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meso-Pyrimidinyl-Substituted A_2B-Corroles

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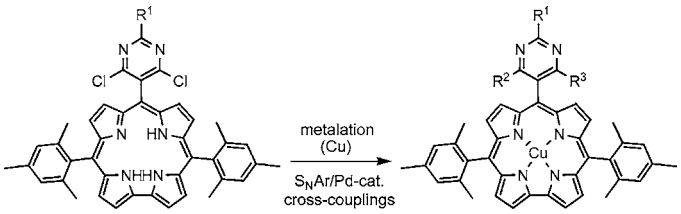
ABSTRACT



***meso*-Pyrimidinyl-substituted A_2B-corroles were synthesized in good yields by condensation of 5-mesityldipyrromethane and 2-substituted 4,6-dichloropyrimidine-5-carbaldehydes. A simple reduction of the amount of Lewis acid (BF_3·OEt_2) resulted in the formation of A_2B-corroles, which was optimized to maximize the corrole yield. Nucleophilic aromatic substitution, Suzuki, and Stille cross-coupling reactions were performed on the Cu-metalated pyrimidinylcorroles to obtain sterically encumbered triarylcorroles, while the substitution pattern at the 2-position of the pyrimidinyl substituent was altered through Liebeskind–Srogl cross-couplings.**

Corroles, contracted porphyrin analogues lacking one *meso*-carbon, have long been rather rare compounds due to their challenging synthesis.[1] Since 1999, however, novel one-step synthetic pathways toward *meso*-triarylcorroles, and the discovery that these macrocycles stabilize unusually high metal oxidation states, have caused a revival of corrole chemistry.[2] Nowadays, a number of well-established synthetic protocols are available for the preparation of substituted triarylcorroles and therefore an increasing amount of effort is devoted to the study of their properties and applications.[2,3] Further investigations into synthetic pathways toward novel more sophisticated functional corroles are, however, still required to fully elucidate and exploit the potential of these macrocycles in a number of promising applications, e.g., catalysis,[4] sensors,[5] and photodynamic therapy.[6,7]

Synthetic pyrimidine chemistry is a well-studied part of organic chemistry since the versatile pyrimidine skeleton is commonly found in pharmaceutical drugs, fungicides, and herbicides.[8a] Dihalopyrimidines have been used extensively

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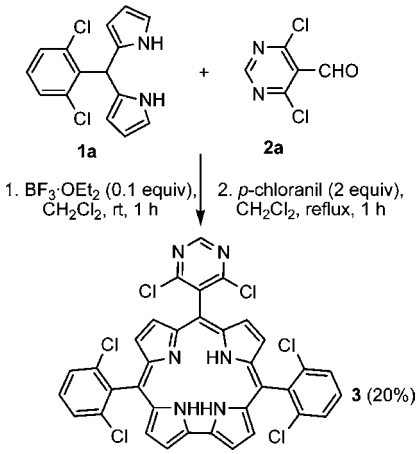
by Lehn et al. for the synthesis of multitopic ligands suitable for the preparation of grid-type metal ion architectures.[8b] In previous work we have been studying the synthesis and reactivity of 4,6-dichloropyrimidines as structural components of *meso*-pyrimidinyl-substituted porphyrinoids,[9] heteracalixarenes,[10] and dendrimers.[11] The major advantage concerning the introduction of dichloropyrimidinyl moieties on the *meso*-positions of oligopyrrolic macrocycles is the fact that these pyrimidinyl substituents allow a variety of post-macrocyclization synthetic modifications. Earlier work on pyrimidinylporphyrins pointed out that the chlorine atoms on the pyrimidine group(s) can easily be substituted by nucleophilic aromatic substitution (S_NAr)[9b,f] or Suzuki cross-coupling[9d] reactions. Similar reactions on pyrimidinylcorroles hence could give access to a diversity of functional corroles that is unprecedented in synthetic corrole chemistry. To date, the majority of corrole functionalizations involve simple functional group transformations on the (limited amount of) *meso*-aryl groups, or introduction of functions on the β-pyrrolic positions, e.g., via bromination, hydroformylation, nitration, and chlorosulfonation.[3] Another unique feature of *meso*-pyrimidinylcorroles is the fact that the substituents are introduced at the ortho,ortho′-positions, and hence are located above and below the corrole macrocycle, which could be advantageous regarding energy transfer properties and stereoselective catalysis.[12]

