Novel synthesis of 5,10,15,20-tetraarylporphyrins using high-valent transition metal salts

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A new synthesis of porphyrins from pyrrole and substituted benzaldehydes, is described, using high-valent transition metal salts [$VOCl_3$, $VO(OEt)Cl_2$, $VO(OPr^i)Cl_2$, $TiCl_4$ and $Mn(OAc)_3$] as aromatizing agents. This process allows higher working concentrations and larger amounts of reagent to be used, than those previously described.

The ubiquitous use of porphyrins in single electron transfer processes[1-4] makes their synthesis of interest.[5] That of 5,10,15,20-tetraphenylporphyrin was first reported by Rothemund,[6] later modified by Adler and Longo[7] and more recently improved by Lindsey.[8] Although there have been recent advances in this area,[9,10] low product yields and purification still prove troublesome. This is particularly true of the key synthetic step, the oxidation of porphyrinogen I to the porphyrin II[11] (Scheme 1), a process induced by oxidants such as 2,3-dichloro-5,6-dicyanobenzoquinone[12] or *p*-chloranil.[13]

Here we describe a new one-pot synthesis which uses transition metal salts [$VOCl_3$ (V^V), $TiCl_4$ (Ti^{IV}), $Mn(OAc)_3$ (Mn^{III})], as an oxidant to promote the formation of carbon–carbon bonds *via* free radical reactions in the transformation of I to II. A mechanism for the generation of radicals by electron transfer from the radical precursor to the metal complex[14] is illustrated in Scheme 1.

The ability of pentavalent vanadium compounds to act as one-electron oxidants,[15] and versatile Lewis acids in organic media, is also true of other oxovanadium(v) compounds, such as $VO(OEt)Cl_2$ and $VO(OPr^i)Cl_2$ (see Table 1).

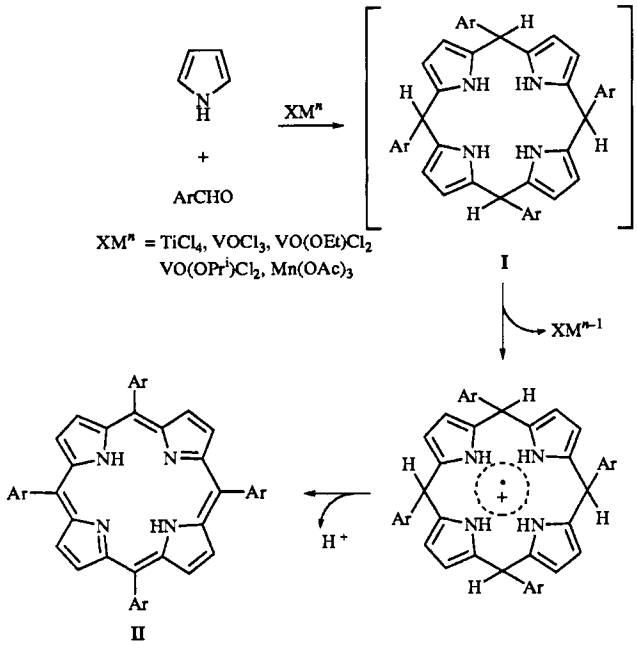
There are few reports of oxidative radical formation promoted by high-valent titanium salts,[17,18] low-valent titanium complexes being known rather as good reducing agents; as such they promote efficient coupling with a variety of carbonyl compounds *via* radical processes.[19] Our experiments show that $TiCl_4$ can be an efficient oxidative aromatizing agent (Table 1).

The oxidation of electron-rich centres by manganese(III) salts to form radical species is well known particularly for radical coupling in the chemistry of natural products.[20] In the synthesis of 5,10,15,20-tetraarylporphyrins, it was found that *in situ* generation of anhydrous manganese(III) acetate [obtained by the removal of H_2O from $Mn(AcO)_3 \cdot 4H_2O$ by means acetic anhydride[21]], improved the final porphyrinic yields. This fact was confirmed when the reaction was carried out in the presence of 3 Å molecular sieves, present to remove the water of hydration. However, in comparision with the V^V or Ti^{IV} salts, manganese(III) acetate gave lower yields of porphyrin products; this is related to the milder oxidant ability of the Mn^{III} species (Table 1).

Fortunately the methodology can be used with benzaldehydes having a wide variety of *para*-substituents, both electron-donating and withdrawing, the product yields being more related to the solubility of the porphyrin in the reaction medium than to the electronic characteristics of the substituents (see Table 1). Sterically hindered aldehydes such as 2,4,6-trimethylbenzaldehyde may also be employed in the reaction.

