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Phthalimidesulfenyl Chloride Part 8[1]. Reaction with Activated Arenes: the First Example of *ortho*-Thioquinones Generation.

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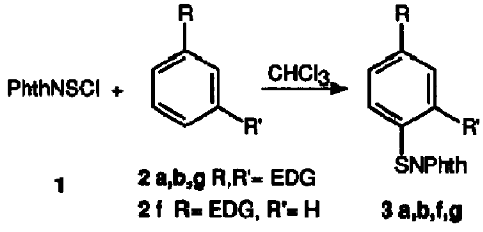
Abstract: *Phthalimidesulfenyl chloride 1 reacts with activated arenes **2a-g**, to give monosubstituted derivatives **3a-g**. Hydroxysulfenyl compounds **3a-d** have been used as suitable source of α - oxothiones (ortho-thioquinones) **4a-d**, which act as heterodienes in 4+2 cycloaddition reactions.*

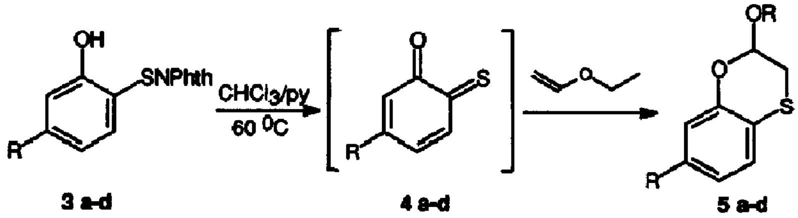
The reaction of sulfenyl chlorides with aromatic compounds to give substitution products is generally performed in the presence of Lewis acids such as zinc chloride, tin(IV) chloride, or boron trifluoride, as catalysts[2]. Examples of direct reactions of reactive sulfenyl halides and activated substrates exist[3], but frequently in these cases polysubstitution is observed[4], especially with phenols[5].

In the development of our studies regarding the reactivity of sulfenic derivatives[1,6,7,8], we observed that phthalimidesulfenyl chloride **1** reacts with activated arenes, at room temperature and without catalysts, giving only monosubstitution products (Scheme 1).

In this communication we report the simple synthesis of aromatic monosulfenyl derivatives **3a-g** from monoactivated and diactivated aromatic rings **2a,b,f,g** (Table 1), or from condensed aromatic hydrocarbons **2c-e** (Table 1). We also report our preliminary investigations on the reactivity of 1-hydroxy-2-phthalimidesulfenyl derivatives **3a-d** as source of α-oxothiones (*ortho*-thioquinones) **4a-d**; these hitherto unknown species can act as heterodienes in inverse electron demand Diels-Alder reactions (Scheme 2).



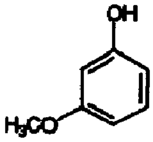
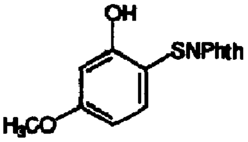
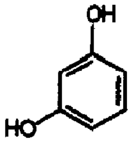
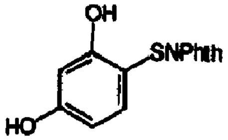
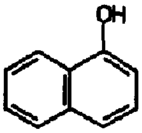
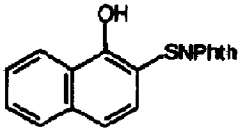
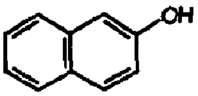
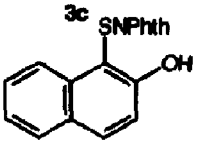
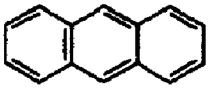
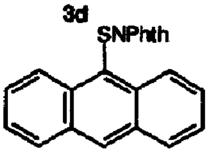
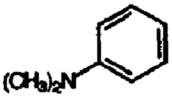
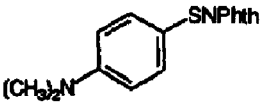
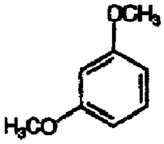
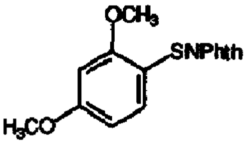
Scheme 1



Scheme 2

The reaction of **1** with **2a-g** is performed at room temperature, in chloroform as solvent; the conversion is generally complete in two hours and isolation of the monosulfenyl derivatives **3a-g** is accomplished washing the reaction mixture with a saturated solution of sodium bicarbonate and extracting the aqueous phase in chloroform (Table 1).

Table 1. Reactions of Phthalimidesulfenyl Chloride with Aromatic Compounds

Substrates	Products	Yield(%)
 **2a**	 **3a**	64
 **2b**	 **3b**	92
 **2c**	 **3c**	35
 **2d**	 **3d**	98
 **2e**	 **3e**	72a)
 **2f**	 **3f**	77
 **2g**	 **3g**	46

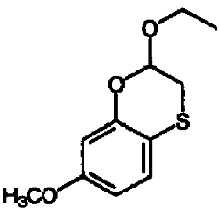
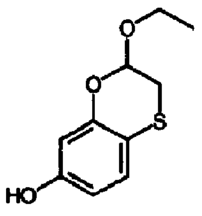
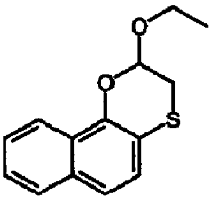
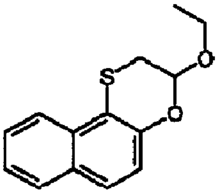
a) The reaction mixture was heated at 60°C for 4 days

Polysubstituted derivatives were not detected neither when activated rings reacted with 2.5 equivalent of **1**, nor when isolated monosubstituted derivative **3b** was reacted with an excess of **1**.

