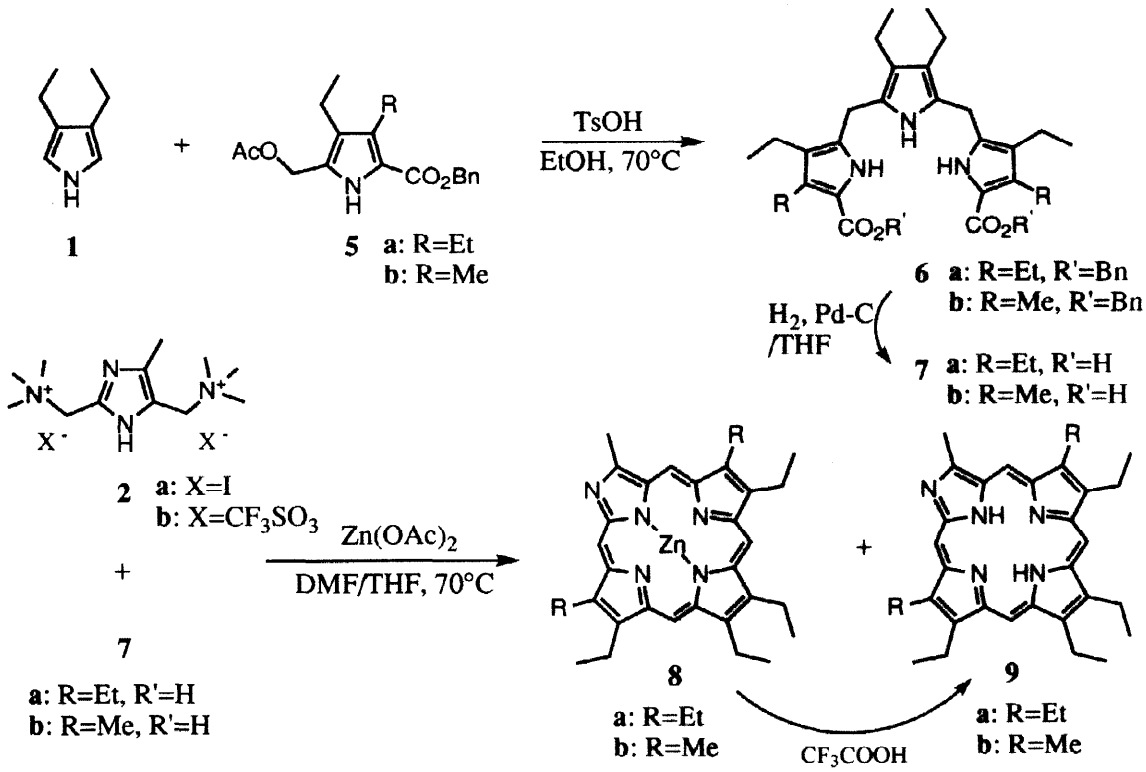
scheme 1

Therefore we turned our focus from one-step synthesis of diazaporphyrins to stepwise synthesis of monoazaporphyrins. Tripyrranes **6** were synthesized by reacting **1** with 5-acetoxymethyl-3-alkyl-2-benzyloxycarbonyl-4-ethylpyrrole derivatives **5a** and **5b** in ethanol in the presence of TsOH.[11] Debenzylation of the tripyrranes **6a** and **6b** was carried out by hydrogenation over Pd-C to give tripyrrane dicarboxylic acids **7a** and **7b**, which were unstable and used in the next step without purification. Condensation of **2a** (2.0 mmol) and the tripyrrane dicarboxylic acids **7a** and **7b** (1.0 mmol) in a solvent mixture (125 ml) of DMF and THF (1/20) in the presence of $Zn(OAc)_2$ (6.0 mmol) at 70 ℃ for 10 h gave the desired compounds,[12] zinc 2-aza-7,8,12,13,17,18-hexaethyl-3-methylporphyrin **8a** and zinc 2-aza-8,12,13,17-tetraethyl-3,7,18-trimethylporphyrin **8b**, respectively in 1.8 % and 1.6 % yield after chromatographic separation. Treatment of the zinc complexes **8a** and **8b** with trifluoroacetic acid at room temperature for 15 min, followed by neutralization, afforded free base porphyrins **9a** and **9b** in quantitative yields respectively. (Scheme 2)

By the use of 2,5-bis[(N,N,N-trimethylammonio)methyl]-4-methylimidazole ditriflate **2b** instead of **2a**, tripyrrane **7a** and **7b** afforded not only zinc porphyrins **8a** and **8b** in 1.8% and 2.3% yield respectively but also free base porphyrins **9a** and **9b** in 4.8% and 3.4% yield respectively. Therefore, treatment of a mixture of **8** and **9** which was collected by chromatography after condensation of **2b** and **7**, with trifluoroacetic acid afforded directly the free bases **9**. The results of the convergent synthesis of free base porphyrins **9a** and **9b** from the imidazole triflate **2b** and tripyrranes **7** are summarized in Table 1.

