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One-step synthesis of isocorroles

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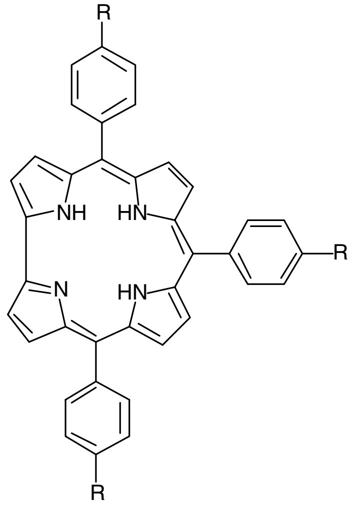
Abstract—A new method for the preparation of isocorroles has been developed based on the reaction of triphenylcorrole with DDQ. Regioisomer **7** where the interruption of the conjugation is at the 5 position, is reported for the first time.

In the past few years, there has been renewed interest in the porphyrinoid field devoted to corrole and a tumultuous growth of Letters related to this macrocycle has been reported in the literature.[1] This interest originates from both the unique coordination chemistry and reactivity of this macrocycle,[2] which makes it quite peculiar among tetrapyrroles, and the development of easy and high yielding synthetic routes to triarylcorroles.[3] The facilitation of corrole synthesis made it accessible to a wider plateau of researchers, and eliminated the complicated purification procedures and low yielding synthetic routes to this macrocycle. Furthermore, it has been possible to study the peripheral functionalization of the corrole macrocycle, and to design and synthesize new and more complex derivatives with tunable features for application in different fields.[1]



1. R = H
2. R = CH_3
3. R = OCH_3
4. R = NO_2

Considering the significant recent progress in corrole chemistry, it is now possible to consider the preparation of corrole isomers, a field that is still in its infancy, although a few examples have been reported in the literature. Among the different isomers, an intriguing compound is isocorrole,[4–6] in which one of the three *meso*-carbons of the aromatic tetrapyrrolic macrocycle is sp^3 hybridized and two inner NH protons, rather than three, are present in an antipodal position (Fig. 1). Although the name of the isocorrole has been used in the past to indicate also the corrole analog [0.2.0.1],[7] for the sake of consistency with porphyrins,[8] we believe that the term isocorrole is more appropriate to indicate the isomers reported in Figure 1. This compound has been quite elusive and only two examples of isocorroles have been reported so far in the literature: Vogel and co-workers, after attempting the synthesis of 2,3,17,18-tetraethyl-7,8,10,10,12,13-hexamethylisocorrole,[5] recently reported the preparation of the corresponding nickel(II) complex[6] as a result of the cyclization of the *a*,*c*-biladiene hydrobromide using nickel acetate in methanol, followed by chloranil for the ring closure reaction. This reaction procedure is not general and the same authors did not obtain the 2,3,7,8,12,13,17,18-octaethyl-10,10-dimethylisocorrolatonickel(II), due to steric hindrance between the

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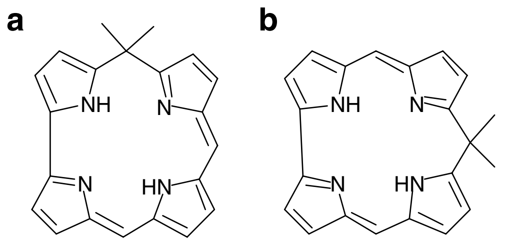
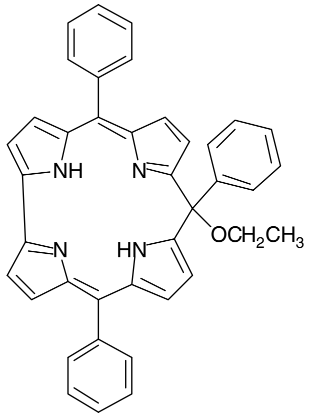


Figure 1. Molecular structures of 5-isocorrole (a) and 10-isocorrole (b).

peripheral ethyl groups. The first example of isocorrole free base has been recently reported by Setsune et al.[4] a bis(azafulvene) derivative of *gem*-dimethyldipyrrylmethane reacted with 2,2′-bipyrrole to give a mixture of *gem*-dimethylisocorrole and higher homologues.

