Organic Letters
Letter
pubs.acs.org/OrgLett

β-Pyrrolopyrazino Annulated Corroles via a Pictet−Spengler Approach

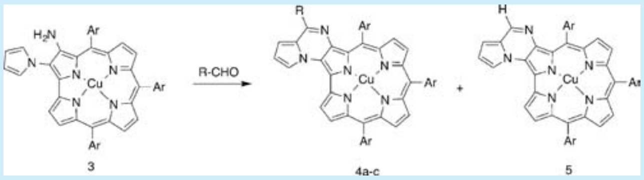
Beatrice Berionni Berna,[†] Sara Nardis,[†] Pierluca Galloni,[†] Andrea Savoldelli,[†] Manuela Stefanelli,[†] Frank R. Fronczek,[‡] Kevin M. Smith,[‡] and Roberto Paolesse*[,†]

[†]Department of Chemical Sciences and Technologies, University of Rome “Tor Vergata”, Via della Ricerca Scientifica, 00133 Rome, Italy

[‡]Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803, United States

Supporting Information

ABSTRACT: Reaction of 2-amino-3-(pyrrol-1-yl)-5,10,15-tris(4-*tert*-butylphenyl)corrolato copper(II) with arylaldehydes affords novel π-extended β,β'-pyrrolo(1,2-*a*)pyrazino-fused corroles via a Pictet−Spengler reaction. Corrole shows an unprecedented reaction pathway, leading to a mixture of phenyl-substituted and nonsubstituted pyrrolopyrazino annulated species as reaction products.



In the compendium of porphyrinoids, corroles have experienced increasing attention in the past decade, due to the disclosure in 1999 of simple routes for the synthesis of meso-triarylcorroles.[1,2] Since then, they have been successfully used in various contexts ranging from catalysis[3−7] to dye-sensitized solar cells.[8−10]

For these applications, it is important to modulate the corrole properties by peripheral modifications, and the synthetic availability of triarylcorroles has allowed a more detailed investigation of the functionalization of the corrole ring. In particular, we are interested in exploring the extension of the porphyrinoid π-system because this modification can enhance the photophysical properties of the macrocycle.[11]

We recently reported the preparation of β,β'-pyrazino-fused corroles.[12] The obtained results prompted us to investigate the development of simple synthetic routes leading to π-expanded corroles with annulated pyrazine units. These groups can be interesting because it has been shown that heterocycles containing a pyrrolo[1,2-*a*]pyrazino moiety can play an important role in pharmacological terms.[13−17]

Very recently, the preparation of a β,β'-fused nickel(II) pyrrolo[1,2-*a*]pyrazino tetraphenylporphyrin by application of the Pictet−Spengler reaction conditions was reported.[18] These results led us to explore the application of the same route in the case of corrole because we already reported the preparation of the potential starting material, the copper complex **1** of 2-amino-3-nitrotris(5,10,15-*tert*-butylphenyl)corrole (Scheme 1).[19] This substrate can be obtained by nitration of the 5,10,15-tris(4-*tert*-butylphenyl)corrolato Cu [Cu(*t*BuTPC)], followed by a vicarious nucleophilic substitution with 4-amino-4*H*-1,2,4-triazole; the amino group was then used as starting point for the synthesis of the pyrrole moiety via a Clauson−Kaas reaction.[20]

Complex **1** was dissolved in a mixture of acetic acid and toluene (6:1) in the presence of 2,5-dimethoxytetrahydrofuran. The solution was heated at reflux for 45 min under a nitrogen atmosphere. TLC of the reaction mixture showed the complete disappearance of the starting material, and a new product with higher R_f was apparent. The solvent was evaporated, and the compound was purified by column chromatography using CH_2Cl_2 as the eluent. The main fraction corresponded to the desired complex **2**, obtained in 90% yield (Scheme 1).