In 2001, our group presented the synthesis of sterically encumbered triarylcorroles starting from aryldipyrromethanes and aromatic aldehydes.[9c] Lewis acid-catalyzed (BF_3·OEt_2) condensation of 5-(2,6-dichlorophenyl)dipyrromethane (**1a**) and electron deficient aromatic aldehydes in CH_2Cl_2, followed by cyclization and oxidation in propionitrile or CH_2Cl_2, in the presence of DDQ or *p*-chloranil, gave corroles in good yields. One particular aldehyde used, 4,6-dichloropyrimidine-5-carbaldehyde (**2a**), afforded a novel *meso*-pyrimidinylcorrole **3** (20% yield) on condensation with dipyrromethane **1a** (Scheme 1). On the other hand, condensation of pyrimidinecarbaldehyde **2a** with 5-mesityldipyrromethane (**1b**) did not result in the formation of any corrole, only the A_2B_2-porphyrin analogue was obtained in a very high yield (53%). These prior observations and the potential of pyrimidinylcorroles toward preparation of particular functional corroles have been investigated in detail.[13]

As part of a project to prepare porphyrin derivatives of 4,6-dichloropyrimidine-5-carbaldehydes, and the use of such

Scheme 1. Synthesis of A_2B-Triarylcorrole **3**



porphyrins for the construction of multiporphyrin dendrimers,[9f] it was discovered that a slight modification of the reaction conditions, as optimized for porphyrins, opens a more general synthetic pathway toward *meso*-pyrimidinyl-substituted A_2B-corroles.[14] On using a tenfold decreased amount of boron-trifluoride catalyst (0.085 equiv) in the condensation of 4,6-dichloropyrimidine-5-carbaldehyde (**2a**) and 5-mesityldipyrromethane (**1b**), in a 1−1 ratio,[15] we obtained, besides the expected A_2B_2-porphyrin **5a** (25%), pyrimidinylcorrole **4a** in 18% yield (Scheme 2).

5-Mesityldipyrromethane (**1b**) was easily synthesized via the recently reported method in water,[16] while 4,6-dichloropyrimidine-5-carbaldehyde (**2a**) was prepared by chloroformylation of 4,6-dihydroxypyrimidine.[17] The pyrimidine building block could be varied by introduction of substituents on the vacant 2-position. 4,6-Dichloro-2-phenylpyrimidine-5-carbaldehyde (**2b**) and 4,6-dichloro-2-(*p*-methoxyphenyl)-pyrimidine-5-carbaldehyde (**2c**) were prepared by similar chloroformylation of the dihydroxypyrimidine precursors, which in their turn were prepared by condensation of the corresponding benzamidines with diethyl malonate.[18] 4,6-Dichloro-2-methylsulfanylpyrimidine-5-carbaldehyde (**2d**) could be obtained through methylation and subsequent chloroformylation of thiobarbituric acid.[19] Flash chromatographic purification of the obtained pyrimidinecarbaldehydes proved to be essential to obtain satisfactory yields for the tetrapyrrolic macrocycles. Pyrimidinylcorroles **4b**−**d** were synthesized easily and in relatively good yields (13% for

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(13) Collman prepared the *meso*-pyrimidinyl-substituted A_3-corrole analogue using either conventional or microwave heating: Collman, J. P.; Decréau, R. A. *Tetrahedron Lett.* **2003**, *44*, 1207.

(14) *meso*-Pyrimidinyl-substituted expanded porphyrins could also be prepared by a slight modification of the Rothemund−Lindsey conditions optimized for porphyrin synthesis (ref 9e).

(15) On using the stoichiometric 1−2 ratio, corrole **4a** was obtained in only 4% yield (23% porphyrin **5a**).

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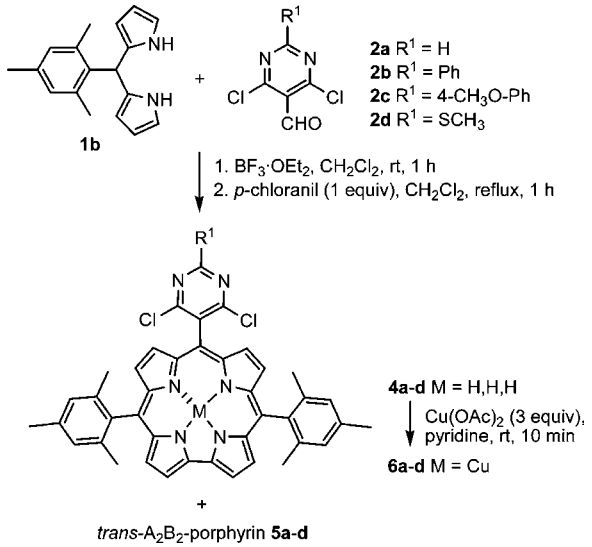
Scheme 2. Synthesis of *meso*-Pyrimidinyl A_2B-Corroles **4a**−**d**



4b and **4c**, 20% for **4d**) from these substituted building blocks under the same reaction conditions (Scheme 2).

