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Synthesis of Corroles Bearing up to Three Different Meso Substituents

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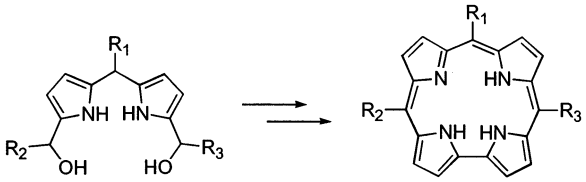
ABSTRACT



We have developed a new method that affords regioisomerically pure corroles possessing up to three different substituents at the meso positions. The corrole formation reaction involves the acid-catalyzed condensation of a dipyrromethane-dicarbinol with pyrrole followed by oxidation with DDQ. ABC-Type corroles were synthesized for the first time according to this procedure.

Corroles,[1] considered as intermediates between corrins and porphyrins, are currently one of the most intriguing research targets among porphyrinoids. Interest in corroles was induced by the discovery of their remarkable ability to stabilize high oxidation states of metals[2] and by the considerable synthetic developments made during past few years. Progress in coordination chemistry of corroles[3] led also to the use of their complexes as catalysts in different oxidation reactions.[4]

The discovery of simple procedures for the synthesis of meso-substituted corroles[5] has prompted several groups to develop a research program in this area.[6−8] Although these methods provide efficient routes to A_3-corroles and *trans*-A_2B-corroles, the inevitable formation of porphyrins as side-products is a troublesome limitation. Indeed, it is well-known that the separation of porphyrins and corroles is very difficult due to their similar physical properties. Moreover, for particular purposes corroles with up to three different meso substituents are needed. The recent synthesis of ABCD-porphyrins appeared to us as a model pathway for the preparation of meso-substituted ABC-corroles.

Indeed, the reaction of dipyrromethane-dicarbinols with dipyrromethanes under carefully optimized nonscrambling conditions afforded porphyrins in 14−40% yield.[9−11]

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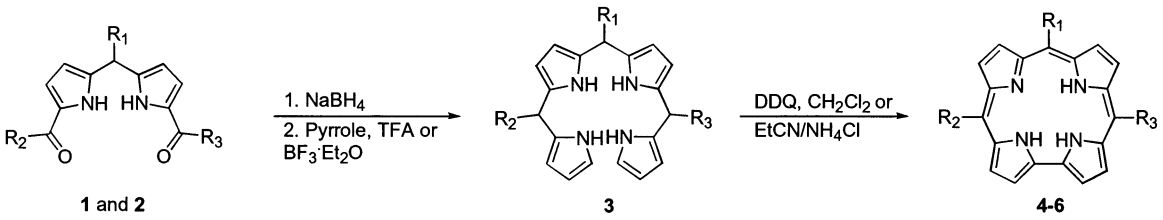
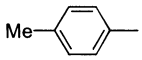
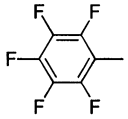
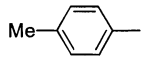
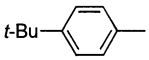
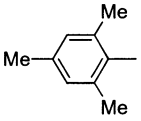
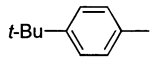
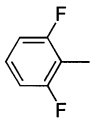
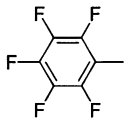
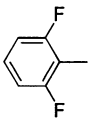
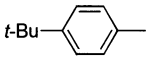
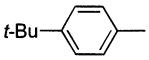
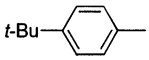
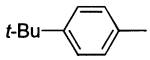
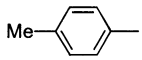
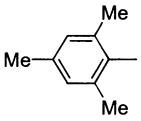
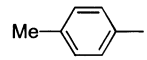
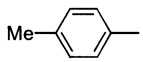
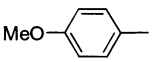
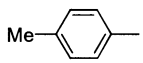
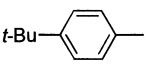
Scheme 1[a]



diacyl compound	R_2	R_1	R_3	product	method	yield
A_3						
1a				**4**	A	25%
***trans*-A_2B**						
1b				**5a**	A	30%
1c				**5b**	A	17%
1d				**5c**	A	54%
1e		H		**5d**	A	0%
1f				**5e**	A	16%
1g				**5f**	B	41%
ABC						
2a				**6a**	B	36%
2b				**6b**	A	51%

[a] Method A: Dicarbinol, (prepared via the reduction of 1.0 mmol of diacyldipyrromethane) was dissolved in pyrrole (3.5 mL, 50 mmol), and 0.2 mL of the pre-prepared solution of TFA (100 μl) in MeCN (10 mL) was added with vigorous stirring. After 10 min at room temperature the whole reaction mixture was transferred to larger flask using CH_2Cl_2 (400 mL). Then DDQ (680 mg, 3 mmol) in THF (3 mL) was added and the reaction mixture was stirred for 1 h and purified by chromatography.
Method B: Dicarbinol, (prepared via the reduction of 1.0 mmol of diacyldipyrromethane) was dissolved in pyrrole (10 mL, 145 mmol) and $BF_3{\cdot}Et_2O$ (18.7 μL, 0.15 mmol) was added with vigorous stirring. After 7 min at room temperature the whole reaction mixture was transferred to larger flask using CH_2Cl_2 (300 mL) and neutralized with NaOH (0.1 M). The organic layer was washed with water, dried and evaporated. The oily residue was chromatographed. Bilane (0.5 mmol) was dissolved in EtCN (250 mL) and NH_4Cl (267 mg, 5.0 mmol) was added. Subsequently DDQ (340 mg, 1.5 mmol) was added, the reaction mixture was stirred for 1 h, filtered, evaporated and purified by chromatography.