Spectroscopic characterization of **2** was in agreement with the proposed structure. Although the ^1H NMR spectrum exhibited severe line broadening, with overlapped signals of the β-pyrrolic and phenyl protons, it was possible to observe two multiplets, with double integration value, centered at 7.16 and 6.40 ppm (Figure S1), which underscores the presence of pyrrole in position 2 of the macrocycle, in agreement with the chemical shifts observed in the case of porphyrin functionalization.[18]

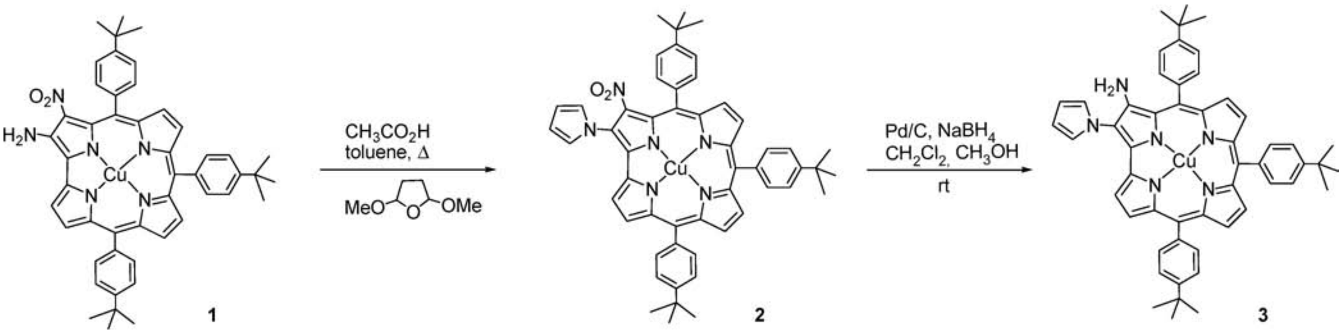
Compound **2** was unequivocally characterized by X-ray analysis of a single crystal obtained from slow diffusion of methanol into a dichloromethane solution (Figure 1). The Cu atom in **2** had slight tetrahedrally distorted square-planar coordination, with the four N atoms an average of 0.154 Å above and below their best plane and Cu−N distances in the range of 1.879(5)−1.906(6) Å. The corrole core has a saddle distortion with β-C atoms an average of 0.394 Å from the 23 atom best plane. The pyrrole and nitro substituents at the 2 and 3 positions are twisted out of the plane of the core pyrrole on which they are substituted, forming dihedral angles of 41.1 and 49.2° respectively, with it.

Corrole **2** was successfully reduced, using 10% Pd/C-$NaBH_4$ in a 4:1 mixture of CH_2Cl_2/CH_3OH to produce [2-(pyrrol-1-yl),3-(NH_2)-*t*BuTPC]Cu (**3**) (Scheme 1) in 83% yield. In this case, crystallization from a dichloromethane/methanol solution provided crystals for X-ray characterization of **3** (Figure 2). The

Received: May 5, 2016
Published: July 5, 2016

DOI: 10.1021/acs.orglett.6b01314
Org. Lett. 2016, 18, 3318−3321

Scheme 1. Synthesis of Compound 2 and Further Reduction



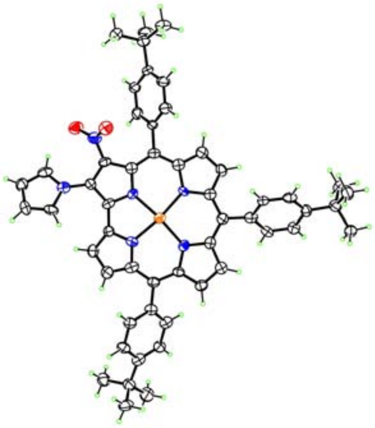


Figure 1. Crystal structure of **2**.