The results show that 5,10,15,20-tetraarylporphyrins can be prepared in excellent yield using this procedure and better results are obtained than with the Lindsey method and without the addition of Lewis acids (BF_3, TFA)[13] or montmorillonite K10[22] as is described for other oxidants. This method allows us to work with concentrations of substrates higher than the 0.01 mol dm^{-3} considered as the optimum value in the literature.[16]

We are currently studying whether the high-valent salts of other metals (Fe, Co and Cu) may be used as oxidants.



Porphyrin II

1: Ar = Ph
2: Ar = *p*-MeC_6H_4
3: Ar = *p*-$MeOC_6H_4$
4: Ar = *p*-ClC_6H_4
5: Ar = *p*-BrC_6H_4
6: Ar = *p*-HOC_6H_4
7: Ar = *p*-$NO_2C_6H_4$
8: Ar = mesityl

Scheme 1

Experimental

NMR Spectra were obtained in $CDCl_3$ and recorded with a Bruker AC-250 spectrometer. δ Values are given relative to tetramethylsilane; in spectral assignments, the term 'C-β-pyrr' refers to the C-2, -3, -7, -8, -12, -13, -17 and -18 positions.

Table 1 % Yield of 5,10,15,20-tetraarylporphyrin **II** using high-valent transition metal salts

Porphyrin II	Lindsey conditions[a]	$TiCl_4$	$VOCl_3$	$VO(OEt)Cl_2$	$VO(OPr^i)Cl_2$	$Mn(OAc)_3$[b]
1: Ar = Ph	39	63	68	61	60	42
2: Ar = *p*-MeC_6H_4	35	48	50	49	48	40
3: Ar = *p*-$MeOC_6H_4$	40	57	55	53	51	43
4: Ar = *p*-ClC_6H_4	20	63	65	60	59	50
5: Ar = *p*-BrC_6H_4	38	45	40	40	38	39
6: Ar = *p*-HOC_6H_4	5	11	9	9	8	7
7: Ar = *p*-$NO_2C_6H_4$	4	6	8	5	6	9
8: Ar = mesityl	29	51	45	50	49	39

[a] See refs. 8, 16. [b] Anhydrous form.

Electronic spectra were recorded on a Shimadzu UV-2100A instrument. Melting points were measured on a hot-stage Reichert apparatus and are uncorrected. Column chromatography was carried out with SDS silica gel 60 Å, and with Merck aluminium oxide 90, Activity II–III mesh size 70–230. TLC chromatography was carried out using Merck PSC 5745 2 mm alumina plates and Scharlau SiF_{254} silica plates. Elemental analyses were determined with a 'Perkin-Elmer 2400-CHN' analyser and were performed at the Microanalytical Service, Faculty of Pharmacy, Universidad Complutense de Madrid.

Dichloromethane was distilled from potassium carbonate and stored over 4 Å molecular sieves. Pyrrole and substituted benzaldehydes obtained from commercial sources (Aldrich and Fluka) were used as received. Oxovanadium(v) compounds $VO(OEt)Cl_2$ and $VO(OPr^i)Cl_2$ were synthesized and purified according to published procedures.[23,24]

General procedure for 5,10,15,20-tetraarylporphyrins using Ti^{IV} and V^V

A 500 cm^3 three-necked round-bottomed flask fitted with a septum, reflux condenser and nitrogen inlet port was charged with dry CH_2Cl_2 (100 cm^3), the corresponding benzaldehyde (10 mmol) and pyrrole (10 mmol). After the solution had been purged with N_2 for 10 min, $TiCl_4$ (3.79 g, 20 mmol) or an oxovanadium(v) compound (20 mmol) in CH_2Cl_2 (200 cm^3) was added *via* syringe. The reaction mixture was stirred at room temperature for 1 h, after which small amounts of conc. HCl (2 cm^3) and saturated aq. NaCl (2 cm^3) were slowly added to it. Any solid material was removed by filtration through silica gel and washed with ethyl acetate or CH_2Cl_2 (60 cm^3). The combined filtrates, containing the free-base porphyrin, were concentrated by evaporation and adsorbed on Florisil (2 g). The adsorbate was placed on the top of an Al_2O_3 column and eluted with the appropriate solvent.

