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o-Thioquinones on [2.2]paracyclophanes: an example of totally stereocontrolled hetero Diels–Alder reactions

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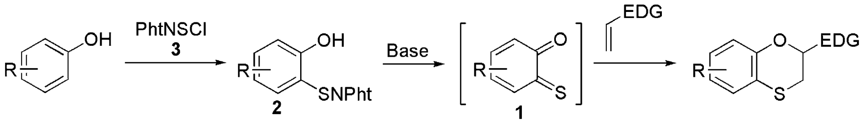
Abstract—The reaction of 4-hydroxy[2.2]paracyclophane with phthalimidesulfenyl chloride allowed the preparation of a suitable precursor for a paracyclophane-*o*-thioquinone. This species participates in an inverse electron demand hetero Diels–Alder reaction with different electron-rich alkenes to give the expected benzoxathiin cycloadducts with complete control of regio- and stereochemistry.

1. Introduction

Normal electron demand Diels–Alder reaction of [2.2]paracyclophane-based dienes is a well documented process that allowed the preparation of a variety of cyclophanes, especially chiral [2.2]paracyclophanes containing helical condensed aromatic subunits.[1] Helicenophanes, and more generally planar chiral cyclophanes are promising ligands to prepare catalysts for asymmetric processes, and are interesting for their potential applications as new materials.[2] There is now an increasing attention for paracyclophanes condensed with heterocyclic rings, and the hetero Diels–Alder reaction represents an useful tool for this task.[3] Mono-*o*-thioquinones,[4] of general formula **1**, are reactive intermediates potentially useful in this chemistry. As recently reported,[5] they can be obtained under very mild conditions by reacting the corresponding *o*-hydroxy-*N*-thiophthalimides **2** with bases (Scheme 1).

Compounds **2**, in turn, are the products of the *ortho* regiospecific S_EAr of phthalimidesulfenyl chloride **3** (PhtNSCl, Pht=Phthaloyl) with phenols, the key step of this procedure.[5] *o*-Thioquinones **1** are efficient electron-poor dienes with a plethora of electron-rich dienophiles[6] (Scheme 1), thus we envisaged their development with [2.2]paracyclophane substrates.

This paper reports the results of the study of (i) the sulfenylation reaction of 4-hydroxy[2.2]paracyclophane (**4**) with **3** (Scheme 2); (ii) the inverse electron demand Diels–Alder reaction of a [2.2]paracyclophane-*o*-thioquinone (**8**) obtained by this procedure.



Scheme 1. General procedure for the generation and trapping of *o*-thioquinones **1**.

Keywords: [2.2]Paracyclophanes; *o*-Thioquinones; Hetero Diels–Alder reactions; Stereoselectivity; Sulfur heterocycles.

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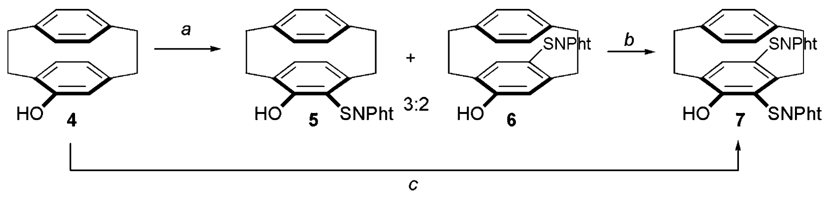


Scheme 2. Products formed on the phthalimide sulfenylation of 4-hydroxy[2.2]paracyclophane (**4**). Reagents: (a) **3** (1 equiv), $CHCl_3$, 0 °C, 2 h; (b) **3** (1 equiv), $CHCl_3$, rt, 1 h; (c) **3** (2.2 equiv), $CHCl_3$, rt, 2 h.

2. Results and discussion

2.1. Sulfenylation reaction of 4-hydroxy[2.2]paracyclophane (4)

The sulfenylation reaction of 4-hydroxy[2.2]paracyclophane (**4**) with **3** turned out to be a nontrivial extension of previously reported chemistry. After several attempts we realized that by carrying out the sulfenylation by adding 1 equiv of **3**, over 2 h at 0 °C, the expected *o*-hydroxy substituted derivative **5** could be isolated by flash chromatography on silica gel in 58% yield (Scheme 2). ^{1}H NMR spectroscopy of the crude reaction mixture showed (see Section 4) the contemporary formation of *para* isomer **6** (**5**:**6**=3:2), which was not isolated due to its poor stability and sensitivity to silica gel (Scheme 2).

