Pergamon

*Tetrahedron Letters*, Vol. 38, No. 23, pp. 4113-4116, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00839-3

# An Improved Synthesis of Corrole

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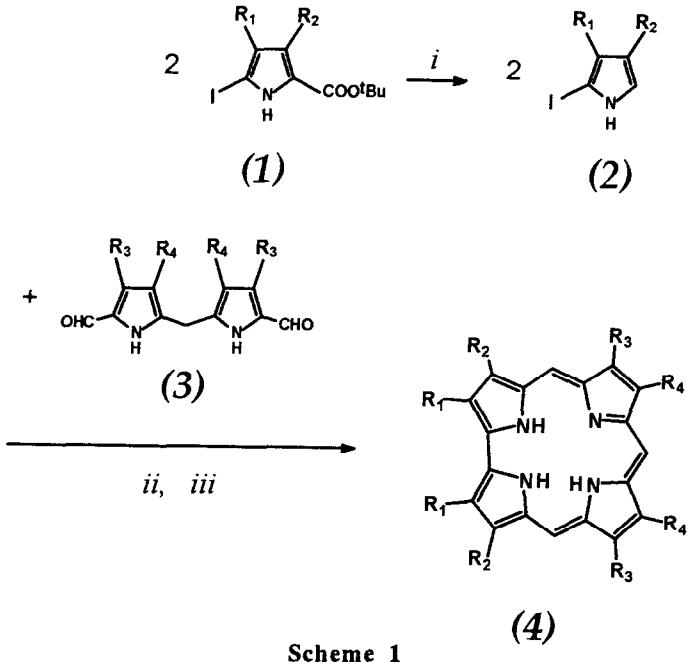
**Abstract:** Reaction of two equivalents of 5-iodo-3,4-dialkylpyrrole, *in situ*-generated from the corresponding tertiary butyl ester, with 5,5'-diformyldipyrromethane afforded corrole macrocycle in 20% yield. Utilization of readily available tertiary butyl 5-iodo-3,4-dialkylpyrrole-2-carboxylate and 5,5'-diformyldipyrromethane opens a simple route to corrole. © 1997 Elsevier Science Ltd.

Corrole, a cyclic tetrapyrrole with an aromatic 18 π-electron system, contains a direct linkage between the two adjacent pyrrole rings,[1,2] just as the corrin skeleton in vitamin $B_{12}$. Corrole is formally derived from porphyrin macrocycle by deleting one of the four *meso*-carbons. The physical properties of corrole are quite distinct from those of porphyrin due to the absence of a single carbon atom. It has been reported, for instance, that the iron atom of corrole[3] is in ferryl Fe(IV) state at room temperature, in marked contrast to the ferric iron in porphyrin. The direct pyrrole-pyrrole linkage in corrole is generally formed by ring closure of a linear tetrapyrrole, 1,19-dideoxybiladiene-*ac*. Unfortunately, the requisite pyrrole precursors for the biladiene are obtained only after lengthy synthesis. In view of recent increasing attention to corroles,[1-4] a simple pathway is to be developed. We report here a convenient synthesis of corrole with readily available materials.

Conventional corrole synthesis utilizes 1,19-dideoxybiladiene-*ac* dihydrobromide as the direct precursor.[1,2] The biladiene is prepared from condensation of two equivalents of a 3,4-dialkylpyrrole with a 5,5'-diformyldipyrromethane.[1] Alternatively, the biladiene is obtained from a dipyrromethane-5,5'-dicarboxylic acid and two equivalents of a 2-formyl-3,4-dialkylpyrrole as well.[5-7] Preparation of 3,4-dialkylpyrroles[5,8] in the first method is rather laborious, and 2-formyl-3,4-dialkylpyrroles in the second route are derived from 3,4-dialkylpyrroles with Vilsmeier formylation.[5] A third approach[9] using 1,19-dibromobiladiene-*ac* dihydrobromide was proposed in 1966 by Harris et al. However, the dibromobiladiene procedure[9] has been little used because the preceding bromoaldehyde is much less accessible than 3,4-dialkylpyrrole.[1,9] Pandy et al.[10] recently improved the third route. They synthesized 2-bromo-5-formyl-3,4-dialkylpyrroles with less effort after modification of the recipe of Paine and Dolphin.[11] The modified procedure[10], however, still involves a series of transformations starting from careful oxidation for the methyl

group in the initial pyrrole, subsequent protection of the resultant formyl function, brominative decarboxylation of acid residue, and the final regeneration of the protected group.