General procedure for 5,10,15,20-tetraarylporphyrins using Mn^{III}

A three-necked round-bottomed flask (250 cm^3) equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with a solution of acetic acid (24 cm^3) and acetic anhydride (8 cm^3) after which manganese acetate tetrahydrate (20 mmol) was added with stirring under N_2. The reaction mixture was stirred at room temperature for 2 h after which a mixture of the corresponding benzaldehyde (10 mmol) and pyrrole (10 mmol) in acetic acid (100 cm^3) was added to it. After the reaction mixture had been heated to reflux under N_2 for 1 h it was evaporated under reduced pressure and the residue dissolved in water (100 cm^3). The solution was then extracted with dichloromethane (3 × 100 cm^3) and the combined extracts were dried (Na_2SO_4), filtered and concentrated with Florisil to yield a damp powder. The adsorbate was placed on the top of an Al_2O_3 column and eluted with the appropriate solvent.

5,10,15,20-Tetraphenylporphyrin 1

Column chromatography of the adsorbate with hexane–ethyl acetate (9:2) as eluent gave porphyrin **1**, mp > 300 °C (Found: C, 85.7; H, 5.25; N, 8.9. $C_{44}H_{30}N_4$ requires C, 85.90; H, 4.92; N, 9.12%); δ_H(250 MHz; $CDCl_3$) −2.80 (2 H, br s, NH), 7.72 (12 H, m, *p*- and *m*-Ph), 8.21 (d, 8 H, *o*-Ph) and 8.80 (s, 8 H, pyrrole-H); δ_C(250 MHz; $CDCl_3$) 120.2 (C-5, -10, -15 and -20), 126.7, 127.8 (C-β-pyrr), 134.6, 139.2 and 142.7; $\lambda_{max}(C_6H_6)$/nm (log ε) 419 (478), 485 (3.4), 415 (18.7), 549 (8.1), 591 (5.3) and 647 (3.4).

5,10,15,20-Tetra(*p*-methylphenyl)porphyrin 2

Column chromatography of the adsorbate with hexane–ethyl acetate (9:2) as eluent gave porphyrin **2**, mp > 300 °C (Found: C, 85.7; H, 5.7; N, 8.2. $C_{48}H_{38}N_4$ requires C, 85.97; H, 5.67; N, 8.36%); δ_H(250 MHz; $CDCl_3$) −2.77 (2 H, br s, NH), 2.71 (12 H, s, Me), 7.56 (8 H, d, *m*-Ph), 8.11 (8 H, d, *o*-Ph) and 8.86 (8 H, s, pyrrole-H); δ_C(250 MHz; $CDCl_3$) 21.4, 120.2 (C-5, -10, -15 and -20), 127.5, 131.2 (C-β-pyrr), 134.7, 137.5 and 139.5; $\lambda_{max}(C_6H_6)$/nm (log ε) 420 (490), 485 (3.7), 516 (18.9), 550 (8.2), 594 (5.4) and 651 (4.1).

5,10,15,20-Tetra(*p*-methoxyphenyl)porphyrin 3

Column chromatography of the adsorbate with $CHCl_3$ as eluent gave porphyrin **3**, mp > 300 °C (Found: C, 78.7; H, 5.3; N, 7.5. $C_{48}H_{38}N_4O_4$ requires C, 78.45; H, 5.21; N, 7.62%); δ_H(250 MHz; $CDCl_3$) −2.77 (2 H, br s, NH), 4.2 (12 H, s, OMe), 7.30 (8 H, d, *m*-Ph), 8.11 (8 H, d, *o*-Ph) and 8.81 (8 H, s, pyrrole-H); δ_C(250 MHz; $CDCl_3$) 56.1, 119.9 (C-5, -10, -15 and -20), 128.5, 133.6 (C-β-pyrr), 134.9, 137.0 and 140.4; $\lambda_{max}(C_6H_6)$/nm (log ε) 424 (485), 488 (4.3), 419 (17.0), 555 (11.9), 595 (5.5) and 653 (4.5).

5,10,15,20-Tetra(*p*-chlorophenyl)porphyrin 4

Column chromatography of the adsorbate with $CHCl_3$ as eluent gave porphyrin **4**, mp > 300 °C (Found: C, 70.2; H, 3.6; N, 7.45. $C_{44}H_{26}Cl_4N_4$ requires C, 70.23; H, 3.48; N, 7.44%); δ_H(250 MHz; $CDCl_3$) −2.86 (2 H, br s, NH), 7.75 (8 H, d, *m*-Ph), 8.14 (8 H, d, *o*-Ph) and 8.85 (8 H, s, pyrrole-H); δ_C(250 MHz; $CDCl_3$) 119.1 (C-5, -10, -15 and -20), 127.2, 131.4 (C-β-pyrr), 134.6, 137.7 and 140.0; $\lambda_{max}(C_6H_6)$/nm (log ε) 421 (515), 485 (4.0), 515 (21.0), 549 (9.0), 591 (6.0) and 649 (3.7).