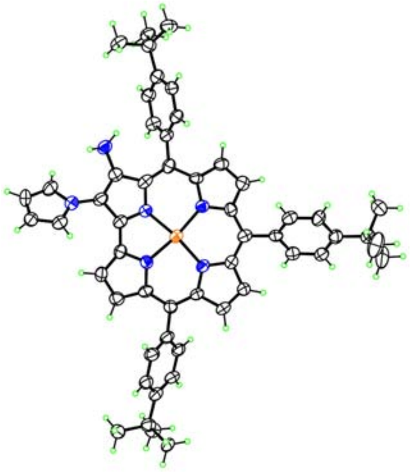


Figure 2. Crystal structure of **3**.

molecular structure of **3**, as the chloroform solvate, is very similar to that of **2**, with a slightly greater tetrahedral distortion from the square-planar Cu coordination (mean deviation of four N atoms 0.177 Å) and Cu−N distances in the range of 1.889(5)−1.909(5) Å.

The corrole core has a slightly less pronounced saddle distortion, with *β*-C atoms an average of 0.228 Å from the 23 atom best plane. The out-of-plane twist of the pyrrole substituent is comparable at 44.8°. As already experienced for complex **2**, the ^{1}H NMR spectrum showed broad signals, but it was possible to observe a signal at 2.97 ppm, attributable to the NH_2 protons. It is interesting to note that both complexes **2** and **3** were obtained in yields higher than those for the analogous porphyrins, an unusual feature for corrole functionalizations.

Corrole **3** was then reacted with *p*-tolualdehyde, following the Pictet−Spengler route reported for the analogous Ni porphyrin.[18] To a solution of **3** and aldehyde in 1,4-dioxane (4 mL) was added dodecylbenzenesulfonic acid (DBSA, 10% molar ratio), and the reaction mixture was stirred at room temperature. Progress of the reaction was monitored by TLC, which showed incomplete conversion of the starting corrole.

We tried to improve the reaction of **3** by prolonging the reaction time, but this attempt led to an increase of decomposition products, while an increase of the DBSA amount was unsuccessful.

For these reasons, we decided to stop the reaction after 2 h. TLC analysis of the crude mixture showed, apart from the starting material, two reaction products. Chromatographic separation of the corresponding bands afforded the expected *β*,*β*′-pyrrolo[1,2-*a*]pyrazino-fused corrole **4a** as a fast moving fraction in moderate yields (Table 1).

Table 1. Relative Yields for the Synthesis of 4a−c and 5[a]

R	product	yield (%)
p-$CH_3C_6H_4$	**4a**	32
	5	19
p-BrC_6H_4	**4b**	21
	5	16
p-$NO_2C_6H_4$	**4c**	29
	5	9

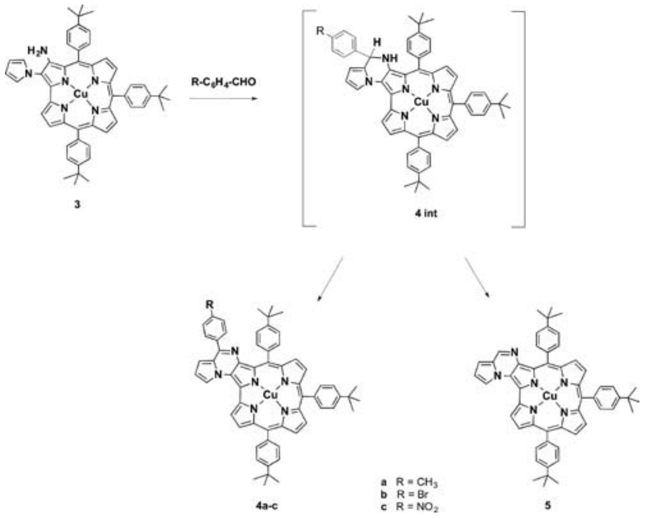
[a] Calculated based on unreacted starting material.

Spectroscopic characterization of **4a** was in agreement with the proposed structure, with the fast atom bombardment (FAB) mass spectrum showing a molecular peak at 934 amu (Figure S9) and the ^{1}H NMR spectrum showing a 3-proton singlet at 2.43 ppm, in keeping with the presence of the CH_3 moiety (Figure S7). The second fraction was obtained in lower amount than **4a** (Table 1), and the ^{1}H NMR spectrum of the compound showed the absence of the resonances attributable to the 4-methylphenyl substituent, while an additional singlet at 8.56 ppm was present.

