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Oxidation with dilute aqueous ferric chloride solutions greatly improves yields in the '4+1' synthesis of sapphyrins[1]

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Abstract

The use of dilute aqueous $FeCl_3$ as an oxidant, instead of DDQ, greatly improves the yields of sapphyrin products by the '4+1' methodology; yields for carbasapphyrins were somewhat lower but also greatly benefited from this approach. © 1999 Elsevier Science Ltd. All rights reserved.

Sapphyrins (e.g., **1**) are perhaps the best known examples of expanded porphyrins,[2] and were first identified by R. B. Woodward and colleagues during their early investigations into the total synthesis of Vitamin B_{12}.[3] These beautiful pentapyrrolic compounds were named for the intense blue colored crystals that they produce. They are generally prepared by a '3+2' approach whereby a tripyrrane (e.g. **2**) condenses with a bipyrrole dialdehyde (e.g. **3**) to give, following an oxidation step (O_2 or DDQ), the macrocyclic product.[3–5] These fully aromatic 'larger than life' porphyrinoids have attracted considerable attention due to the possibilities for metal complex formation within the expanded core, as well as for their well documented abilities for anion binding.[2,6] In addition, medicinal applications have been intensively investigated with particular regard to their utility as photosensitizers in photodynamic therapy and viral photoeradication.[7] Not surprisingly, new routes to the sapphyrin system continue to be developed.[8–10] In the early work by Woodward's group,[3] a '4+1' MacDonald-type approach to the sapphyrins was briefly considered and this methodology has recently been revived (see Scheme 1) for the synthesis of sapphyrin analogues.[8,10] In both the '3+2' and '4+1' routes (Scheme 1), acid catalyzed condensation of the dialdehyde and oligopyrrole units gives rise to a dihydrosapphyrin and an oxidation step is required to produce the fully conjugated sapphyrin. This oxidation step can be the source of problems as the use of traditional dehydrogenation catalysts such as DDQ can lead to substantial decomposition. Air oxidation can provide better yields, but this necessitates prolonged reaction times and is not always effective. In this communication, we report a simple high yielding procedure for carrying out this oxidation that greatly improves upon earlier studies.

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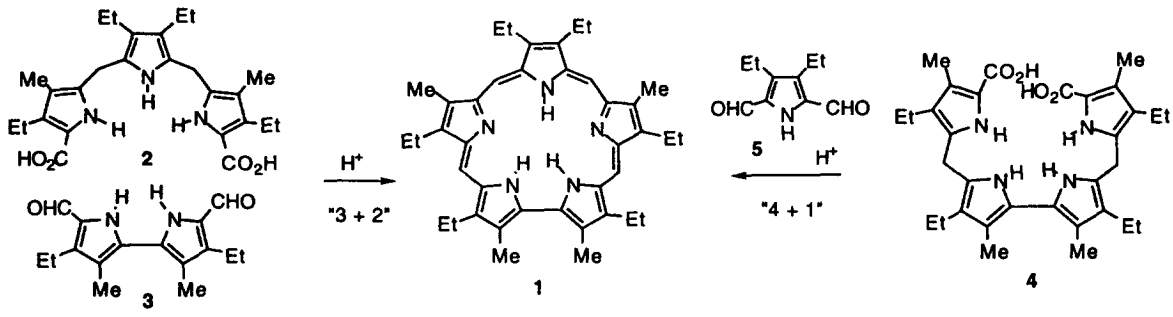
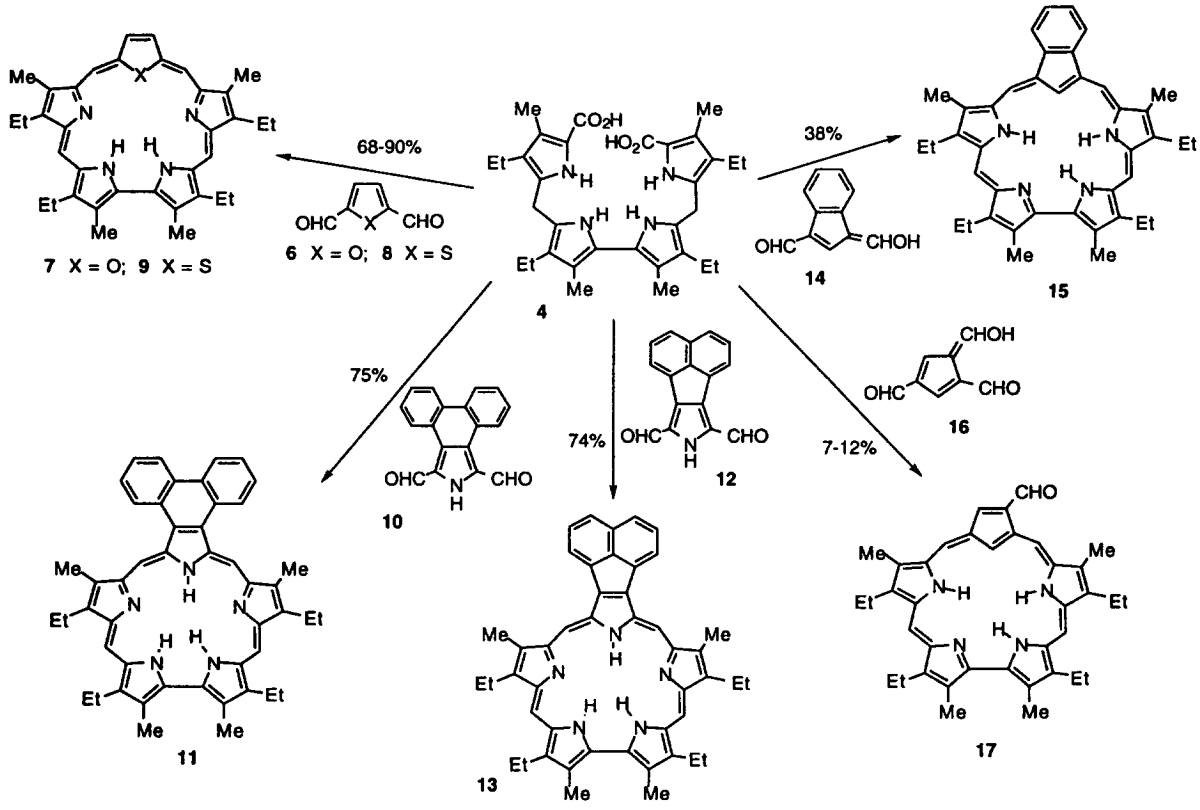


Scheme 1.