**Scheme 1**

Reagents and conditions: i) 30% HBr in acetic acid, r.t., 30 min. ii) 60°C, 30 min. in methanol. iii) pyridine:methanol = 1:10 (v/v), reflux, 30 min.

In the course of our corrole synthesis, it occurred to us that 3,4-dialkyl-5-iodopyrrole rather than 2-bromo-5-formyl-3,4-dialkylpyrroles[9, 10] may be used. In addition, the formyl group in 2-bromo-5-formyl-3,4-dialkylpyrrole may be transferred into the dipyrromethane unit. These alterations in the synthetic design can be accomplished if we employ two distinct precursors, *tert*-butyl 3,4-dialkyl-5-iodo-2-carboxylate (**1**) and the dipyrromethane dialdehyde (**3**) (Scheme 1). Utilization of the derivatives **1** and **3**, readily accessible with the established procedures,[13-15] offers advantage to circumvent the tedious preparation of 3,4-dialkylpyrrole, 3,4-dialkyl-2-formylpyrrole, or 2-bromo-3,4-dialkyl-5-formylpyrrole. The tertiary butyl ester functionality in **1** can be effectively cleaved and decarboxylated by hydrogen bromide dissolved in acetic acid. The *in situ*-generated 2-free iodopyrrole (**2**) was reacted with **3** to yield an intermediate linear tetrapyrrole, 1,19-diiodobiladiene-*ac* dihydrobromide. The biladiene, without isolation, was cyclized into corrole (**4**) in refluxing methanol-pyridine. With the one-pot procedure as illustrated in Scheme 1, we obtained corroles in 15 to 20% yields, in comparable

with those in the previous syntheses. A small amount of contaminating porphyrin from the self-condensation of 5,5'-diformyldipyrromethane can be easily separated by column chromatography. The present method making use of readily accessible materials is not only promising for a large scale preparation but also flexible to afford various corroles with diverse substituent patterns[16-18] if we select appropriate β-substituents on the pyrrole precursors.

## ACKNOWLEDGMENTS

This work was supported by the Scientific Research Foundation of Kyoto Pharmaceutical University.

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16. 2,8,12,18-Tetraethyl-3,7,13,17-tetramethylcorrole (**4a**: $R_1=R_4=C_2H_5$, $R_2=R_3=CH_3$). *5-tert*-Butyloxycarbonyl-3-ethyl-4-methylpyrrole-2-carboxylic acid[13] was treated with iodine/potassium iodide in methanol[15] to afford *tert*-butyl 4-ethyl-5-iodo-3-methylpyrrole-2-carboxylate (**1a**: $R_1=C_2H_5$, $R_2=CH_3$) in 82% yield. The iodopyrrole **1a** (0.256 g, 0.77 mmole), dissolved in 1.5 ml of 30% hydrogen bromide in acetic acid, was stirred at room temperature for 30 minutes to change it into the 5-iodopyrrole **2a** ($R_1=C_2H_5$, $R_2=CH_3$). 5,5'-Diformyl-3,3'-diethyl-4,4'-dimethyldipyrromethane[14] (**3a**:

$R_3$=$CH_3$, $R_4$=$C_2H_5$) (100 mg, 0.35 mmole) dissolved in 10 ml methanol was subsequently added dropwise to the iodopyrrole solution, and the mixture was stirred at 60°C for 30 minutes. Thin-layer silica-gel chromatography at this stage indicated the formation of corrole as well as a trace amount of porphyrin. After solvent evaporation and addition of 1 ml pyridine and 10 ml methanol to the residue, the solution was refluxed for 30 more minutes. The solvent was evaporated to dryness, and the residue was subject to column chromatography (silica gel, 2% methanol in dichloromethane). A small amount (less than 3% relative to corrole) of contaminating porphyrin from self-coupling of the diformyldipyrromethane first appeared, followed by the main fraction of corrole **4a**. Crystallization (dichloromethane/petroleum ether) afforded dark thin-needles (37 mg, 22 %). $^1$H NMR ($CDCl_3$): δ 9.81 (s, 2H, *meso*-H), 9.67 (s, H, *meso*-H), 3.96 (m, 8H, 4x$CH_2$$CH_3$), 3.48 (s, 6H, 2x$CH_3$), 3.44 (s, 6H, 2x$CH_3$), 1.74 (m, 12H, 4x$CH_2$$CH_3$), -3.19 (br s, 3H, NH). UV/vis (dichloromethane/1% pyridine): $\lambda_{max}$ (logε); 395 (5.17), $405_{sh}$, 535 (4.26), 547 (4.24), and 591 (4.33). Ms: m/z, 467 ($MH^+$). Anal. calcd. for $C_{31}H_{38}N_4$: C, 79.79; H, 8.21; N, 12.00. Found: C, 79.5; H, 7.9; N, 12.2.