In our conditions monosubstituted arenes, except **2f**, did not react. In fact the presence of two activating groups or of one electron donating substituent and a condensed ring is necessary, meaning that a considerable activation of the reaction centre is requested[9].

As we previously underlined phthalimide anion is an efficient leaving group[1,6-8,10] leading to thiocarbonyl species[7,8]; looking at aromatic sulfenyl derivatives we observed that treating compounds **3a-d** with pyridine they undergo an 1,4-elimination of the phthalimide residue to form reactive α-oxothiones (*ortho*-thioquinones) **4a-d**. These latter species have been trapped by ethyl vinyl ether with consequent rearomatization of the benzene rings (Scheme 2). The reaction was monitored by ^1H nmr and when the conversion was complete the crude was washed with saturated ammonium chloride and extracted with *n*-pentane, which allows the elimination of the insoluble phthalimide. Flash chromatography gave pure cycloadducts **5** in satisfactory yields (Table 2).

Table 2. Reactions of Ethyl Vinyl Ether with α-Oxothiones 4 a-d

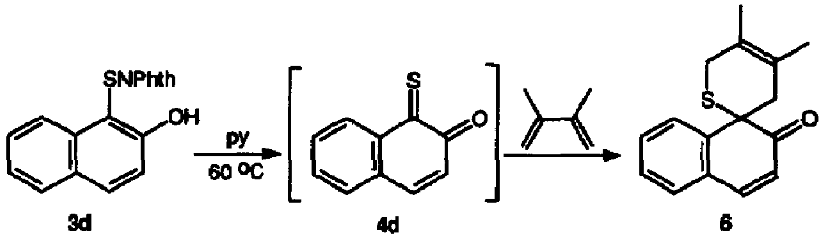
Cycloadducts	 **5a**	 **5b**	 **5c**	 **5d**
React.time(h)	50$^{a)}$	90$^{b)}$	24$^{a)}$	15$^{a)}$
Yield(%)	58	80	87	65

a) At 80°C in $CHCl_3$. b) At room temperature in DMF

Another remarkable result obtained using *ortho*-thioquinones species as diene is represented by the total regio control occurring during the reaction which affords a single isomer. Indeed *ab initio* molecular calculations[11] allowed to rationalize these results, since, as already reported for aliphatic oxothiones[8], they indicated a most favourable interaction between the LUMO of the oxothiones and the HOMO of the ethyl vinyl ether, typical for inverse electron demand Diels-Alder reactions, and showed a higher electron density on the C=S bond of the *ortho*-thioquinone's LUMO and on the CH_2 of the ethyl vinyl ether's HOMO leading to a preferred regioisomer formation[8].

Spectroscopic data confirmed the proposed structures for cycloadducts **5a-d** which have diagnostic acetalic protons whose signals are in the 5 to 6 ppm range[12].

A second aspect of α-oxothiones reactivity we studied regard their chemical behaviour in presence of dienes. When product **4d** reacted with 2,3-dimethylbutadiene, the spiro cycloadduct **6** was formed albeit in low yield (46%) (Scheme 3).



Scheme 3

In this case only the C-S double bond of **4d** was involved in the cycloaddition, and **4d** no longer acted as a diene. Indeed in the presence of the diene the oxothione reactivity as dienophile is preferred.

Probably owing to the lack of rearomatization of the naphthalenic ring the reaction is very slow ; it was performed at 60 °C in chloroform, but after ten days starting material was still present. Higher temperatures did not substantially improve the conversion.

The spiro compound **6** is stable and it can be easily purified by flash chromatography on silica gel.

Detailed studies regarding *ortho*-thioquinones role in 4+2 cycloadditions are currently in progress in our laboratories.

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9. *Para*-methoxyphenol react with **1** in the same conditions reported for **2a-g** to give the expected 2-thiophthalimide-4-methoxyphenol.
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11. *Ab initio* molecular calculations have been performed with the SPARTAN program at 3-21 G* level.
12. Acetalic proton signal for compounds **5a**: δ= 5.37(X part of an ABX system, 1H, J_{AX}= 4.8 Hz, J_{BX}= 2.2 Hz); **5b**: δ= 5.37(X part of an ABX system, 1H, J_{AX}= 4.6 Hz, J_{BX}= 2.2 Hz); **5c**: δ= 5.60(X part of an ABX system, 1H, J_{AX}= 4.4 Hz, J_{BX}= 2.2 Hz); **5d** δ= 5.49(X part of an ABX system, 1H, J_{AX}= 4.4 Hz, J_{BX}=2.6 Hz).

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