The structure of monoazaporphyrins obtained was confirmed by spectroscopic analysis.[13] The electronic spectrum (Q band) of azaporphyrins **9a** and **9b** didn't show the 'Etio type spectrum' which is found in all porphyrins where six or more peripheral positions are substituted with alkyl groups, but exhibited the 'Rhodo type spectrum' which is found in porphyrin bearing electron-withdrawing groups at the peripheral positions.[14] Upon addition of 1 equiv. trifluoroacetic acid, **9b** showed the bathochromic shift (10 nm) of the lowest energy band (620 nm) of the Q band, although the corresponding phenomenon is not observed for octaethylporphyrin under the same conditions.[14]

In conclusion we synthesized new monoazaporphyrins **9** which have a nitrogen atom at the peripheral position by use of '3+1' condensation of tripyrranes **7** and 2,5-bis[(N,N,N-trimethylammonio)methyl]-4-



scheme 2

Table 1. Synthesis of monoazaporphyrins **9a** and **9b** [a]

entry	Tripyrranes	Imidazole deriv. **2b** (equiv.)	$Zn(OAc)_2$ (equiv.)	Time (h)	Yield of free base porphyrins (%)	
1	**7a**	1	1	10	**9a**	0.5
2	**7a**	2	1	10	**9a**	1.1
3	**7a**	2	3	10	**9a**	4.6
4	**7a**	2	6	5	**9a**	4.3
5	**7a**	2	6	10	**9a**	5.7
6	**7a**	3	6	12	**9a**	6.5
7	**7b**	2	6	10	**9b**	6.6

[a] The cyclocondensation reaction was carried out in the concentration of 8 mmol/L for tripyrranes in the solvent mixture of DMF and THF (1/20).

methylimidazole ditriflate **2b** under non-acidic conditions. Investigations of the photochemical properties of these compounds and transformations to the chlorins are in progress.

References and notes

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10. Spectroscopic data for compound **3** or **4** HRMS (EI^+) calculated for $C_{28}H_{30}N_6Zn$ 514.1823, found 514.1843; ^1H NMR($CDCl_3$): δ 1.95 (12H,m), 3.75(6H, s), 3.85 (8H,m,), 9.55 (2H,s), 9.81 (2H,s)
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12. In the extensive trials for cyclocondensation of **2a** and **7a** or **7b**, yields of the monoazaporphyrins **8a** and **8b** were improved by using excess equivalents of tripyrranes **7** and $Zn(OAc)_2$, because **2a** decomposed easily on heating to evolve trimethylamine which may be caught with $Zn(OAc)_2$: for the reaction of **2b** and **7a**, see entry 1~3 in Table 1.
13. Spectroscopic data for compound **8a** HRMS (EI^+) calculated for $C_{32}H_{37}N_5Zn$ 555.2340, found 555.2324; **8b** HRMS (EI^+) calculated for $C_{30}H_{33}N_5Zn$ 527.2027, found 527.2045; **9a** ^1H NMR($CDCl_3$) : δ -3.47 (2H,s), 1.91(18H,m), 3.99(3H,s), 3.99(4H,m), 4.14(8H,m), 10.03(1H,s), 10.05(1H,s), 10.13(1H,s), 10.32(1H,s); ^{13}C NMR($CDCl_3$): δ 16.3, 16.9, 18.2, 18.3, 18.3, 18.5, 19.6, 19.9, 29.3, 96.3, 97.0, 97.4, 99.7, 135.0, 136.4, 136.6, 137.5, 139.1, 139.4, 140.0, 140.8, 145.1, 145.3, 146.2, 154.2, 154.9, 169.8; HRMS (FAB^+/ m-Nitrobenzylalcohol) calculated for $C_{30}H_{36}N_5$ 493.3205, found 493.3201; UV-vis($CHCl_3$) λ_{max}nm ($\varepsilon/M^{-1}cm^{-1}$): 619(800), 567(9,000), 543(16,000), 506(11,000), 399(210,000); **9b** ^1H NMR($CDCl_3$): δ -3.65(2H,bs), 1.87(12H,m), 3.55(3H,s), 3.64(3H,s), 3.94(3H,s), 3.95(4H,m), 4.10(4H,m), 9.96(2H,s), 9.98(1H,s), 10.25(1H,s); ^{13}C NMR($CDCl_3$):δ 11.1, 11.2, 16.2, 17.4, 18.5, 19.5, 19.6, 19.8, 96.0, 96.6, 97.2, 99.6, 133.2, 134.2, 135.6, 136.2, 137.5, 139.5, 139.9, 145.0, 145.2, 146.1, 154.0, 154.7, 158.7, 169.7; HRMS (FAB^+/ m-Nitrobenzylalcohol) calculated for $C_{30}H_{36}N_5$ 466.2970, found 466.2964; UV-vis($CHCl_3$): λ_{max}nm ($\varepsilon/M^{-1}cm^{-1}$): 620(560), 567(8,900), 543(16,000), 506(11,000), 400(220,000); UV-vis($CHCl_3$-TFA) λ_{max}nm ($\varepsilon/M^{-1}cm^{-1}$): 630(5,600), 516(6,800), 556(14,000), 399(120,000)
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