Keeping this in mind, we assumed that the reaction of the corresponding dicarbinols with pyrrole would lead to bilanes (tetrapyrranes) then into corroles by oxidative radical coupling.[12] This multiple-step method would eliminate competitive formation of porphyrinogens and thereby open an avenue to the synthesis of a broad range of corroles bearing various substituents in different positions.

The dipyrromethane-dicarbinol precursor is the key de-

rivative of such a method. Either it can be directly transformed to the desired corrole in a one-pot reaction (method A) or the cyclization can be performed in two steps with intermediate purification of the bilane (method B).

Symmetrical diacyl dipyrromethanes **1a**−**g** were obtained according to Lindsey procedures (see Supporting Information).[9] Diacyldipyrromethane **1b** has been chosen to optimize the reaction conditions in method A (Table 1, Scheme 1).

Table 1. Optimization of Conditions for Transformation of Dicarbinol Derived from Diacyldipyrromethane **1b** into Corrole **5a**[a]

entry	solvent (first step)	time of first step (min)	solvent (second step)	TFA/**1b** (mM/mM)	yield of **5a** (%)[b]
1[c,d]	CH_3CN	5	CH_3CN	12	0
2	CH_3CN	1	CH_3CN	1.2	15
3	CH_2Cl_2	40	CH_2Cl_2	$Yb(OTf)_3$	2
4[e]	CH_3CN	1	CH_3CN	1.2	14
5[f]	CH_3CN	1	CH_3CN	1.2	0
6	pyrrole	4	CH_3CN	0.026	15
7	pyrrole	4	CH_2Cl_2	0.026	25
8	pyrrole	4	CH_2Cl_2	1.3	7
9	pyrrole	4	CH_2Cl_2	0.13	12
10	pyrrole	10	CH_2Cl_2	0.026	30
11	pyrrole	15	CH_2Cl_2	0.026	21
12	pyrrole	10	CH_2Cl_2[g]	0.026	18

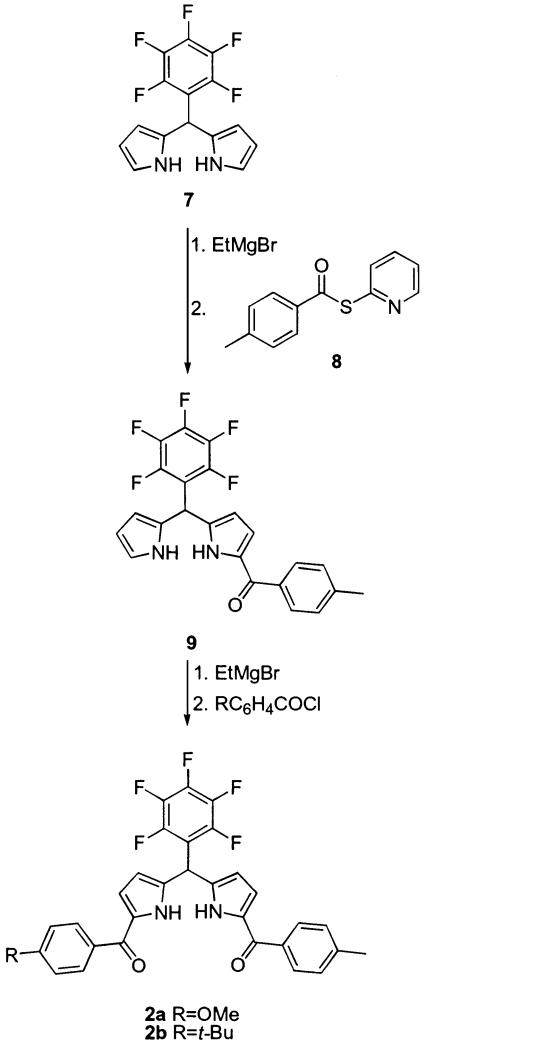
[a] All reactions were performed under the following conditions. First step: reduction of diacyldipyrromethane to dicarbinol, 1:3 MeOH/THF, 50 equiv of $NaBH_4$. Second step: scale of 0.1 mmol of diacyldipyrromethane-dicarbinol, 50 equiv of pyrrole. Third step: 40 mL of solvent, 3 equiv of DDQ. [b] Isolated yields. [c] Used 2 equiv of DDQ. [d] Used 6 equiv of pyrrole. [e] In this experiment, pyrrole has been evaporated. [f] Used 6 equiv of DDQ. [g] Used 10 mL of CH_2Cl_2.

