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Corrole synthesis by dipyrromethane–dicarbinol and 2,2′-bipyrrole condensation

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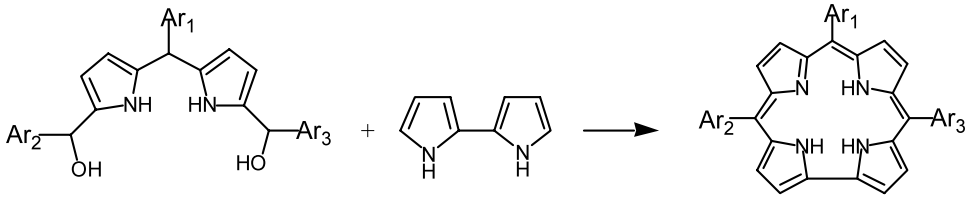
Abstract—A_3 and *trans*-A_2B tris-aryl corroles **1a–c** have been synthesized in up to 12% yield by $BF_3{\cdot}Et_2O$-catalyzed condensation of dipyrromethane–dicarbinol and 2,2′-bipyrrole (1:1 ratio) in acetonitrile at room temperature for 24 h. © 2003 Elsevier Science Ltd. All rights reserved.

Corroles are porphyrin analogues with a bipyrrole ring junction. Recent improvements in their synthetic methodologies have made them affordable, and they have been studied as catalysts, photosensitizers for PDT, etc.[1a–g] One can envision that recently reported efficient synthetic methodologies of corroles (which have a corrin-like molecular skeleton) might be a starting point for the development of the synthesis of vit B12 mimics. Indeed innovations in synthetic methodologies have been growing since 1997 allowing corroles to be prepared in higher yields than the previous *a*,*c*-biladiene cyclization method described by Johnson and Kay.[2] Gryko recently reviewed these new methods which for the most part derive from optimization of conditions used for porphyrin synthesis.[3] Briefly, the way to obtain corrole is by condensation of aldehyde and pyrrole either following a modified Rothemund reaction under acid-catalysis,[4a,b] or under solvent-free conditions on a solid support.[5a–c] Corroles and structurally modified corroles may be synthesized from dipyrromethane condensation with aldehydes[6a–c] and [2+2] condensation of dipyrromethane,[6d] [3+1] condensation of tripyrrane and pyrrole carboxaldehyde,[7] coupling of tetrapyrromethane,[8a–c] or template reaction of 2,2′-bisdipyrrins with manganese.[9] Corroles can result from a porphyrin ring contraction, by detrifluoromethylation of porphyrin,[10] which is reminiscent of a previous method of sulfur extrusion with *meso*-thiaporphyrin.[11a] Finally, methods of corroles and modified corroles synthesis that involve the introduction of a bipyrrole or bifurryl unit at a last stage of the synthetic scheme appear to be unfavorable. Indeed MacDonald condensation of 5,5′-dicarboxylic acid–dipyrromethane with 5,5′-diformyl-2,2′-bifuryl led to 21,24-dioxacorrole in low yield,[11a] while the same condensation performed with 5,5′-diformyl-2,2′-bipyrrole was unsuccessful.[11b,c] The new method described in here[11d,e] for the synthesis of the new 5,10,15-trimesityl



3a-c **4** **1a-c**

Scheme 1. Synthesis of corroles **1a–c** by condensation of dipyrromethane dicarbinols **3a–c** and 2,2′-bipyrrole **4**. a: $R_1=R_2=R_3=$ mesityl; b: $R_1=R_2=R_3=$4-methylphenyl; c: $R_1=$4-methylphenyl, $R_2=R_3=$phenyl.

Keywords: dipyrromethane-dicarbinol; 2,2′-bipyrrole; corrole synthesis.

