



Reactivity of tetrapyrrolyl nitrones towards dipolarophiles bearing electron-withdrawing groups



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ABSTRACT

The reactivity of porphyrinyl and corrolyl nitrones towards dipolarophiles bearing electron-withdrawing groups was studied and it was found that the two nitrones behave differently in 1,3-dipolar cycloaddition reactions. While porphyrinyl nitronone reacts with dimethyl fumarate, dimethyl acetylenedicarboxylate and ethyl propiolate to afford the expected isoxazolidine and isoxazoline cycloadducts, the corrolyl nitronone reacts with dimethyl fumarate to provide an isoxazolidine-substituted corrole but with dimethyl acetylenedicarboxylate it gives amide derivatives.

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Transformations of porphyrins and corroles at the β -pyrrolic positions through halogenation, formylation, nitration and cycloaddition reactions, among others have been explored as a way to gain access to new derivatives with suitable features to be used in different areas such as medicine, catalysis, electronic devices, sensors or dyes for solar cells.¹

We have already shown that porphyrins can be used as precursors of porphyrinyl azomethine ylides, which participate in 1,3-dipolar cycloaddition (1,3-DC) reactions with a range of dipolarophiles to give β -pyrrolidine-*meso*-tetraphenylporphyrins.²

Following our interest in 1,3-DC reactions,³ we decided to synthesize porphyrinyl and corrolyl nitrones and to study their reactivities. Nitrones are remarkably versatile building blocks in organic synthesis and are known to take part in 1,3-DC reactions with a wide range of dipolarophiles, including alkenes and alkynes, to give isoxazolidines and isoxazolines, respectively, often with a high degree of stereochemical control.⁴ Examples of isoxazolidine- and isoxazoline-fused chlorins resulting from the 1,3-DC reactions of porphyrins with a wide range of nitrones and nitrile oxides are also described in the literature.^{3b,5}

It is worth mentioning that isoxazolidines have attracted considerable attention mainly due to their potential biological activities.⁶ These heterocycles have also been used as precursors of γ -amino alcohols through the reductive cleavage of the N–O bond, and are potential precursors for the synthesis of natural products such as alkaloids and β -lactam antibiotics.⁷

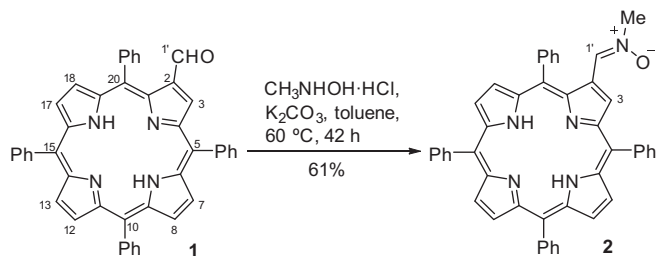
The key goal of this work is the preparation of porphyrinyl and corrolyl nitrones and to compare their reactivities in 1,3-DC reactions with dipolarophiles bearing electron-withdrawing groups, including dimethyl fumarate, dimethyl acetylenedicarboxylate (DMAD) and ethyl propiolate.

Based on our previous results, in which 5,10,15,20-tetraphenylporphyrin-2-carbaldehyde (**1**) was used as a precursor of a porphyrinyl azomethine ylide,² we decided to use this aldehyde to synthesize the corresponding nitronone **2** (Scheme 1) through the condensation with *N*-methylhydroxylamine hydrochloride. The reaction was carried out in toluene at 60 °C for 42 h, in the presence of K₂CO₃, to afford the expected porphyrinyl nitronone **2** in 61% yield.⁸

The ¹H NMR spectrum of the porphyrinyl nitronone **2** reveals that, in a CDCl₃ solution, it exists as a unique isomer, as shown by the presence of only one set of signals corresponding to the CH₃ (a singlet at δ 3.64 ppm) and the H-1' (a singlet at δ 6.94 ppm) and the aromatic protons. The NOE cross-peak between H-1' and CH₃ observed in the NOESY spectrum of nitronone **2** indicates that it adopts a *Z*-configuration.

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Scheme 1. Synthesis of the porphyrinyl nitrone **2**.

With nitrone **2** in hand, we investigated the 1,3-DC reactions with three representative dipolarophiles bearing electron-withdrawing groups, as outlined in Scheme 2. All reactions were carried out in toluene at 60 °C, under a nitrogen atmosphere. The reaction times were dependent on the reactivity of the dipolarophile used in each reaction.⁹

The reaction of nitrone **2** with dimethyl fumarate afforded, after 48 h, a mixture of the two diastereoisomeric adducts **3a** and **4a** in a 1:1 ratio with a 33% global yield. However, 15% of nitrone **2** and 10% of the formyl precursor **1** were also recovered. In order to elucidate the formation of **1** in this reaction (degradation of the nitrone or the cycloadduct) a toluene solution of nitrone **2** was heated (60 °C, 24 h) in the absence of the dipolarophile, affording **1** in 43% yield. This experiment confirms that aldehyde **1** results from the thermal degradation of **2**.