The above reported syntheses of isocorrole require the preparation of difficult to obtain precursors and probably for this reason further investigations on isocorroles have not yet been conducted. A facile synthetic route to isocorrole would use the corrole macrocycle as a more convenient starting material, since new expeditious synthetic routes to triarylcorroles have been reported,[3] making this type of macrocycle readily accessible. One of the key features of corrole is its easy oxidation to generate π-cation radicals; recently radical species have been reported to be intermediates in the formation of dimeric derivatives of Cu[9] and Co.[10] This feature seems to be interesting for the formation of isocorrole, considering that the first example of an isoporphyrin was observed upon the reaction of oxidized ZnTPP with methanol.[11] We envisioned the application of such a route in the case of corrole, using a strong oxidative system as DDQ-Sc(OTf)$_3$ where the scandium salt is used to enhance the oxidizing ability of the quinone.



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A toluene solution of corrole **1** with scandium triflate and DDQ (1:5:5 ratio) under nitrogen was complete in about 5 min, as indicated by UV–visible spectrophotometry. TLC indicated the formation of two main reaction products, as well as significant decomposition of the starting material.

Chromatographic separation (silica gel, CHCl$_3$/hexane 1:1) afforded two fractions that were re-crystallized from CHCl$_3$/methanol. The ^{1}H NMR spectrum of the first yellow-green fraction (obtained in 20% yield) displayed the *β*-pyrrolic proton resonances shifted upfield with respect to those of the starting material **1**: this feature, along with the presence of a signal at 15 ppm, characteristic of NH protons not affected by the ring current, strongly suggested the formation of a non-aromatic structure. This hypothesis was corroborated also by the UV–visible spectrum of the compound and by MS (see ESI). The macrocycle was unambigously characterized as isocorrole **5** by X-ray crystallography[12] (Fig. 2), performed on a crystal obtained by slow diffusion of MeOH into a CHCl$_3$ solution. In this structure an ethoxy group is inserted at the 10 position, resulting in the interruption of the aromatic conjugation. The source of the ethoxy group was the ethanol used for the stabilization of the CHCl$_3$, the solvent employed in the reaction work-up.

The 23-atom isocorrole core of the molecule is approximately planar, with mean deviation from planarity 0.044 Å and maximum deviation 0.141(3) Å for C3. The four N atoms are coplanar to 0.033(2) Å, and distortion from closer coplanarity results from the two directly linked pyrroles being slightly twisted with respect to each other. The N1–C1–C19–N2 torison angle is 6.6(4)°, and the dihedral angle formed by these two pyrrole planes is 8.6(6)°. The phenyl groups at C5 and C15 are twisted in opposite directions, such that they form respective dihedral angles of 60.88(5)° and 56.33(3)° with the isocorrole best plane, and a dihedral angle of 63.11(6)° with each other.

The ^{1}H NMR spectrum of the second fraction also confirmed the non-aromatic character of this reaction product, as well as lower symmetry than compound **5**. However, this product was obtained in very low amount