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corrole **1a**, the known 5,10,15-tris(4-methylphenyl) corrole **1b** and 5,15-bis(phenyl),10-(4-methylphenyl) corrole **1c** (Scheme 1) involving the [2+2] condensation of dipyrromethane-dicarbinol and 2,2′-bipyrrole, is interesting for two reasons: porphyrin analogues have been successfully synthesized this way by dipyrromethane dicarbinol condensation with dipyrromethane,[12a–e] and recently Pawlicki et al. similarly showed that pyrrole-carbinols undergo condensation with pyrroles leading to corroles.[13a,b]

Both building blocks were prepared following literature procedure[12b,17a–d] with some major modifications. Diacyl dipyrromethane **2a**–**c**[12b] were prepared by acylation of 5-mesityldipyrromethane[14a,b] in 55% yield[15a] (instead of the 19% reported[12b]) and 5-(4-methylphenyl)dipyrromethane[14a,b] in 42% yield,[15b] respectively. The same methodology was applied for the synthesis of **2b**[14a,b] following reported procedures.[12,14] Subsequent reduction of **2a** with $NaBH_4$ (300 mol equiv.) afforded the dipyrromethane dicarbinol **3a**; the low conversion is probably due to steric hindrance of the methyl groups at positions 2,6.[16] However the conversion of **2b**–**c** into **3b**–**c** using 50 mol equiv. $NaBH_4$ was almost quantitative.[12,16b,c] Bi-pyrrole **4**[17a–d] was prepared by benzoyl-pyrrole coupling catalyzed by palladium acetate (5% mol equiv.) in hot acetic acid, followed by amide hydrolysis.[18]

Inspired by previously reported work on condensation reactions of dipyrromethane dicarbinol with dipyrromethane leading to porphyrins,[12a–f] condensation of **3a**–**c** and **4** was performed after careful examination of each of the following parameters: the nature of solvent and of the acid catalyst, concentration of reagents and the acid, and the reaction time (Table 1).[19a] Published conditions which work well for the synthesis of porphyrins were selected for the synthesis of **1a**–**c**: the reaction was performed in acetonitrile at 0°C or at room temperature, using $BF_3{\cdot}Et_2O$ 2 mM as catalyst in the presence of NH_4Cl or NaCl 100 mM, or TFA 15–30 mM without salt (previous reports indicated that condensations catalyzed by TFA showed little or no salt effect[12b]), 30 min reaction time, followed by DDQ oxidation.[12a–e] The reported condensation of dipyrromethane–dicarbinol and dipyrromethane leading to porphyrin used a 1:1 ratio, similarly the ratio dipyrromethane–dicarbinol **3a**–**c** to bipyrrole **4** was 1:1 since both species contain two pyrrole units. A prior modification had to be introduced to the published method due to the limited solubility of **4**. The maximum affordable concentration of **4** was 1.1 mM which is in contrast to 2.5 and 10 mM optimum concentration reported.[12a,b]

Yields of **1a** on a micro-scale synthesis appears to be strongly dependent upon the reaction time. A reaction time of 30 min led to a maximum of 1.5% yield (entries 1–4) while prolonging the reaction time to 24 h gave yields up to 12% (entries 5–9). The formation of **1a** is also dependent on the choice of acid-catalyst. After 30 min reaction time, **1a** was obtained in 1.5% yield with $BF_3{\cdot}Et_2O$ catalyst (entries 1–2), but **1a** was not formed when TFA was used (entries 3–4). Similarly at 24 h reaction time, a 9–12% yield of **1a** was obtained with $BF_3{\cdot}Et_2O$ (entries 5–6) and 4–5% with *p*-toluenesulfonic acid (PTSA) (entry 7). These experiments clearly show that $BF_3{\cdot}Et_2O$ is the best catalyst for the synthesis of **1a** in contrast to TFA. The possible advantage of TFA was that previous reports showed that 5-mesityl dipyrromethane species are less susceptible to acidolysis in the presence of TFA than in the presence of $BF_3{\cdot}Et_2O$.[20] But in fact no corrole is formed. However, our results are in good agreement with previous reports showing that $BF_3{\cdot}Et_2O$ was a good catalyst for the synthesis of oxa-corroles species, in condensations of hydroxymethylfuran and pyrroles,[13] and also dipyrromethane carbinols[11e] and dipyrromethane presumably due to its templating effect which should favor the formation of corrole.[11e,13] The temperature seems to have a substantial effect in the formation of **1a** since