The separation of the isomeric adducts **3a** and **4a** revealed to be very difficult due to the similarity of their R_f values. This problem was overcome by preparing the corresponding Ni(II) complexes (**3b** and **4b**) which were then successfully separated by preparative TLC. The analysis of their COSY and NOESY spectra allowed the assignment of all proton resonances and the relative configuration of the isoxazolidine ring for both compounds.¹⁰ The stereochemistry was assigned mainly based on the resonance of H-3', which in compound **3b** (the one with slightly higher R_f) appears as a doublet at δ 4.92 ppm ($^3J_{H3'-H4'}$ 4.9 Hz). NOESY studies confirmed the

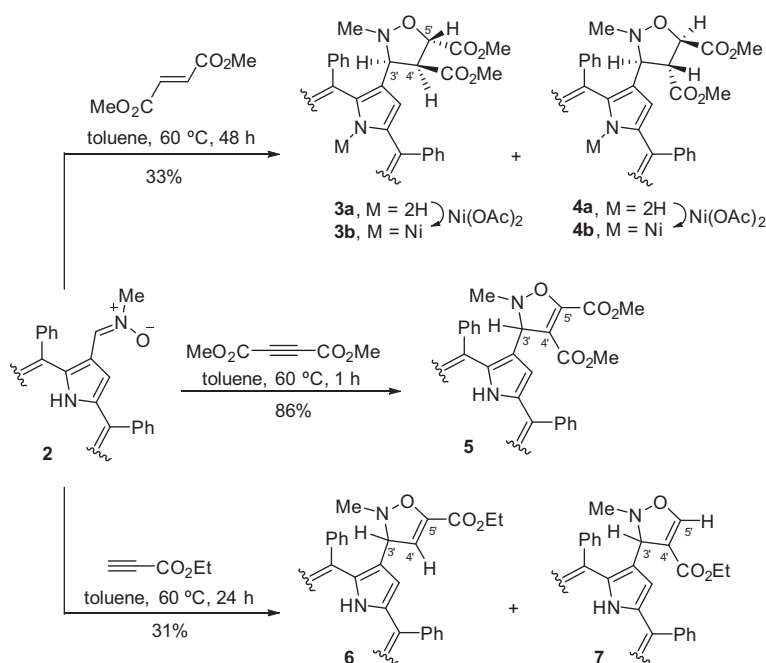
cis configuration in compound **3b** since intense NOE cross-peaks were observed between H-3' and H-4'. The absence of NOE cross-peaks between these two protons in **4b** supports the *trans* configuration of this diastereomer.

The reaction of nitrone **2** with DMAD took place in only 1 h, affording the expected single adduct **5** in 86% yield; 10% of the aldehyde **1** was also isolated. The ¹H NMR spectrum of **5** showed a singlet at δ 5.34 ppm corresponding to the resonance of H-3' and three singlets at δ 2.68, 3.37 and 3.94 ppm corresponding to the resonances of 5'-CO₂CH₃, 4'-CO₂CH₃ and N-CH₃, respectively, confirming the presence of the isoxazoline ring.¹¹

The reaction of nitrone **2** with ethyl propiolate required 24 h to give the two expected regioisomeric cycloadducts **6** and **7** in 18% and 13% yield, respectively. The structures of these isomers were confirmed by MS and NMR data. The ¹H NMR spectrum of compound **6**¹² (the one with higher R_f) shows, in the aliphatic region, two doublets at 4.87 and 5.90 ppm, assigned to protons H-3' and H-4', respectively. These data are consistent with the 5'-substituted isomer **6** and the value obtained for the coupling constant ($^3J_{H3'-H4'}$ 2.6 Hz) is in agreement with similar values found in the literature for other related isoxazolines.¹³ The ¹H NMR spectrum of 4'-substituted isomer **7** shows two singlets at 3.48 and 5.31 ppm, attributed to the resonance of the protons H-5' and H-3', respectively.

The configuration of adducts **6** and **7** was confirmed by the NOE cross-peaks observed in their NOESY spectra (Fig. 1). The NOESY spectrum of adduct **6** shows NOE cross-peaks of H-3' with H-4', NCH₃ and with one H_{ortho}-Ph-20. A NOE effect between H-4' and the other H_{ortho}-Ph-20 is also observed. These data show that the two H_{ortho} protons of the Ph-20 are not equivalent, confirming the lack of free rotation in this phenyl group due to steric hindrance of the isoxazoline moiety. The NOESY spectrum of compound **7** shows NOE correlations of H-3' with NCH₃ and one H_{ortho}-Ph-20.

In general, the results obtained from the 1,3-DC reactions of porphyrinyl nitrone **2** with dipolarophiles bearing electron-withdrawing groups were the expected, no diastereoselectivity was achieved for dimethyl fumarate and no regioselectivity was



Scheme 2. Reactions of porphyrinyl nitrone **2** with dimethyl fumarate, dimethyl acetylenedicarboxylate and ethyl propiolate.

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