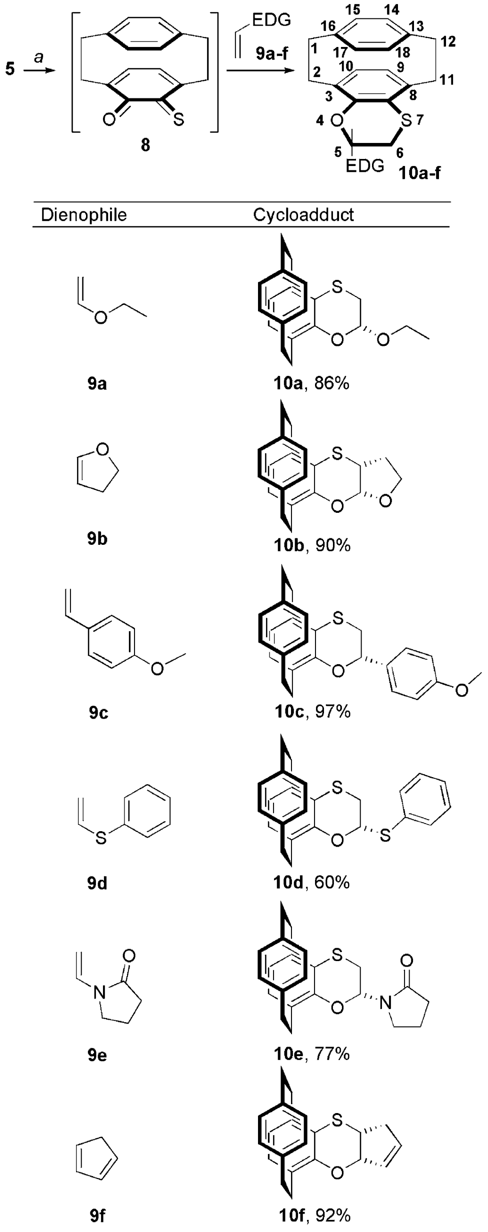
Carrying out the sulfenylation at rt, and/or using 2.2 equiv of **3**, led to the bis-sulfenylated thiophthalimide **7**, isolated as the sole reaction product in 82% yield (Scheme 2).

The sulfenylation of more than 50 different substituted phenols reported in the last decade,[5,6] afforded the *o*-monosubstituted *N*-thiophthalimide as the sole reaction product. However, the reaction of **3** with 2,5-dimethyl phenol, chosen as a simplified model of **4**, gave, after 3 h at rt, a 2:1 mixture of the corresponding *o*- and *p*-*N*-thiophthalimides indicating that a 2,5-dialkyl substitution can cause the lack of *ortho* regioselectivity. On the other hand, the possibility of bis-sulfenylation, with formation of **7**, is peculiar of this system. It has been demonstrated that a *N*-thiophthalimide substituent strongly depletes the nucleophilicity of aromatic rings[7] avoiding poly-substitution even with high reactive aromatics, like resorcin or 2,7-dihydroxynaphthalene. The isolation of **7**, that is formed even under very mild conditions, suggested that the paracyclophane system, due to the particular stereo-electronic situation offered by the proximity of the two aromatic rings, is able to overcome the withdrawing effect of the first thiophthalimide group. As a matter of fact, 2,5-dimethyl phenol or the corresponding *o*- and *p*-thiophthalimides, did not undergo bis-substitution neither using excess amounts of **3**, nor carrying out the reaction at 60 °C for several hours.

2.2. Inverse electron demand Diels–Alder reaction of the [2.2]paracyclophane-*o*-thioquinone (8)

Having derivative **5** in hand we decided to verify the possibility to generate the corresponding *o*-thioquinone **8** as a new interesting electron-poor diene possessing diastereotopic faces.

Reacting *o*-hydroxy-*N*-thiophthalimide **5** with 1 equiv of Et_3N in the presence of 5 equiv of ethyl vinyl ether (**9a**), after 20 h at 60 °C in $CHCl_3$, the expected benzoxathiin **10a** was obtained in 86% yield (Scheme 3).



Scheme 3. Generation and [4+2] cycloadditions of *o*-thioquionone **8**. Reagents: (a) Et_3N (1 equiv), dienophile **9** (2–5 equiv), $CHCl_3$, 60 °C, 20 h.