Table 1. Yields of corroles **1a** (entries 1–9), **1b** (entries 10–11) and **1c** (entries 12–13) by condensation of dipyrromethane–dicarbinol **3a**–**c** and bipyrrole **4** (each at 0.038 mmol/36 mL solvent) under various reaction conditions

Entry	Solvent	Acid-cat.	Salt	*T* (°C)	Time (h)	Yield (%)[c]
1	MeCN	$BF_3{\cdot}Et_2O$	NH_4Cl	25	0.5	1.5
2	MeCN	$BF_3{\cdot}Et_2O$	NH_4Cl	0	0.5	Trace[d]
3	MeCN	TFA	–	0	0.5	0
4	MeCN	TFA	–	25	0.5	0
5	MeCN	$BF_3{\cdot}Et_2O$	NH_4Cl	25	24	12.0
6	MeCN–$CHCl_3$	$BF_3{\cdot}Et_2O$	NH_4Cl	25	24	9.0
7	MeCN	PTSA	NaCl	25	24	5.0
8[a]	MeCN	$BF_3{\cdot}Et_2O$	NH_4Cl	25	24	3.2
9[b]	MeCN	$BF_3{\cdot}Et_2O$	NH_4Cl	25	24	1.0
10	MeCN	$BF_3{\cdot}Et_2O$	NH_4Cl	25	0.5	0
11	MeCN	$BF_3{\cdot}Et_2O$	NH_4Cl	25	24	6.2
12	MeCN	$BF_3{\cdot}Et_2O$	NH_4Cl	25	0.5	Trace
13	MeCN	$BF_3{\cdot}Et_2O$	NH_4Cl	25	24	8.1

Other amounts of **3a** or **4**:

[a] 0.258 mmol/245 mL.

[b] 0.088 mmol/36 mL (suspension).

[c] Isolated yields.

[d] This fraction (entry 2) was characterized by MS (ESI^+) only, and checked by TLC against authentic standard.

after 30 min only a trace amount of **1a** was detected when the reaction was performed at 0°C (entry 2), while 1.5% yield was obtained at room temperature (entry 1). The reaction depends very little on the solvent since 9% were obtained in a $MeCN/CHCl_3$ mixture (entry 6), while 12% was obtained in 100% MeCN (entry 5). Scale-up appears to have a dramatic effect on the corrole yield. Indeed the reaction performed under the conditions described in entry 5 but after scale-up by 6.8 fold (0.254 mmol) led to **1** in only 3.2% yield (entry 8) while 12% yield was obtained on a 0.038 mmol scale (entry 5). Finally using an excess of reagents, getting over the solubility limit by employing a suspension (0.088 mmol/36 mL) and sonicating the mixture before introducing acid, did not lead to any improvement (entry 9). In all cases (entries 1–9) the formation of significant side products was observed,[19a] whose origin was not investigated (scrambling, acidolysis…). Conditions described in entries 1 and 5 were applied for the synthesis of less sterically encumbered corroles **1b** and **1c**. It was found that A_3 corrole **1b** was not formed after 5 min (data not shown), neither after 30 min (entry 10), and was obtained in 6.2% yield after 24 h reaction time (entry 11).[21a] Similarly *trans*-A_2B corrole **1c** was obtained in trace amount after 30 min (entry 11), and in 8.1% yield after 24 h reaction time (entry 12).[21b] It appeared that long reaction times are crucial for the formation of corroles **1a**–**c**.

Other methods were checked for the preparation of **1a** to obtain a comparison of yields. Paolesse's method[4a,b] using condensation of mesitaldehyde and pyrrole in refluxing acetic acid afforded **1a** in only 0.32%,[19b] while 6% yield was reported with **1b**.[4b] This condensation performed under Gross's conditions did not afford **1a**[5c] or **1b**–**c** neither. Gryko's approach[6a–c] applied to the preparation of **1a**, using the condensation of mesityl dipyrromethane and mesitaldehyde, did not work well in our hands since **1a** was always obtained in only 0.5% yield.[19c] However **1b**–**c** were obtained in 5 and 6%, respectively.