The FAB mass spectrum also indicated a molecular peak at 849 amu, confirming the absence in the product of the peripheral 4-methylphenyl unit. These features led us to hypothesize the formation of **5** (Scheme 2), which was unambiguously confirmed by X-ray characterization (Figure 3).

The structure of **5** as the chloroform solvate is very similar to those of **2** and **3**. Coordination geometry of the Cu atom is also square-planar with a small tetrahedral distortion, with the N atoms lying alternately an average of 0.145 Å above and below

Scheme 2. DBSA-Catalyzed Synthesis of β,β′-Fused Copper(II) Pyrrolo[1,2-*a*]pyrazinocorrolates (4a−c and 5)



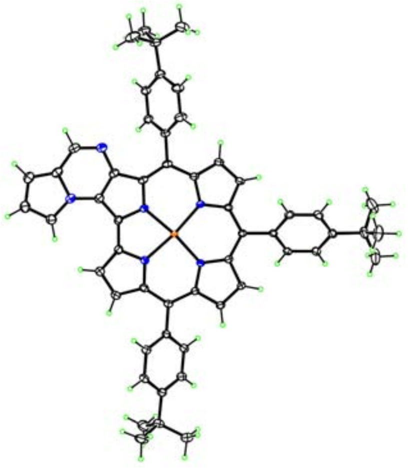


Figure 3. Crystal structure of **5**.

their best plane. The Cu−N distances are experimentally indistinguishable, in the range of 1.903(2)−1.905(2) Å. The corrole core has a saddle distortion with β-C atoms an average of 0.391 Å from the 23 atom best plane. Cyclization prevents the pyrrolopyrazino substituent from deviating much from coplanarity with the core pyrrole to which it is fused, with the dihedral angle between those moieties being 3.5°. To the best of our knowledge, the formation of **5** is novel for the Pictet−Spengler reaction, and a similar pathway has not been observed in the reaction of Ni tetraphenylporphyrin.[18] Formation of **5** probably occurs after the formation of the cyclic adduct, with the subsequent aromatization occurring with the competing elimination of H_2 or toluene, leading to **4a** or **5** (Scheme 2). To investigate the generality of this reaction and the relative influence of benzaldehyde substituents on the product pattern, we reacted **3** with two additional benzaldehydes, bearing at the 4-position a strongly or a weakly electron-withdrawing group, to complete the series with the electron-donating character of the methyl group. In all cases, the expected products (**4b**,**c**) were obtained with formation of **5** (Scheme 2).

The highest yields were obtained with 4-methylbenzaldehyde, where the **5**/**4** molar ratio was also the highest. This result seems to indicate that electron-rich benzaldehydes can favor the formation of **5**; however, more aldehydes should be tested to confirm this hypothesis.

UV/vis absorption spectra of Cu[*t*BuTPC], complexes **4a**−**c**, and compound **5** are shown in Figure 4. These molecules display characteristic Soret bands between λ_{max} 425 and 433 nm, which are red-shifted compared to the starting complex (Soret band at λ_{max} 418 nm). Bathochromic shifts observed for these complexes are similar to those observed for the analogous corroles bearing β-annulated aromatic rings,[12,21] thereby confirming the increase in π-conjugation in these corrole analogues. To further elucidate the influence of the β-annulation on the corrole properties, we carried out the cyclic voltammetry of **4a** and **5** (Figures S19−S22). For both compounds, we observed an appreciable shift of the first oxidation potential to values lower than that of Cu(*t*BuTPC),[19] which is further confirmation of the π-conjugation increase operated by the annulated pyrrolopyrazino ring (Table 2).