Since the content of borontrifluoride catalyst appeared to be a crucial parameter to obtain either the *meso*-pyrimidinyl A_2B-corrole or the A_2B_2-porphyrin as the major product, an optimization study of the amount of Lewis acid was performed to maximize the corrole yield (Table 1).[20] The optimization was performed for corrole **4a** and a 1−1 ratio of dipyrromethane **1b** and pyrimidinecarbaldehyde **2a** was used, rather than the stoichiometric 2−1 ratio. The excess of pyrimidinecarbaldehyde could, however, easily be recovered on chromatographic purification of the corrole. On using 0.85 equiv of $BF_3{\cdot}OEt_2$, only A_2B_2-porphyrin **5a** was formed in a very high yield (50%), and the porphyrin amount gradually decreased when less catalyst was used. For a $BF_3{\cdot}OEt_2$ content ranging from 0.027 up to 0.102 equiv, both the A_2B-corrole and the A_2B_2-porphyrin were formed, and the maximum corrole yield was observed on adding 0.043 equiv of Lewis acid.[21] Under these conditions, the desired corrole **4a** was obtained, after column chromatographic purification, in as much as 35% yield, which is among the highest yields ever reported for corroles. On applying this optimized amount of $BF_3{\cdot}OEt_2$ to the synthesis of corroles **4b** and **4d**, the yield for **4b** could be increased to 22%, while the yield for **4d** dropped to 14%. The highest yield (27%) for corrole **4d** was obtained on using 0.068 equiv of catalyst. The optimum Lewis acid concentration hence seems to be strongly dependent on the substitution pattern of the pyrimidinecarbaldehyde.[22]

Table 1. Optimization of the Yield for A_2B-Corrole **4a**[a]

$BF_3{\cdot}OEt_2$ (equiv)	corrole **4a**[b] (%)	porphyrin **5a**[b] (%)
0.850	0	50
0.102	9	35
0.085	18	25
0.068	25	17
0.054	29	10
0.043	**35**	**6**
0.034	27	3
0.027	15	2

[a] General conditions: (1) [**1b**] = [**2a**] = 2.8 mM, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, Ar, 1 h; (2) *p*-chloranil (1 equiv), CH_2Cl_2, reflux, 1 h. [b] Isolated yield.

The *meso*-dichloropyrimidinyl moiety allows easy functionalization of the corrole macrocycle, e.g., via S_NAr and Pd-catalyzed cross-coupling reactions. Due to the inherent lower stability of free-base (Fb) corroles, as compared to the porphyrin analogues, it was preferred to perform the functionalization study for the pyrimidinylcorroles on the more stable metallocorrole derivatives. For this purpose, Cu was chosen as the preferred metal, due to its easy insertion, absence of axial ligands, and the diamagnetic ground state.[2a,23,24] Cu-corroles **6a**−**d** were obtained in high yields (78−95%) from the Fb corroles on stirring them with $Cu(OAc)_2$ in pyridine at ambient temperature for 10 min (Scheme 2).[23c] S_NAr of phenols on *meso*-pyrimidinyl-substituted porphyrins proceeds smoothly at 90 °C in DMF with K_2CO_3 base (for 48 h).[9b,f] However, on applying these conditions to the substitution of A_2B-corrole **6a** with 4-*tert*-butylphenol (4 equiv), monosubstituted A_2B-corrole **7a** was observed as the only product in 87% yield. Disubstitution could only be achieved on using harsh substitution conditions; DMSO, K_2CO_3, 6 equiv of 4-*tert*-butylphenol, 175 °C (microwave irradiation), 1 h. In this way the desired disubstituted A_2B-corrole **7b** was obtained in 85% yield (Scheme 3).[25]

Pd-catalyzed Suzuki cross-coupling reactions were already performed on 5,15-bis(4,6-dichloropyrimidin-5-yl)porphyrin **5a** with a number of arylboronic acids.[9d] Extension of this method to *meso*-pyrimidinylcorroles would enable the preparation of unique highly sterically shielded corroles. A simple Suzuki reaction with phenylboronic acid was performed on Cu-corrole **6a** under standard reaction conditions,[9d] and the desired disubstituted A_2B-corrole **8** was obtained in 75% yield (Scheme 3).[26] The method could also be extended to

(20) The effect of the $BF_3{\cdot}OEt_2$ content was somewhat underestimated in our previous work (ref 9b,c). The importance of the concentration of TFA as an acid catalyst in corrole synthesis was recognized and extensively investigated by Gryko et al. (ref 2f−h).

(21) A similar optimization study of the amount of Lewis acid is currently being explored for the stoichiometric 2−1 ratio.

(22) See the Supporting Information for more details.