In conclusion, we have developed a new methodology for corrole synthesis based on condensation of 2,2′-bipyrrole and dipyrromethane dicarbinol giving up to 12% yield for the preparation of **1a**–**c**. For comparison, porphyrins synthesized by condensation of dipyrromethane dicarbinol and dipyrromethane are usually obtained in about 10–30% yield.[12a–e] The particular case described here may suffer from the low solubility of **4** which might be overcome by introduction of substituents increasing solubility (e.g. alkyl chains). A particular application of this method would be (1) the regioselective introduction of substituents at the bipyrrole unit of corrole, by a prior preparation of substituted bipyrrole synthon before condensation with dipyrromethane–dicarbinol species, and (2) the synthesis of ABC-corroles.

Acknowledgements

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15. (a) **1,9-Bis(mesitoyl)-5-mesityldipyrromethane (2a)**: Following reported procedure[12a] but modified as follows: a solution of EtMgBr (1.98 mL, 5 mmol) was carefully added to a solution of mesityl–dipyrromethane[14] (0.264 g, 1 mmol) in THF (25 mL) under N_2. The pale-tan yellowish solution was stirred for 30 min at room temperature then a solution of mesitoyl chloride (prepared in situ) (0.831 mL, 5 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for an additional 2 h at room temperature, then quenched with a saturated solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2. After washings with 1 M NaOH (250 mL) and water (2×150 mL), the solvent was evaporated, the residue dried and subjected to chromatography (SiO_2, 17×3 cm, eluent CH_2Cl_2–EtAc (25:1 vol.)). After elution of some red–pink stuff, the desired yellow fraction was collected. Evaporation of solvent afforded a red–brown residue which was resuspended in hexanes (50 mL, sonication), and filtered to afford a white solid (0.254 g, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.03 (brs, 2H), 6.91 (s, 2H), 6.84 (s, 4H), 7.94 (m, 4H), 6.40 (s, 2H), 6.11 (s, 2H), 5.84 (s, 1H), 2.29 (s, 3H), 2.28 (s, 6H), 2.13 (s, 12H), 2.07 (s, 6H). HR-MS (EI$^+$, m/z) = 556.3097 (calcd for $C_{38}H_{40}N_2O_2$ 556.3090), 410.2370 (M^+–MesCO), 263.1518 (M^+–MesCO). TLC (silica, ethyl acetate–dichloromethane, 1:25 vol.) R_f 0.40. (b) **1,9-Bis(4-methylbenzoyl)-5-(4-methylphenyl)dipyrromethane (2b)** was prepared following the procedure described for **2a** on a same scale of starting material (1 mmol) to afford **2b**[12e] (0.188 g, 40%). TLC (silica, ethyl acetate–dichloromethane, 1:25 vol.) R_f 0.35. (b) **1,9-Bis(benzoyl)-5-(4-methylphenyl)dipyrromethane (2c)** was not prepared following Wallace et al.[12f] methodology but following the procedure described for **2a–b** using a same scale of starting material (1 mmol) to afford **2c** as brownish flakes (0.115 g, 20%). TLC (silica, ethyl acetate–cyclohexane, 4.5:6.5 vol.) R_f 0.30. Mp 80–85°C (lit.[12e] mp 93–95°C.