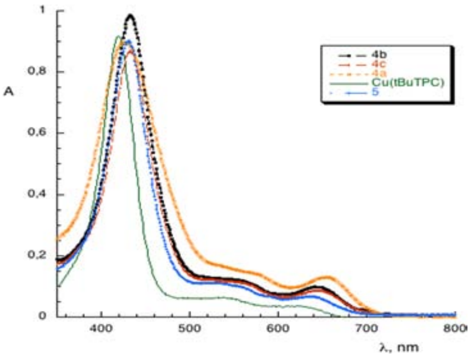


Figure 4. Electronic absorption spectra of Cu(*t*BuTPC), corroles **4a**−**c**, and **5** in CH_2Cl_2 solution.

Table 2. Half-Wave Potentials (V vs SCE) of Cu Corroles in CH_2Cl_2 Containing 0.1 M TBAH

R	E_{ox}	E_{red}
Cu(*t*BuTPC)	0.71	−0.17
4a	0.64	−0.22
	0.86[a]	
5	0.64	−0.24
	0.85[a]	

[a] Upon TFA addition.

Furthermore, we did not observe a second oxidation process up to 1.5 V, where an irreversible reaction occurs. Since for Cu(*t*BuTPC) the second oxidation process occurs at 1.31 V,[19] this result further indicates a strong influence operated by the annulated ring. It is also interesting to note that this influence can be modulated by acids. A drop of TFA, inducing the protonation of the fused pyrrolopyrazino ring, strongly reduces the π-conjugation of the β-annulated aromatic ring, resulting in the blue shift of the corrole Soret bands in the UV−vis spectrum (Figure 5), which becomes similar to that of Cu(*t*BuTPC). For the same reason, in the cyclic voltammogram, we observe a significant increase of about 200 mV of the first oxidation potential for both **4a** and **5**. The presence of the charged pyrazino ring induces a shift similar to that of a peripheral nitro group.[19] The process is reversible because, with the addition of a base, the original spectral features are recovered. We thank the referees for this helpful suggestion.

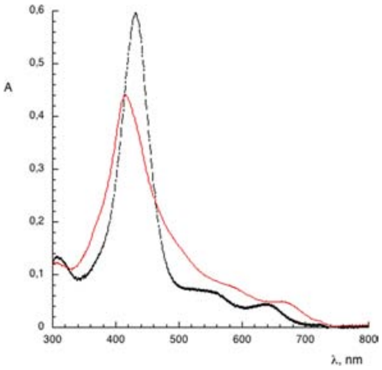


Figure 5. Electronic absorption spectra of **5** (dotted line) and **5** upon addition of a few drops of TFA (solid line) in CH_2Cl_2 solution.

The developed synthetic route permits simple preparation of β,β'-fused copper(II) pyrrolo[1,2-*a*]pyrazinocorroles. The annulated aromatic group opens a novel opportunity to modulate the photophysical and redox properties of corroles. In this reaction, corrole reveals once again an unusual reactivity pattern, affording the unsubstituted pyrrolopyrazino substituent by an unprecedented reaction pathway. This route is very encouraging for the development of new π-extended corrole architectures, particularly appealing as useful functional materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01314.

Experimental procedures and ^{1}H NMR, ^{13}C NMR, FAB spectra of complexes **2**, **3**, **4a–c**, **5** (PDF)

X-ray data for **2**,**3**, **5** and CVs for **4a**, **5** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: roberto.paolesse@uniroma2.it.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the Italian MIUR (FIRB project no. RBFR12WB3W) is gratefully acknowledged.

■ REFERENCES

(1) Paolesse, R.; Mini, S.; Sagone, F.; Boschi, T.; Jaquinod, L.; Nurco, D. J.; Smith, K. M. *Chem. Commun.* **1999**, No. 14, 1307–1308.

(2) Gross, Z.; Galili, N.; Saltsman, I. *Angew. Chem., Int. Ed.* **1999**, *38*, 1427–1429.

(3) Luobeznova, I.; Raizman, M.; Goldberg, I.; Gross, Z. *Inorg. Chem.* **2006**, *45*, 386–394.

