Phthalimidesulfenyl Chloride 12:[1] Generation and Trapping of *para*-Monothioquinones

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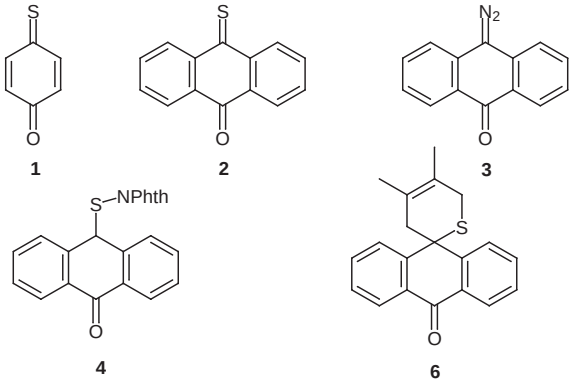
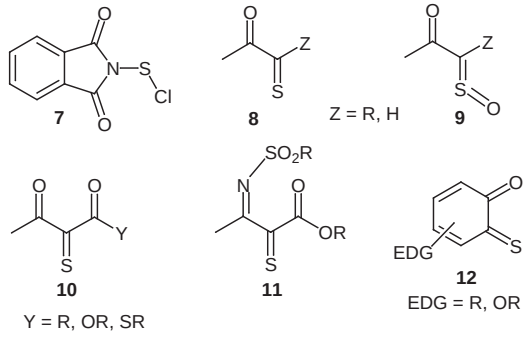
Abstract: The reaction of phthalimidesulfenyl chloride **7** with *o,o'*-disubstituted phenols affords *p*-hydroxythiophthalimides which are the precursors of the corresponding *p*-thioquinones. The latter species are generated under mild conditions and efficiently trapped with 1,3-dienes.

Key words: phthalimidesulfenyl chloride, *p*-thioquinones, hetero Diels–Alder reaction, spiro dihydrothiopyrans, desulfurization

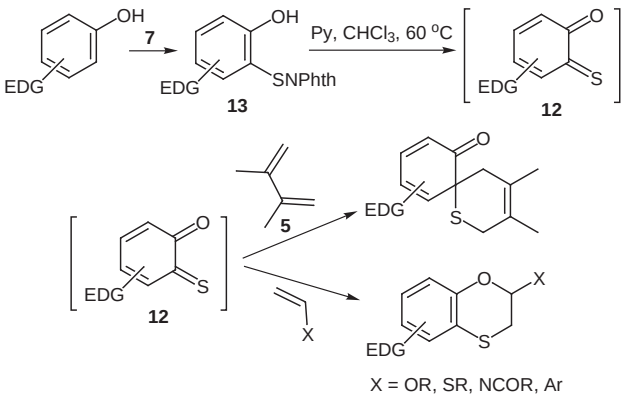
In contrast to *p*-quinones the corresponding monothionated compounds, namely *p*-monothioquinones, are very elusive species. In particular, as unique example, the parent *p*-monothiobenzoquinone **1** has been pyrolytically obtained and spectroscopically identified in argon matrix at 4°K.[2] Other examples of such species available in the literature have been revealed to be misinterpreted.[3] On the other hand the crystalline stable *p*-thioanthraquinone **(2)** has been prepared by heating 10-diazoanthrone **(3)** with elemental sulfur in DMF,[4,5] or reacting thiophthalimide derivative **4** with tertiary bases.[6] In both cases the dienophilic carbon–sulfur double bond of **2** was shown to be able to react with electron-rich dienes, such as 2,3-dimethylbuta-1,3-diene (**5**), to give spiro cycloadducts of type **6**.[4–6]



In the last few years we have demonstrated the utility of the phthalimidesulfenyl chloride **(7)** (PhthNSCl, Phth = phthaloyl) for the generation of several α-functionalized thiocarbonyl compounds such as α-oxothiones[7] **8**, α-sulfines[8] **9**, α,α'-dioxothiones[9] **10**, α-iminothiones[10] **11** and *o*-thioquinones[1,11] **12**. These are useful intermediates which react as electron-poor dienophiles or heterodienes in direct or inverse electron demand Diels–Alder reactions.



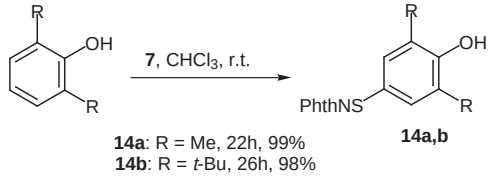
In particular *o*-thioquinones **12** are generated by reacting *o*-hydroxythiophthalimides **13** in chloroform at 60 °C with tertiary bases, like pyridine, and are directly trapped by electron-rich dienes or dienophiles (Scheme 1) to give spiro dihydrothiopyrans or 1,4-benzoxathiins respectively.[1,11] The selective *ortho*-sulfenylation of phenols with **7** affords derivatives **13** in high yields (Scheme 1).[1,12]



Scheme 1

Thus the possibility to drive the substitution of the thiophthalimido moiety *para* to the hydroxy group could end up with the formation of *p*-thioquinone derivatives.