16. (a) **1,9-Bis(mesitoyl)-5-mesityldipyrromethane-diol (3a)** was prepared as follows by adaptation of Cho's procedure reported for other dipyrromethane dicarbinol.[12a] A solution of diacyl–dipyrromethane **2a** (0.230 g, 0.413 mmol) in dry THF/methanol (2:1 vol., 50 mL) under magnetic agitation was reduced with portions of $NaBH_4$ (3.12 g, 82.4 mmol) and stirred for 3 h at room temperature (internal temperature control sometimes indicated temperature increase at ca. 38°C). As described for other dipyrromethane–dicarbinol species,[12a–e] an initial yellow spot showed up (supposed to be the mono-reduced species R_f 0.3) followed by a second one (supposed to be the bis-reduced compound (TLC, SiO_2, ethyl acetate–dichloromethane, 1:25 vol. R_f 0.15, ethyl acetate–hexanes 1:2 vol. R_f 0.5). Before complete reduction of **2** (ca. 30% conversion) was achieved, new spots showed up on TLC. The reaction was quenched with water (50 mL) at that stage and the reaction mixture was extracted with CH_2Cl_2 (3×100 mL) and dried (K_2CO_3). The solvent was evaporated, then the residue was resuspended in MeCN, filtered and the yellow filtrate was evaporated to afford a yellow oil containing **3a** as the main product. Since **3a** is metastable (as previously reported with other dipyrromethane dicarbinol species[12a–e]) no attempt of purification or isomer separation was done, and the crude mixture (IR: 3300 cm^{-1} (br s, OH)) was used for the next step. (b) **1,9-Bis(benzoyl)-5-(phenyl)dipyrromethane-diol (3b)** was prepared following the procedure described for **2a** on a 232 μmol scale of starting material **2b** (110 mg) to afford **3b** as a pale yellow oil assuming quantitative yield. TLC (silica, ethyl acetate–cyclohexane, 1:3 vol.). (c) **1,9-Bis(benzoyl)-5-(4-methylphenyl)dipyrromethane-diol (3c)** was not prepared by $LiAlH_4$ reduction as described by Wallace et al.,[12g] but following an adaptation of the procedure described for **3a–b** on a 258 μmol scale of starting material **2c** (115 mg) to afford **3c** as a yellow oil. ^{1}H NMR TLC (silica, ethyl acetate–cyclohexane, 1:3 vol.) R_f 0.40.
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18. **2,2′-Bipyrrole (4)** was prepared according to Itahara's procedure, but since the published conditions did not work in our hands, the following modifications were introduced. A solution of 1-benzoylpyrrole (1 g, 5.84 mmol) and palladium acetate (0.131 g, 0.584 mmol) in acetic acid (800 mL) was heated at 65°C for several hours and monitored by TLC. The mixture was evaporated to give an orange oil which was filtered through an alumina pad (8×2 cm, CH_2Cl_2–hexanes, 3/7 vol.). The residue was treated in methanol–water (2:1 vol.) at 60°C for 6 h to afford **4** (0.092 g, 12%). Spectroscopic data[17c] and the melting point were compared against an authentic standard purchased from Alfa Aesar. Mp 185–188°C (lit.[17a] mp 189–190°C).