(4) Gross, Z.; Golubkov, G.; Simkhovich, L. *Angew. Chem.* **2000**, *112*, 4211–4213.

(5) Lei, H.; Fang, H.; Han, Y.; Lai, W.; Fu, X.; Cao, R. *ACS Catal.* **2015**, *5*, 5145–5153.

(6) Jung, J.; Liu, S.; Ohkubo, K.; Abu-Omar, M. M.; Fukuzumi, S. *Inorg. Chem.* **2015**, *54*, 4285–4291.

(7) Bose, S.; Pariyar, A.; Biswas, A. N.; Das, P.; Bandyopadhyay, P. *Catal. Commun.* **2011**, *12*, 1193–1197.

(8) Salvatori, P.; Amat, A.; Pastore, M.; Vitillaro, G.; Sudhakar, K.; Giribabu, L.; Soujanya, Y.; De Angelis, F. *Comput. Theor. Chem.* **2014**, *1030*, 59–66.

(9) Srikanth, M.; Sastry, G. N.; Soujanya, Y. *Int. J. Quantum Chem.* **2015**, *115*, 745–752.

(10) Giribabu, L.; Kanaparthi, R. K.; Velkannan, V. *Chem. Rec.* **2012**, *12*, 306–328.

(11) Mandoj, F.; Nardis, S.; Pudi, R.; Lvova, L.; Fronczek, F. R.; Smith, K. M.; Prodi, L.; Genovese, D.; Paolesse, R. *Dyes Pigm.* **2013**, *99*, 136–143.

(12) Berionni Berna, B.; Nardis, S.; Mandoj, F.; Fronczek, F. R.; Smith, K. M.; Paolesse, R. *Org. Biomol. Chem.* **2016**, *14*, 2891–2897.

(13) Fisher, T. E.; Kim, B.; Staas, D. D.; Lyle, T. A.; Young, S. D.; Vacca, J. P.; Zrada, M. M.; Hazuda, D. J.; Felock, P. J.; Schleif, W. A.; Gabryelski, L. J.; Anari, M. R.; Kochansky, C. J.; Wai, J. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6511–6515.

(14) Rault, S.; Lancelot, J.-C.; Prunier, H.; Robba, M.; Renard, P.; Delagrange, P.; Pfeiffer, B.; Caignard, D.-H.; Guardiola-Lemaitre, B.; Hamon, M. *J. Med. Chem.* **1996**, *39*, 2068–2080.

(15) Dawidowski, M.; Chońska, J.; Mika, W.; Turło, J. *Bioorg. Med. Chem.* **2014**, *22*, 5410–5427.

(16) Arban, R.; Bianchi, F.; Buson, A.; Cremonesi, S.; Fabio, R. D.; Gentile, G.; Micheli, F.; Pasquarello, A.; Pozzan, A.; Tarsi, L.; Terreni, S.; Tonelli, F. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5044–5049.

(17) Micheli, F.; Bertani, B.; Bozzoli, A.; Crippa, L.; Cavanni, P.; Di Fabio, R.; Donati, D.; Marzorati, P.; Merlo, G.; Paio, A.; Perugini, L.; Zarantonello, P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1804–1809.

(18) Singh, D. K.; Nath, M. *Org. Biomol. Chem.* **2015**, *13*, 1836–1845.

(19) Stefanelli, M.; Mandoj, F.; Mastroianni, M.; Nardis, S.; Mohite, P.; Fronczek, F. R.; Smith, K. M.; Kadish, K. M.; Xiao, X.; Ou, Z.; Chen, P.; Paolesse, R. *Inorg. Chem.* **2011**, *50*, 8281–8292.

(20) *Comprehensive Organic Name Reactions and Reagents*; Wang, Z., Ed.; John Wiley & Sons, Inc., 2010.

(21) Pomarico, G.; Nardis, S.; Paolesse, R.; Ongayi, O. C.; Courtney, B. H.; Fronczek, F. R.; Vicente, M. G. H. *J. Org. Chem.* **2011**, *76*, 3765–3773.