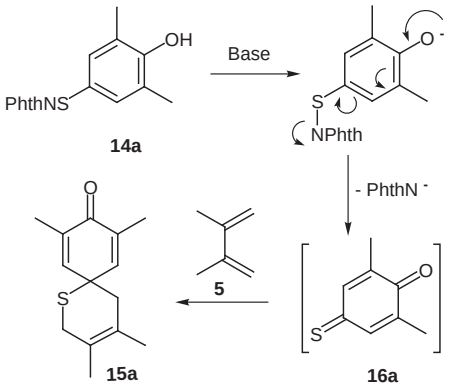
In this paper we report our methodology for the preparation of valuable precursors of *p*-monothioquinones which can be generated under mild conditions and trapped as electron-poor dienophiles. The reaction of phthalimidesulfenyl chloride **7** with 2,6-dimethylphenol and 2,6-di-*tert*-butylphenol occurs smoothly in chloroform at room temperature to give the corresponding 4-hydroxy-3,5-dialkylthiophthalimides **14a,b** in almost quantitative yields (Scheme 2).



Scheme 2

Compounds **14** are crystalline solids which can be purified by column chromatography and stored at room temperature for several months without decomposition.

We decided to verify the possibility to use derivatives **14** to generate *p*-thioquinones using the same reaction conditions which were effective for the formation of *o*-thioquinones[12] (see Scheme 1). Thus thiophthalimide **14a** was heated at 60 °C in chloroform in the presence of 1 equivalent of pyridine and 2,3-dimethylbuta-1,3-diene **(5)** as trapping reagent (Scheme 3).



Scheme 3

In this case, however, even using an excess of pyridine, high temperature and prolonged reaction time, we obtained only poor yield of the spiro dihydrothiopyran **15a**, which is the result of the cycloaddition reaction of dienophilic *p*-thioquinone **16a** with the diene **5**, while large amounts of unreacted thiophthalimide **14a** were recovered from the reaction mixtures (Scheme 3, Table 1).

Nevertheless using stronger tertiary bases like triethylamine or DBU it was possible to isolate cycloadduct **15a** in very good yields even working at room temperature and with catalytic amounts of base (Table 1).

Table 1 Effect of Base and Temperature on the Synthesis of **15a**.

Entry	Base (equiv)	Reaction Conditions			Yield (%)[a]
		Solvent	Temp (°C)	Time (h)	
1	pyridine (1)	$CHCl_3$	60	80	12
2	pyridine (2)	$CHCl_3$	60	80	14
3	pyridine (1)	benzene	80	80	18
4	pyridine (1)	tolnene	110	80	32
5	DBU (1)	$CHCl_3$	60	1	69
6	Et_3N (1)	$CHCl_3$	60	1	65
7	Et_3N (1)	$CHCl_3$	23	7.5	93
8	Et_3N (0.2)	$CHCl_3$	23	24	90

[a] Isolated yield of **15a** after column chromatography.

The generality of this approach for the generation of dienophilic *p*-thioquinones was simply demonstrated since, in our optimized reaction conditions (Table 1, Entry 7), it was possible to obtain from thiophthalimides **14b** the corresponding thioquinone **16b** which reacted with **5** to give the cycloadduct **15b**, isolated in 85% yield. Moreover thione **16a** reacted with cyclohexa-1,3-diene and 2-methylbuta-1,3-diene (isoprene) affording spiro derivatives **17** and **18** in 80% and 98% yields, respectively. Derivative **18** was obtained as a 7:1 mixture of regioisomers. The relative regiochemistry of compounds **18** was determined by the analysis of their ^1H NMR. spectra in comparison with those of similar mixtures deriving from the reaction of isoprene with different thiocarbonyl compounds[13].