19. **5,10,15-Tris(mesityl) corrole (1a)**. (a) *Dipyrromethane–dicarbinol method*. Diol **3a** (22 mg, 0.038 mmol (entries 1–7); or 150 mg, 0.258 mmol (entry 8) or 50 mg, 0.088 mmol (entry 9)) was immediately dissolved in 36 mL (entries 1–7) or 245 ml (entry 8) of solvent (MeCN (entries 1–4, 8–9) or MeCN–$CHCl_3$ 1:1 vol. (entry 6)) with **4** (4.8 mg, 0.038 mmol (entries 1–7); 32.6 mg, 0.258 mmol (entry 8), or 11 mg, 0.088 mmol (entry 9) from a stock solution sonicated for 5 min). After stirring for a few minutes (and cooling the solution at 0°C (ice bath)(entries 2–3)), NH_4Cl (46 mg, 0.887 mmol (entries 1–2, 5–6, 9); or 313 mg, 6 mmol (entry 8); or 46 mg, 0.887 mmol (entry 9)) or NaCl (51 mg, 0.887 mmol (entry 7)) was added followed by catalyst solution: $BF_3{\cdot}Et_2O$ (100 μL of a stock solution mM in MeCN, 0.008 mmol, 2 mM; entries 1–2, 5–6, 8; or 681 μL (entry 8)) or TFA (81 μL, 1.056 mmol, 30 mM, entries 3; or 40 uL, 0.525 mmol, 15 mM, entry 4) or PTSA (100 uL of a mM solution in MeCN, entry 7) over a period of 1 min. While stirring, the reaction was monitored by TLC and absorption spectroscopy following Rao et al. procedure.[12b] After 30 min (entries 1–4) or 24 h (entries 5–8) stirring at room temperature, DDQ (10 mM solution in toluene) was carefully added to the system and stirring was carried on for 1 h (portionwise addition (ca. 0.2–0.4 mL in total) was carried out on 3 mL aliquots until the desired spot becomes intense, making sure not to add too much DDQ, that would lead to corrole over-oxidation and an incorrect diagnosis of no corrole formation). Then Et_3N (0.139 mL, 1 mmol) was added and after 5 min stirring, the entire reaction mixture was filtered through a silica pad (13×3 cm) and eluted with CH_2Cl_2 until the eluent was no longer dark (ca. 100 mL). After evaporation of the solvent, the residue was subjected to chromatography (SiO_2, 20×5 cm, gradient elution using hexanes–CH_2Cl_2 until the ratio reaches 2:1 vol.) the violet fraction containing **1a** (TLC SiO_2, CH_2Cl_2/toluene 95:1 vol. R_f 0.95) shows up just before a pink and blue fractions at R_f 0.50–0.70. **1a** was obtained as a violet-green solid (0.3–3.2 mg, 1–12% (entries 1–7); 5.3 mg, 3.2% (entry 8)) after recrystallisation in hexanes–CH_2Cl_2 (1:9 vol.). (b) *Paolesse's method*[4a,b] was applied to the synthesis of **1a** by refluxing a solution of mesitaldehyde (2.9 mL, 20 mmol) and pyrrole (4.2 mL, 60 mmol) in acetic acid (250 mL) for 4 h. After cooling, addition of H_2O (300 mL), NaCl (10 g) and stirring for 30 min, the mixture was filtered. The resulting cake was washed with CH_2Cl_2 (3×150 mL) and the solution was filtered through a silica pad and chromatographed as described in Ref. 19a to afford **1a** (0.010 g, 0.32%). (c) *Gryko's method*[6a–c] applied to the synthesis of **1a**: to a degassed solution of mesityldipyrromethane (0.264 g, 1 mmol) and mesitaldehyde (0.072 mL, 0.5 mmol) in CH_2Cl_2 (109 mL) was added BF_3Et_2O (0.052 mL, 0.038 mmol). After stirring for 4 h at room temperature under N_2, DDQ powder was added (0.227 g, 1 mmol) and the reaction mixture was stirred for an additional 15 min. After filtration through a silica pad (13×2 cm, eluent CH_2Cl_2) and evaporation of the solvent, the residue obtained was subjected to chromatography using the same conditions as in Ref. 19a to afford **1a** (0.017 g, 0.5%) and tetramesityl-porphyrin (0.035 g, 9%). (d) *Spectroscopic data of **1a***. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.82 (d, $J=3.38$ Hz, 2H), 8.39 (d, $J=4.72$ Hz, 2H), 8.27 (d, $J=3.90$ Hz, 2H), 8.22 (d, $J=4.67$ Hz, 2H), 7.20 (m, 6H), 2.58 (s, 5,15-*p*-CH_3, 6H), 2.56 (s, 10-*p*-CH_3, 3H), 1.90 (s, 5,15-*o*-CH_3, 12H), 1.85 (s, 10-*o*-CH_3, 6H), –3.0 (vbrs, 3H). UV–vis. (CH_2Cl_2) λ (Abs.): 391 (sh, 0.87), 406 (1.05), 423 (sh, 1.19), 561 (0.11), 604 (0.07), 635 (0.04) nm. HR-MS (EI^+, m/z) = 652.3566 (calcd for $C_{46}H_{44}N_4$: 652.3566). TLC (silica, hexane/dichloromethane, 2:1) R_f 0.51.

20. Lee, C.-H.; Li, F.; Iwamoto, K.; Dadok, J.; Bothner-By, A. A.; Lindsey, J. S. *Tetrahedron* **1995**, *51*, 11645–11672.

21. (a) **5,10,15-Tris(4-methylphenyl) corrole (1b)**[8c] and **5,15-bis(phenyl)-10-(4-methylphenyl) corrole (1c)**[4b] were prepared by adaptation of the dipyrromethane–dicarbinol procedure described in Ref. 19 (a). They were characterized by ^1H NMR, MS and UV–vis and were as previously described.[4b,8c]