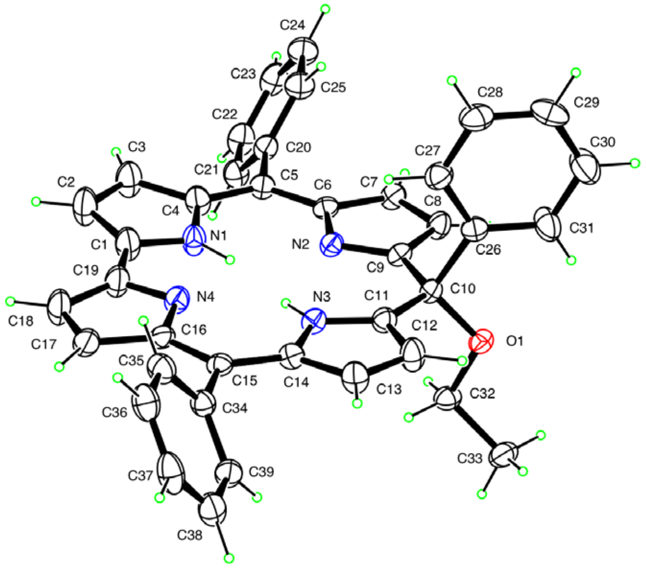


Figure 2. Molecular structure of **5**.

(less than 5% yield) and always contaminated with **5**, which did not allow its complete characterization.

With these first results in mind, we carried out the reaction in methanol rather than in toluene, since methanol has the advantage of dissolving all the reagents. We also decided to carry out the reaction on corrole **2**, in order to have additional information on the symmetry of the products by NMR, using the resonances of the peripheral methyl groups, and to improve product solubility and chromatographic separation.

Considering the extensive decomposition of **1**, along with the observation previously reported that DDQ can induce overoxidation of triphenylcorroles,[13] we decided to carry out the reaction using one equivalent of DDQ and without $Sc(OTf)_3$, obtaining the two products in 74% overall yield. The higher yields obtained under these conditions allowed the chromatographic separation and isolation of the second reaction product. The ^1H NMR spectrum confirmed the lower symmetry of this compound, showing two different resonances for the inner NHs and the spread of the signals of the β-pyrrolic protons (see ESI).

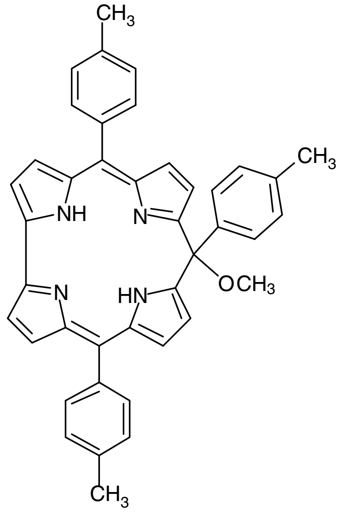
This result indicated the formation of isocorrole **7**, where the addition of the methoxy group and the consequent interruption of the aromatic conjugation occurred at the 5 position. To the best of our knowledge, this is the first report of such a regioisomer of isocorrole even though the reactivity of the 5-meso position is not unprecedented; we observed similar behaviour in the case of the reaction of triphenylcorrole with CI_4, where the ring expansion to hemiporphyricene occurred exclusively at the 5-*meso* position.[14]

To evaluate the influence of the substituents at the corrole periphery on the formation of the isocorroles, we reacted under the same conditions corroles **3** and **4**, which bear *meso*-aryl groups of opposite electronic behaviour. In the case of tris(4-methoxyphenyl)corrole, bearing electron releasing groups at the peripheral positions of the macrocycle, the corresponding isocorroles were isolated in good yields (75% overall yield), while in the case of tris(4-nitrophenyl)corrole, bearing electron withdrawing groups, only traces of the products were obtained along with a mixture of decomposition products.

These results are in good agreement with the hypothesis that the formation of isocorroles occurs after the oxidation of the starting corrole by DDQ, however, there is no indication of the reactive intermediate. The stoichiometry of the reaction implies the removal of two electrons and two protons from corrole by DDQ, and the subsequent addition of one molecule of alcohol to give the isocorrole. However, we have to consider that the oxidation behaviour of corrole is quite complicated and involves the formation of different species, as recently reported by Kadish and co-workers.[15] The first oxidation step of corrole involves the formation of a radical cation, which, being a strong acid, rapidly loses a proton to give the neutral radical **8**, while the liberated H^+ reacts with an other molecule of corrole to give the corresponding protonated species **9**. The second oxidation can occur on both these species at very close potentials, to give **10** and the radical corrole dication **11** (Scheme 1).