5,10,15,20-Tetra(*p*-bromophenyl)porphyrin 5

Column chromatography of the adsorbate with $CHCl_3$ as eluent gave porphyrin **5**, mp > 300 °C (Found: C, 56.8; H, 2.8; N, 6.0. $C_{44}H_{26}Br_4N_4$ requires C, 56.80; H, 2.81; N, 6.02%); δ_H(250 MHz; $CDCl_3$) −2.86 (2 H, br s, NH), 7.74 (8 H, d, *m*-Ph), 8.11 (8 H, d, *o*-Ph) and 8.80 (8 H, s, pyrrole-H); δ_C(250 MHz; $CDCl_3$) 118.1 (C-5, -10, -15 and -20), 127.5, 131.6 (C-β-pyrr), 133.9, 136.9 and 139.4; $\lambda_{max}(C_6H_6)$/nm (log ε) 421 (514), 514 (4.1), 548 (9.9), 591 (5.7) and 649 (3.5).

5,10,15,20-Tetra(*p*-hydroxyphenyl)porphyrin 6

Column chromatography of the adsorbate with ethyl acetate as eluent gave porphyrin **6**, mp > 300 °C (Found: C, 77.9; H, 4.25;

N, 8.3. $C_{44}H_{30}N_4O_4$ requires C, 77.86; H, 4.45; N, 8.25%); δ_H(250 MHz; $CDCl_3$ + trifluoroacetic acid) 7.63 (8 H, d, *m*-Ph), 8.10 (8 H, d, *o*-Ph) and 8.81 (8 H, s, pyrrole-H); δ_C(250 MHz; $CDCl_3$ + trifluoroacetic acid) 125.1 (C-5, -10, -15 and -20), 130.5, 132.6 (C-β-pyrr), 135.9, 138.9 and 140.0; λ_{max}(pyridine)/nm (log ε) 425 (488), 485 (3.7), 515 (19.0), 552 (12.0), 590 (5.1) and 648 (3.4).

5,10,15,20-Tetra(*p*-nitrophenyl)porphyrin 7

Column chromatography of the adsorbate with hexane–ethyl acetate (7:3) as eluent gave porphyrin **7**, mp > 300 °C (Found: C, 66.4; H, 3.4; N, 14.0. $C_{44}H_{26}N_8O_8$ requires C, 66.49; H, 3.30; N, 14.10%); δ_H(250 MHz; $CDCl_3$) 7.80 (8 H, d, *m*-Ph), 8.30 (8 H, d, *o*-Ph) and 8.87 (8 H, s, pyrrole-H); δ_C(250 MHz; $CDCl_3$) 118.1 (C-5, -10, -15 and -20), 127.5, 131.6 (C-β-pyrr), 133.9, 136.9 and 141.1; λ_{max}(pyridine)/nm (log ε) 421 (515), 485 (4.0), 515 (21.0), 549 (9.0), 591 (6.0) and 649 (3.7).

5,10,15,20-Tetramesitylporphyrin 8

The reaction was carried out using dry $CHCl_3$ (distilled from P_2O_5) instead of CH_2Cl_2. Column chromatography of the adsorbate with hexane–ethyl acetate (9:1) as eluent gave porphyrin **8**, mp > 300 °C (Found: C, 85.8; H, 7.2; N, 7.3. $C_{56}H_{54}N_4$ requires C, 85.90; H, 7.00; N, 7.20%); δ_H(250 MHz; $CDCl_3$) −2.51 (2 H, br s, NH), 1.85 (24 H, s, *o*-Me), 2.62 (12 H, s, *p*-Me), 7.27 (8 H, s, *m*-Ph) and 8.61 (8 H, s, pyrrole-H); δ_C(250 MHz; $CDCl_3$) 21.8, 31.0, 120.1 (C-5, -10, -15 and -20), 131.5, 133.6 (C-β-pyrr), 135.9, 139.6 and 140.3; λ_{max}(C_6H_6)/nm (log ε) 418 (368), 483 (2.9), 515 (4.2), 547 (3.5), 592 (3.7) and 646 (3.4).

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