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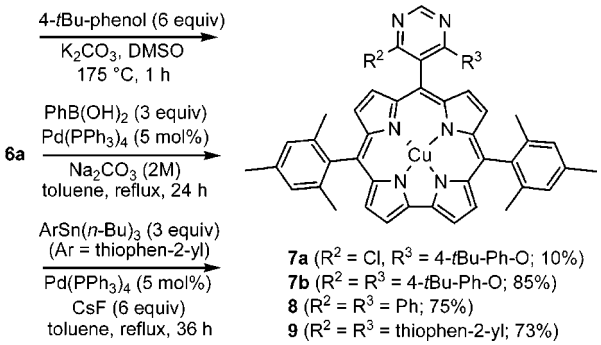
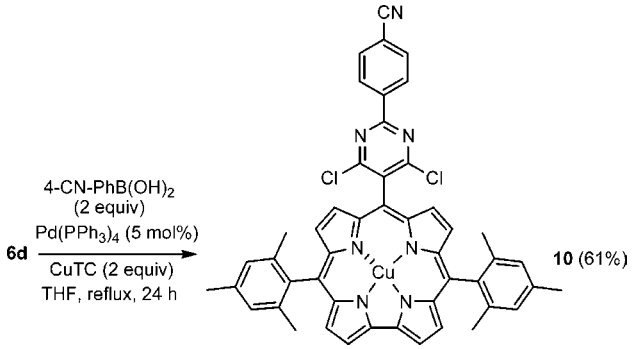
(25) In tris(pentafluorophenyl)corrole, the most studied corrole derivative to date, the *p*-fluorine substituents can also be replaced by S_NAr, as was demonstrated in the reaction with *o*-pyridyllithium (1 h at −78 °C in THF, 35% yield, ref 2b).

(26) Both S_NAr and Suzuki reactions were also successful on Fb corrole **4a**, but the obtained yields are significantly lower due to the (oxidative) lability of the corroles.

Scheme 3. Functionalization of *meso*-Pyrimidinyl-Substituted Corroles via S_NAr or Pd-Catalyzed Suzuki/Stille Reactions



Scheme 4. Functionalization of *meso*-Pyrimidinyl-Substituted Corroles via Liebeskind−Srogl Cross-Coupling



Stille cross-couplings. Reaction of 2-(tributylstannyl)thiophene with **6a** in the presence of CsF afforded *o*,*o*′-dithienyl-substituted pyrimidinylcorrole **9** in 73% yield (Scheme 3).

The substituent at the 2-position of the *meso*-pyrimidinyl group can be introduced at the pyrimidinecarbaldehyde stage. This implies, however, that a number of synthetic steps have to be performed in order to obtain each of the pyrimidinecarbaldehyde precursors individually. Therefore, an alternative strategy was developed that enables introduction of functional moieties at the corrole stage by Pd-catalyzed Liebeskind−Srogl[27] cross-coupling reactions on thiomethyl functionalized corrole **6d**. This is particularly useful if the pyrimidinecarbaldehyde precursor is hard to obtain. Reaction of **6d** with 4-cyanophenylboronic acid in the presence of copper(I) thiophene-2-carboxylate (CuTC) afforded Cu-corrole **10** in 61% yield (Scheme 4). On reaction of Fb corrole **4d** with phenylboronic acid in the presence of $Pd(PPh_3)_4$ and a small excess of CuTC (1.2 equiv), only metalation of the corrole was observed. On addition of a fresh amount of CuTC (2 equiv), the desired phenyl-substituted corrole **6b** was obtained in 80% yield, essentially without any Suzuki-type reaction at the chlorine substituents.

In summary, novel *meso*-pyrimidinyl-substituted A_2B-corroles have been synthesized in high yields by condensation of 5-mesityldipyrromethane and 2-substituted 4,6-dichloropyrimidine-5-carbaldehydes, in a 1−1 ratio, catalyzed by $BF_3{\cdot}OEt_2$. The borontrifluoride content was optimized to maximize the corrole yield (up to 35%) and reduce the porphyrin formation. The presented corroles are very attractive scaffolds for the preparation of sophisticated functional corroles (useful toward applications, e.g., catalysis or cancer therapy) due to the ease and broad scope of functionalization of the dichloropyrimidinyl moiety. The *o*,*o*′-chlorine groups on the pyrimidine substituent can easily be exchanged via S_NAr and Pd-catalyzed Suzuki or Stille cross-couplings, affording sterically shielded "double picket fence" corroles in high yields. On the other hand, the 2-pyrimidinyl position can be equipped with various substituents ready for further elaboration of the corrole macrocycle, either by introduction on the pyrimidinecarbaldehyde building blocks or by introduction at the corrole stage via Liebeskind−Srogl reactions. Further exploration of the synthesis and functionalization of various types of *meso*-pyrimidinyl-substituted (metallo)-corroles will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization data, ^1H and ^{13}C NMR and selected UV−vis spectra for the novel A_2B-corroles, and some details regarding the optimization of the corrole yield. This material is available free of charge via the Internet at http://pubs.acs.org.

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