17. 2,3,7,8,12,13,17,18-Octamethylcorrole (**4b**: $R_1$=$R_2$=$R_3$=$R_4$=$CH_3$). Corrole **4b** (yield, 20%) was prepared from *tert*-butyl 3,4-dimethyl-5-iodopyrrole-2-carboxylate[15] (**1b**: $R_1$=$R_2$=$CH_3$) and 5,5'-diformyl-3,3',4,4'-tetramethyldipyrromethane[14] (**3b**: $R_3$=$R_4$=$CH_3$) just as for corrole **4a**. $^1$H NMR ($CDCl_3$): δ 10.14 (s, 2H, *meso*-H), 9.98 (s, H, *meso*-H), 3.59 (s, 6H, 2x$CH_3$), 3.51 (s, 6H, 2x $CH_3$), 3.55 (s, 6H, 2x$CH_3$), 3.40 (s, 6H, 2x$CH_3$), -3.46 (br s, 3H, NH). UV/vis (dichloromethane/1% pyridine): $\lambda_{max}$ (logε); 396 (5.31), $405_{sh}$, 535 (4.32), 548 (4.29), and 592 (4.38). Ms: m/z 411 ($MH^+$). Anal. calcd. for $C_{27}H_{30}N_4$: C, 78.99; H, 7.36; N, 13.65. Found: C, 78.5; H, 7.2 ; N, 13.2.

18. 3,17-Diethyl-8,12-di(2-methoxycarbonylethyl)-2,7,13,18-tetramethylcorrole (**4c**: $R_1$=$C_2H_5$, $R_2$= $R_3$ =$CH_3$, $R_4$=$CH_2CH_2COOCH_3$). Corrole **4c** (yield, 16%) was prepared from *tert*-butyl 4-ethyl-5-iodo-3-methylpyrrole-2-carboxylate (**1a**: $R_1$=$C_2H_5$, $R_2$=$CH_3$) and 5,5'-diformyl-3,3'-di(2-methoxy-carbonylethyl)-4,4'-dimethyldipyrromethane[14] (**3c**: $R_3$=$CH_3$, $R_4$=$C_2H_4CO_2CH_3$) just as for corrole **4a**. $^1$H NMR ($CDCl_3$): δ 9.36 (s, 2H, *meso*-H), 9.18 (s, H, *meso*-H), 4.23 (t, 4H, 2x$CH_2$$CH_2CO$), 3.83 (q, 4H, 2x$CH_2$$CH_3$), 3.70 (s, 6H, 2x$OCH_3$), 3.57 (s, 6H, 2x$CH_3$), 3.45 (s, 6H, 2x$CH_3$), 3.19 (t, 4H, 2x$CH_2CH_2$$CO$), 1.72 (t, 6H, 2x$CH_2$$CH_3$), -3.26 (br s, 3H, NH). UV/vis (dichloromethane/1% pyridine): $\lambda_{max}$ (logε); 397 (5.20), $407_{sh}$, 537 (4.28), 548 (4.30), and 591 (4.34). Ms: m/z, 582 ($M^+$). Anal. calcd. for $C_{35}H_{42}N_4O_4$: C, 72.14; H, 7.26; N, 9.61. Found: C, 71.7; H, 7.1; N, 9.4.

(*Received in Japan* 21 *March* 1997; *revised* 21 *April* 1997; *accepted* 28 *April* 1997)