The potential reactive intermediate can be **8**, **10** or **11**, excluding **9**, which is stable in MeOH. To obtain further information on the reaction intermediate we used I_2 as the oxidant instead of DDQ, since this reagent was used in the past to obtain **8** and **9** from octaethylcorrole.[16] Under these conditions we observed the immediate formation of a mixture of **8** and **9**, evidenced by their characteristic UV–vis spectrum, but no isocorroles were formed. This result indicates that **8** can be excluded as the reactive intermediate. In respect to the other two species, **10** is the analogous in the corrole field of the Zn porphyrin dication, which has been reported as the precursor of Zn isoporphyrin,[11] and can afford isocorrole by nucleophilic attack of the alcohol (Scheme 2).

However, to investigate **11** as a possible intermediate, we decided to carry out the reaction in the presence of an



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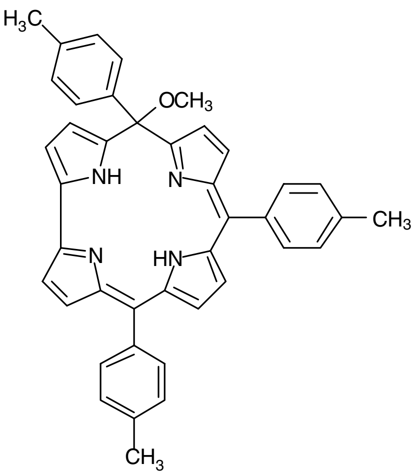

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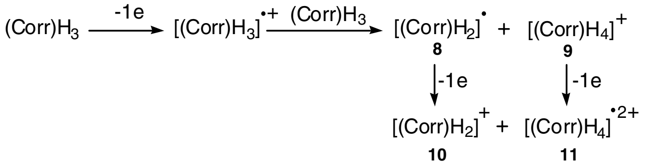
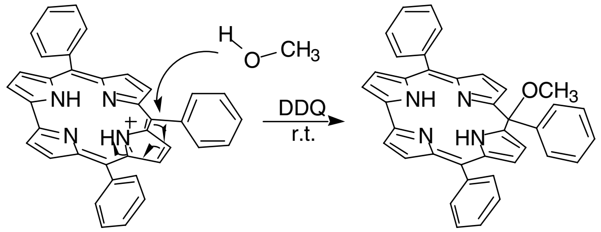


Scheme 1.



Scheme 2.

excess of TFA, therefore having **9** as the starting material and then **11** as the oxidation product, following Kadish's procedure.[15] Also in this case the reaction was successful, suggesting that **11** can be considered as a precursor in the formation of isocorroles. This result indicates that both **10** and **11** can undergo nucleophilic attack of alcohol to give isocorroles, in a pathway similar to that of porphryin, where both the dication and the radical cation of porphyrin have been demonstrated to be the precursors of the corresponding isoporphyrin.[11,17]

Our studies give further insight into the oxidation of the corrole macrocycle and provide a one-step, facile and high yielding preparation of both 5- and 10-isocorrole. The 5-regioisomer isocorrole is herein reported for the first time.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.033.

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12. *Crystal data for* **5** *at 90 K*: $C_{39}H_{30}N_4O$, monoclinic, space group $P2_1/n$, $a = 10.250(2)$, $b = 11.507(2)$, $c = 25.263(4)$ Å, $\beta = 101.519(9)°$, $V = 2919.7(9)$ Å^3, $Z = 4$, 40617 reflections collected with $\theta < 25.0°$, 5140 unique; $R_1 = 0.058$, $wR_2 = 0.124$ refined on F^2. A disorder exists, in which the OEt and Ph substituents at C10 are swapped. Refinement of group population parameters indicates that the orientation shown in Figure 2 is present with 69.6(3)% occupancy, and the alternate orientation 30.4(3)%. The NH hydrogen atoms also exhibit disorder, and were treated as half-populated on all four N atoms. CCDC 648456.
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