A simple, rational synthesis of *meso*-substituted A_2B-corroles†

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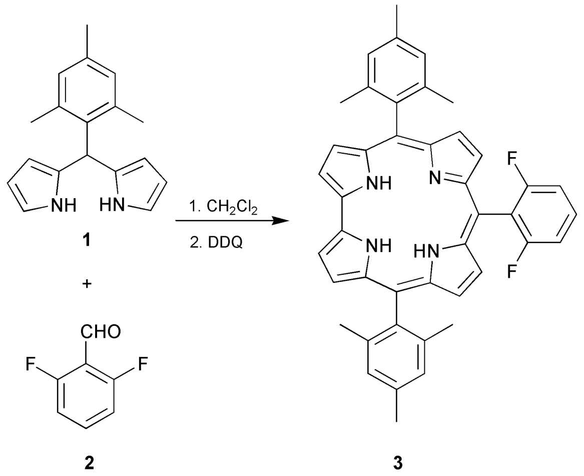
Five unsymmetrically *meso*-substituted corroles have been synthesized from dipyrromethanes and aldehydes in yields of up to 19% *via* a new two-step one-flask procedure.

Although the existence of corroles was reported a long time ago,[1] their chemistry has been overshadowed by the easy accessibility of porphyrin chemistry.[2] Corroles are aromatic tetrapyrrole macrocycles bearing a direct pyrrole–pyrrole link, thereby constituting a bridge between porphyrins (*e.g.* heme) and corrins (*e.g.* vitamin B_{12}). Recently, corrole chemistry has received new impetus due to the discovery of novel ligand properties of this contracted macrocycle[3–5] as well as the advent of efficient synthetic methodologies affording corroles in gram quantities.[6–8] Most of the corrole syntheses known till 1999 (biladiene cyclization,[9] *meso*-carbon or sulfur extrusion of *meso*-thiaporphyrin,[10] or direct synthesis from monopyrrole precursors[11,12]) are lengthy. The very recently reported syntheses of core-modified corroles also require preparation of several precursors.[13,14]

Pioneering studies by Paolesse *et al*.[6] and Gross *et al*.[7,8] have demonstrated that the non-catalyzed reaction of pyrrole with aldehydes results in the formation of *meso*-substituted A_3-corroles. These simple and efficient synthetic methods have already opened a new avenue for in-depth studies of the coordination chemistry of corroles.[5] Nevertheless a potential use of corroles as surrogates for vitamin B_{12} and related compounds in biomimetic models of enzymic catalysis would benefit significantly from the ability to incorporate different groups at distinct sites at the perimeter of the macrocycle. On the other hand it is known that the acid catalyzed reaction of pyrrole with an aldehyde gives an A_4-porphyrin whereas the acid-catalyzed condensation of a dipyrromethane (DPM) with an aldehyde gives the corresponding *trans*-A_2B_2-porphyrin.[15] Hence I assumed that the non-catalyzed reaction of a DPM with a reactive aldehyde would lead to the formation of the corresponding A_2B-type *meso*-substituted corrole. The preliminary results of this study are presented in this paper.

The conditions for the non-catalyzed reaction of pyrrole with aldehydes[6–8] and the stoichiometry of the envisioned reaction prompted me to initiate studies using the following conditions: aldehyde–dipyrromethane ratio, 1 : 2; reaction time, 2 h; rt; a small amount of solvent; and 1 eq. of DDQ as an oxidant. The reaction of mesityldipyrromethane **1**[16] (a potential precursor of facially-encumbered and hence more soluble corroles) and 2,6-difluorobenzaldehyde **2** (bearing electron-withdrawing substituents) was chosen as a model system for the optimization study (Scheme 1). Indeed, condensation of both substrates in methylene chloride for 2 h followed by subsequent reaction with DDQ smoothly afforded the desired corrole **3** in 11% yield (Table 1, entry 1). This initial success quickly led to the systematic study of reaction conditions. In an effort to improve the yield of corrole **3**, the concentration and ratio of reagents, solvent, time, and amount of DDQ were altered. In addition, the influence of some simple additives (TBABr and TBAF) was examined. The results of this study are presented in Table 1.

When the ratio of aldehyde to DPM was changed to 1 : 1 (corresponding to the stoichiometry of porphyrin forming reaction) (entry 2), an appreciable increase in the yield of corrole **3** to 17% was obtained. An increased amount of DDQ gave no further increase in the yield of corrole (entry 3). It is well known that the porphyrin-forming reaction as well as many other macrocyclisation reactions require a low concentration of reactants to achieve reasonable yields. Thus, the corrole-forming reaction was carried out under more dilute conditions (entries 4 and 5). The decrease in concentration of both substrates to 0.27 mol dm^{-3} resulted in a slight increase while further dilution caused a sudden drop in the yield of corrole **3**. Use of a large excess of aldehyde **2** did not give any improvement (entry 6). Hence, for further reactions the ratio of reactants was kept constant at 1 : 1. Because both substrates were still present in the reaction mixture after 2 h, the condensation time was extended (entries 7 and 8). However,



Scheme 1

Table 1 Effects of various conditions on the reaction of mesityldipyrromethane **1** and aldehyde **2**

Entry	DPM **1** (mol dm^{-3})	Ratio **1** : **2**	Time/h[a]	Ratio DDQ: **1**	Yield of corrole **3**[b] (%)
1	0.53	2 : 1	2	1 : 1	11
2	0.53	1 : 1	2	1 : 1	17
3	0.53	1 : 1	2	1.5 : 1	18
4	0.27	1 : 1	2	1 : 1	19
5	0.13	1 : 1	2	1 : 1	10
6	0.27	1 : 2	2	1 : 1	13
7	0.27	1 : 1	5.5	1 : 1	19
8	0.53	1 : 1	16	1 : 1	0
9[c]	0.27	1 : 1	2	1 : 1	12
10[d]	0.27	1 : 1	2	1 : 1	0
11	0.53	1 : 1	2	0.5 : 1	10
12[e]	0.27	1 : 1	2	1 : 1	9

[a] Time of condensation prior to addition of DDQ. [b] Isolated yield. [c] 0.2 eq. of TBABr was added. [d] 0.2 eq. of TBAF was added.[e] $CHCl_3$ was used instead of CH_2Cl_2.