The absence of scrambling was carefully checked in each experiment, and the starting conditions were analogous to those described for the synthesis of porphyrins (entry 1). When only a slight excess of pyrrole was present in the reaction mixture, corrole did not form. In contrast, when the amount of TFA was decreased by a factor of 10 and at the same time the amount of pyrrole was increased to 50 equiv, corrole **5a** was obtained in 15% yield (entry 2). Taking into account that DDQ may form with pyrrole the so-called "pyrrole red",[13] the amount of DDQ was doubled in the next experiment (entry 5). No corrole was formed, indicating that further reaction of corroles with DDQ is faster than pyrrole red formation. The removal of pyrrole before DDQ addition (entry 4) has no effect on the reaction yield. The reaction in the presence of ytterbium triflate[11] afforded corrole in only 2% yield (entry 3).

The difficulties encountered to improve the yield of reaction led us to use solventless conditions (entries 6−12). In this case, due to the very high reactivity of dicarbinols and being aware of possible scrambling, much lower amounts of TFA were used. After formation of the bilane, the reaction mixture was diluted with solvent and DDQ was added (entries 6−12).

This initial optimization study clearly shows that: (a) a small rather than large amount of TFA should be used (entries 7 and 8); (b) CH_2Cl_2 is a convenient solvent for the final radical oxidative cyclization (entries 6 and 7); (c) dilution of the bilane solution improves the yield of corrole **5a**, which finally reaches 30% (entries 10 and 12). The optimized procedure (bilane formation: 50 equiv of pyrrole as a solvent, TFA (mM)/**1b** (mM) = 0.026, 10 min; oxidative cyclization: CH_2Cl_2, 3 equiv of DDQ) was successfully used in the preparation of various corroles (Scheme 1). Altogether nine diacyldipyrromethanes have been employed in the three-reaction sequence. Among them were one precursor of A_3-type corrole, six precursors of *trans*-A_2B-type corrole and two precursors of ABC-type corrole.

Scheme 2



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Monoacylation of dipyrromethane **7**, using thioester **8**[14] followed by a second acylation,[9] afforded two unsymmetrical diacyl dipyrromethanes **2a** and **2b** in reasonable yields (Scheme 2). The presence of pentafluorophenyl substituents improves the stability of corroles in solution. All but one two-step process gave rise to the expected corroles **4**, **5a**−**e**, and **6b** in 16−54% yield (Scheme 1). The only exception was the reaction starting from diacyldipyrromethane **1e**, which failed to give corrole **5d** probably due to an unfavorable conformation of the corresponding bilane. No scrambling was observed in any of these reactions on the basis of ESI-MS and TLC.

To optimize the conditions further and improve the yield of corroles, the purification of bilanes (method B) was performed according to the findings of Lee and co-workers.[12] In this case, slightly different conditions were chosen for bilane formation with the use of $BF_3{\cdot}Et_2O$ as an acid catalyst (Scheme 1). The best synthesis of the bilane was found to proceed from 1.0 mol of dipyrromethane, 145 equiv of pyrrole as a solvent, and 0.15 equiv of $BF_3{\cdot}Et_2O$. After dilution in CH_2Cl_2 and neutralization by NaOH (0.1 M), the bilane was isolated by column chromatography. Two bilanes **3a** and **3b** were isolated in 62 and 65% yields, respectively. They were oxidized to corroles **5f** and **6a**, respectively, with DDQ using EtCN as a solvent in the presence of NH_4Cl in 66 and 55% yields.

The ultimate choice between the above-described methods depends on the nature of the dipyrromethane precursor. Method A is potentially faster, while the main advantage of Method B is a simpler final chromatographic purification of the desired corrole. Needless to say, the absence of porphyrin greatly simplifies the chromatography in both cases.

The simple analysis of electronic spectra of prepared corroles confirmed the previous observation.[8] For corroles possessing at least two 2,6-disubstituted aryl substituents at the meso positions, the Soret band is split and they exhibit a pink-violet color in solutions (only **5c**). The other compounds have no split Soret band and exhibit a green-blue color in solutions.

The present method is complementary to the previously developed approach from dipyrromethanes and aldehydes for the synthesis of *trans*-A_2B-type corroles.[7] While the latter method is very efficient for polar aldehydes, the separation of corrole from porphyrins is tedious for unpolar ones. However, the phenyl substituents that can be introduced into corroles using the methodology presented here are limited by their compatibility with Grignard reagents.[15] Yet, it is applicable when nonpolar substituents are present at the 10 meso-position of the corrole ring.

This paper establishes the foundation for the first synthesis of meso-substituted ABC-corroles. This approach, based on Lindsey's method, is also particularly efficient for preparing A_3-type and *trans*-A_2B-type corroles. We are now expanding the scope of this preliminary work with a special focus on further simplification of the purification process.

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Supporting Information Available: Experimental procedures and analytical data for compounds **2a**,**b**, **3a**−**b**, **4**, **5a**−**f**, and **6a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Non-Grignard-based methodologies for the synthesis of acyldipyrromethanes are also known (see ref 12a).