In a typical sapphyrin synthesis by the '3+2' approach, **2** was condensed with **3** in the presence of *p*-toluenesulfonic acid and following O_2 oxidation over a period of 18 hours, sapphyrin **1** was isolated in 44% yield.[5] In our applications of the '4+1' method, tetrapyrrole **4**[11] reacted with diformylpyrrole **5** in TFA–CH_2Cl_2 and following oxidation with DDQ, the same system was isolated in 36% yield.[8] While these yields are acceptable for reactions of this type, we felt that superior results could be obtained with the 'right' oxidant and have over the years tried out different procedures for both the sapphyrin chemistry and the related '3+1' syntheses of porphyrin analogues.[12,13] We now report that far better results can be obtained by taking the reaction solutions, and washing them with 0.1% aqueous ferric chloride solution in a separatory funnel for 1–5 min. This simple and convenient method increased the yield of sapphyrin **1** from tetrapyrrole **4** and dialdehyde **5** to 50%,[14,15] and gave substantially better results for a number of related systems. Condensation of **4** with furandialdehyde **6** under these conditions afforded oxasapphyrin **7** in 68% yield (Scheme 2), while the related diformylthiophene **8** gave thiasapphyrin **9** in an extraordinary 90% yield (using the '3+2' method, these compounds were obtained in 26% and 36% yield, respectively[5]). Phenanthropyrrole dicarboxaldehyde **10** gave sapphyrin **11** in 75% yield, while the related acenaphthopyrrole **12** afforded the acenaphthylene fused system **13** in 74% yield (Scheme 2), vast improvements over the 33% and 16% yields reported for reactions using DDQ for the dehydrogenation step.[8] The '4+1' route is potentially valuable because novel subunits can be incorporated into the sapphyrin system, and this method was used in conjunction with a DDQ oxidation step to prepare the first example of an expanded carbaporphyrinoid, benzocarbasapphyrin **14**, from diformylindene **15** in 18% yield.[8] Application of the ferric chloride wash in place of the DDQ oxidation gave the benzocarbasapphyrin **14** in a much improved 38% yield, while triformylcyclopentadiene **16** afforded the new formylsapphyrin **17** for the first time in 7–12% yield. While the latter carbasapphyrin is formed in much lower yields, the initial condensation is compromised by the presence of a third aldehyde moiety that can presumably take part in side reactions (trialdehyde **16** also gives poor yields in the '3+1' synthesis of carbaporphyrins[12i,j]). These improved yields will facilitate investigations on the chemistry of carbasapphyrins.[16]

The ferric chloride method clearly complements the '4+1' methodology extremely well, and our preliminary results indicate that improved yields can also be obtained for other routes to aromatic porphyrinoids such as the '3+1' approach.[12] The simplicity of the procedure will no doubt lead to its widespread use in porphyrin and expanded porphyrin synthesis.



Scheme 2. '4+1' Synthesis of sapphyrin analogues

Acknowledgements

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14. Yields correspond to pure recrystallized sapphyrins that were isolated as their hydrochloride salts.
15. Typical procedure: Tetrapyrrole **4** (27 mg) was stirred with TFA (1 mL) under nitrogen at room temperature for 2 min. The mixture was diluted with dichloromethane (99 mL), diformylpyrrole **5** (9 mg) immediately added and the resulting solution stirred in the dark under nitrogen for a further 16 h. The mixture was washed in a separatory funnel with water, 0.1% $FeCl_3$, water, saturated $NaHCO_3$ and 10% HCl, in that order, and the solvent removed under reduced pressure (vigorous shaking with the aqueous ferric chloride solution was carried out for approximately 2 min). The dark blue residue was chromatographed on silica, eluting with 9% methanol–chloroform and the product fraction collected as a bright blue-green band. Recrystallization from chloroform–hexanes afforded the decaalkylsapphyrin dihydrochloride **1**·2HCl (15 mg; 50%) as deep blue crystals, mp>300°C; UV–vis ($CHCl_3$; dication): λ_{max} [nm] ($\log_{10}\varepsilon$) 433 (4.61), 457 (5.63), 578 (3.43), 624 (4.03), 675 (4.21), 689 (4.13); UV–vis (1% Et_3N–$CHCl_3$; free base): λ_{max} [nm] ($\log_{10}\varepsilon$) 457 (5.45), 610 (3.88), 668 (4.11), 711 (3.84); ^{1}H NMR (400 MHz, $CDCl_3$): δ –4.90 (2H, br s), –4.57 (1H, br s), –4.29 (2H, br s) (5×NH), 2.20, 2.21 (12H, 2 overlapping triplets), 2.32 (6H, t) (6×CH_2CH_3), 4.12 (6H, s), 4.24 (6H, s) (4×sapphyrin–CH_3), 4.55 (4H, q), 4.69–4.77 (8H, 2 overlapping quartets) (6×CH_2CH_3), 11.65 (2H, s), 11.71 (2H, s) (4×*meso*-H).
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