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† Electronic supplementary information (ESI) available: experimental procedures and spectral data for compounds **3** and **10–13**. See http://www.rsc.org/suppdata/cc/b0/b006734m/

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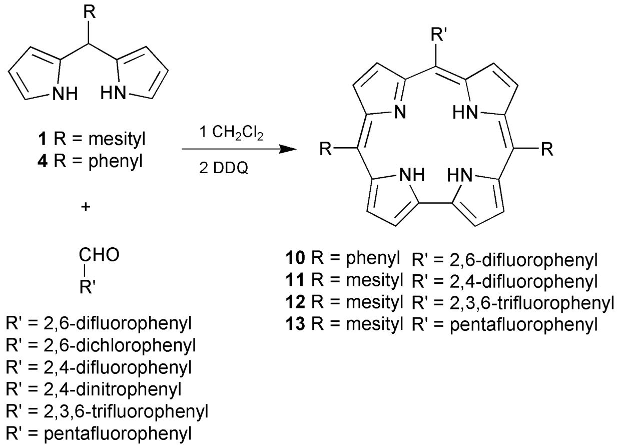
prolonging the reaction time from 2 to 5.5 h did not improve the yield of the product **3** (entry 7). The complete consumption of the substrates was observed after 16 h, then DDQ was added. Surprisingly even traces of corrole **3** were not found in the reaction mixture (entry 8). The idea of adding of soluble inorganic salts was inspired by the beneficial effects of salts observed in the porphyrin-forming reaction.[17] The addition of TBABr resulted in a modest decline in yield whereas no corrole was formed upon reaction in the presence of TBAF (entries 9 and 10). A control experiment with 0.5 eq. of DDQ resulted in a decreased yield of corrole (entry 11). Furthermore, upon changing the solvent from CH_2Cl_2 to $CHCl_3$ the yield of corrole decreased to 9% (entry 12). It is noteworthy to add that no porphyrin was observed under any of these conditions.

The optimized procedure (entry 4) (CH_2Cl_2, conc. of both substrates = 0.27 mol dm^{-3}, 2 h, rt, 1 eq. of DDQ) was applied to a variety of substrates (Scheme 2, Table 2). Reactive aldehydes with various electron-withdrawing groups (F, Cl, NO_2) (**2**, **5**, **6**, **7**, **8**, **9**) were used in conjunction with mesityldipyrromethane **1** and phenyldipyrromethane **4**.[16] In each case with aldehydes possessing at least two fluorine substituents, the corresponding corroles[18] (**10**, **11**, **12** and **13**) were readily isolated in modest yield after straightforward column chromatography. No porphyrin product was observed in these reactions.[19] It was surprising to find that the yields of corroles in the reactions employing 2,4-difluorobenzaldehyde **6** (entry 4) and 2,3,6-trifluorobenzaldehyde **8** (entry 6) were significantly lower than the yield achieved starting from 2,6-difluorobenzaldehyde. On the other hand, 2,6-dichlorobenzaldehyde **5** (entry 3) and 2,4-dinitrobenzaldehyde **7** (entry 5) did not afford any corrole. At present there is no satisfactory explanation for such a significant difference in behavior of these aldehydes. Generally, it is reasonable to assume that a mechanism analogous to that suggested by Gross *et al.*[8] accounts for the formation of corroles from dipyrromethanes. If so, the course of this reaction is not only dependent on the reactivity of the aldehyde (Ar-CHO) but is also influenced by the steric effects of substituents and by the nature of the arylmethylene unit (Ar-CH_2-) as an anionic leaving group.



Scheme 2

Table 2 Yield of corroles formed from various dipyrromethanes (DPM's) and aldehydes

Entry	Aldehyde	DPM	Yield (%)[a]
1	**2**	**1**	19
2	**2**	**4**	9
3	**5**	**1**	0
4	**6**	**1**	4[b]
5	**7**	**1**	0
6	**8**	**1**	10
7	**9**	**1**	8

[a] Isolated yield. [b] Condensation of aldehyde and DPM was performed for 5 h prior to addition of DDQ.

In summary, conditions have been identified for a rational two-step synthesis of A_2B-type *meso*-substituted corroles bearing one fluorinated substituent. The main advantages of this method are as follows: (1) a two-step procedure from commercially available materials, (2) short reaction time, (3) straightforward purification, and (4) reaction at high concentration (thereby easy to scale-up). This approach should prove useful for the preparation of a variety of corroles and may open the door to new practical applications of these macrocycles. Further studies aimed at extending the scope of this method and gaining insight into the influence of various factors on the corrole-forming reaction are in progress.

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18 The purity of each corrole is >99% based on TLC, ^{1}H NMR spectroscopy, and electrospray mass spectrometry. It is noteworthy to add that the ^{1}H NMR spectra of corroles derived from mesityldipyrromethane (**3**, **11**, **12** and **13**) exhibit very sharp signals, in contrast to corrole **10** or 5,10,15-triphenylcorrole[6] which exhibit broad AB patterns.
19 One exception occurred with pentafluorobenzaldehyde **9**, which gave traces (*e.g.* 1%) of 5,15-dimesityl-10,20-bis(pentafluorophenyl)porphyrin.