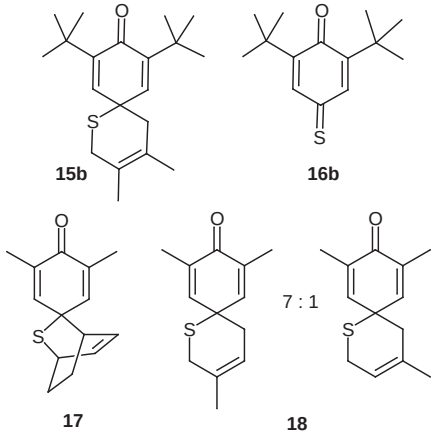
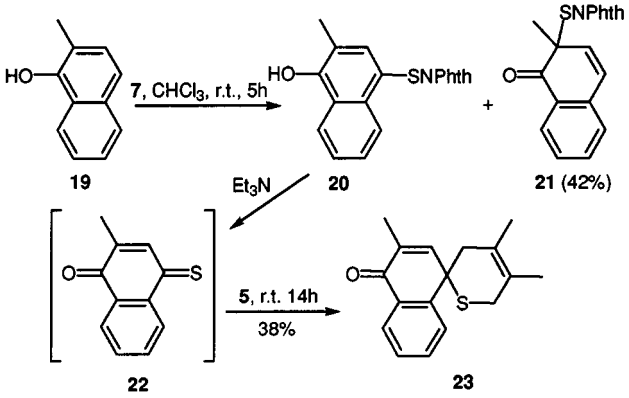


Figure 3

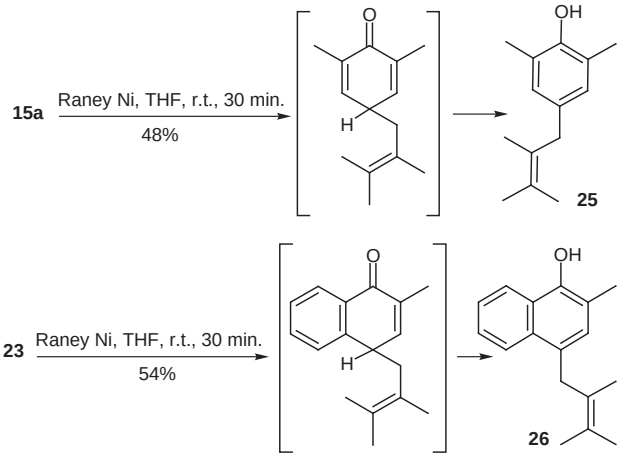
A peculiar result arose when we tried to extend this methodology to other aromatic systems. When sulfenyl chloride **7** was reacted with 2-methyl-1-naphthol **(19)** we observed the formation of an equimolar mixture of the expected thiophthalimide **20** and α,β-unsaturated ketone **21**. The latter is clearly derived from the attack of **7** at the methyl-substituted site of **19** with elimination of HCl.

Since *N*-thiophthalimide **20** was unstable on silica gel, its ability to generate the corresponding *p*-thionaphthoquinone **22** was verified by adding triethylamine and diene **5** to the crude reaction mixture. Under these reaction conditions a mixture of cycloadduct **23** (38%) and unaltered **21** (42%) was isolated (Scheme 4).



Scheme 4

Another intriguing result was obtained when we tried to apply this methodology to the preparation of monothioanthraquinone **2**.[4,6] The reaction of **7** with 9-anthrol gave a complex mixture of compounds. The presence, among the other products, of the expected *N*-thiophthalimide **24** was however confirmed since by adding Et_3N and **5** to the reaction mixture we isolated the cycloadduct **6**,[4,6] albeit in very low yield (10%).



Scheme 5

As an application to this simple access to *p*-thioquinones cycloadducts **15a** and **23** were reacted with Raney Nickel in THF at room temperature. As reported in Scheme 5 the

Table 2 Spectroscopic Data of Spiro Cycloadduts **6**, **15a**, **15b**, **17, 18**, and **23**.

Cycloadduct	MS *m/z* (%)]	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)]	^{13}C NMR ($CDCl_3$) δ
6	306 ($M^{+\cdot}$, 2), 224 (45), 84 (100)	1.67 (br s, 3H), 1.97 (br s, 3H), 2.80 (br s, 2H), 3.22 (br s, 2H), 7.41–7.64 (m, 4H), 7.83–7.88 (m, 2H), 8.28-8.34 (m, 2H)[a]	
15a	234 ($M^{+\cdot}$, 9), 86 (100).	1.72 (br s, 3H), 1.83 (br s, 3H), 1.91 (br s, 6H), 2.32 (br s, 2H), 3.25 (br s, 2H), 6.70 (br s, 2H)	16.1, 19.3 (q), 20.4 (q), 30.3 (t), 41.2 (t), 42.4 (s), 122,7 (s), 124,9 (d), 134.3 (s), 145.3 (s), 186.2 (s)
15b	318 ($M^{+\cdot}$, 13), 303 (6), 236 (8), 84 (100).	1.22 (s, 18H), 1.72 (br s, 3H), 1.84 (br s, 3H), 2.30 (br s, 2H), 3.23 (br s, 2H), 6.60 (s, 2H)	19.3, 20.4 (q), 29.3 (q), 30.6 (t), 34.7 (s), 42.1(t), 42.6 (s), 123.8 (s), 125.3 (d), 141.5 (s), 146.1 (s), 185.5 (s)
17	232 ($M^{+\cdot}$, 4), 152 (13), 79 (100).	1.28–1.47 (m, 1H), 1.65–1.79 (m, 1H), 1.82 (d, 3H, *J* = 1.6), 1.91 (d, 3H, *J* = 1.6), 2.10–2.27 (m, 2H), 2.66–2.71 (m, 1H), 3.58–3.66 (m, 1H), 6.36–6.44 (m, 1H), 6.52–6.58 (m, 1H), 6.61–6.69 (m, 1H), 7.10–7.14 (m, 1H)	15.9, 16.8 (q), 20.0, 28.4 (t), 35.3 (d), 39.6 (d), 53.0 (s), 131.6 (s), 133.2, 134.1, 134.3 (d), 145.9, 148.2 (s), 186.1 (s)
18	Major: 220 ($M^{+\cdot}$, 56), 205 (7), 146 (11), 84 (100).	Major: 1.85 (s, 3H), 1.91 (s, 6H), 2.36–2.41 (m, 2H), 3.24 (s, 2H), 5.55–5.60 (m, 1H), 6.72 (s, 2H). Minor: 1.75 (s, 3H), 1.91 (s, 6H), 2.26 (s, 2H), 3.35–3.38 (m, 2H), 5.70–5.78 (m, 1H), 6.72 (s, 2H)	Major: 16.1 (q), 24.1 (q), 28.7 (t), 35.2 (t), 40.6 (s), 119.5 (d), 129.9 (s), 134.6, 134.7 (d), 144.9 (s), 186.1 (s)
23	270 ($M^{+\cdot}$, 51), 188 (100)	1.74 (br s, 3H), 1.89 (br s, 3H), 2.03 (d, 3H, *J* = 1.4), 2.12–2.27 (m, 1H), 2.97–3.20 (m, 2H), 3.54–3.64 (m, 1H), 6.95–7.01 (m, 1H), 7.39–7.47 (m, 1H), 7.55–7.63 (m, 1H), 7.71–7.76 (m, 1H), 8.21 (dd, 1H, *J* = 1.6, 8.8)	16.3, 19.3 (q), 20.5 (q), 31.8 (t), 42.0 (t), 44.0 (s), 122,5, 126.1, 131.2 (s), 127.0, 127.5, 127.8, 132.5 (d), 131.8 (s), 144.5 (d), 145.4 (s), 184.5 (s).

[a] Lit.[4] ^{1}H NMR (60 MHz, $CDCl_3$/TMS): δ = 1.69 (s, 6H), 2.75 (s, 2H), 3.21 (s, 2H).

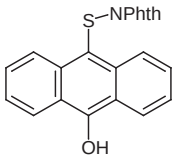


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Figure 4

expected desulfurization, which occurred without affecting the exocyclic carbon–carbon double bond, was followed by a spontaneous aromatization allowing the isolation of the allyl substituted phenols **25** and **26**[14] (Scheme 5).

In conclusion we have shown that phthalimidesulfenyl chloride **7** and *o,o'*-disubstituted phenols can be used as key reagents for the preparation of *p*-thioquinones. In several cases these species are generated and trapped in almost quantitative yields and under mild reaction conditions.

Further applications of the chemistry of **7** to the synthesis of functionalised thiocarbonyl compounds are under investigation in this laboratory.

^{1}H and ^{13}C spectra were recorded in $CDCl_3$ at 200 MHz using the residual $CHCl_3$ at δ = 7.26 as reference. Melting points are uncorrected. $CHCl_3$, CH_2Cl_2, THF, pyridine and triethylamine were dried following standard procedures, all commercial reagents were used without further purification as obtained from freshly opened containers. Petroleum ether used had bp 40–70 °C. Phthalimidesulfenyl chloride **7** was prepared as reported elsewhere.[1]

Compounds 14a, 14b, 20, 21 and 24

The reaction of **7** with the required phenol was performed as previously reported.[1] In the case of **14a**, **14b** and **21** isolation was achieved by flash chromatography (CH_2Cl_2). Thiophthalimides **20** and **24** were not isolated due to their instability on silica gel and the crude mixtures were directly treated with Et_3N to generate the corresponding *p*-thioquinones. Data of compounds **14a**, **14b** and **21** are as follows:

***N*-(3,5-Dimethyl-4-hydroxyphenylthio)phthalimide (14a)**

White solid; mp 173–175 °C.

^{1}H NMR: δ = 2.20 (s, 6 H), 4.97 (s, 1 H, OH), 7.47 (s, 2 H), 7.67–7.76 (m, 2 H, Phth), 7.85–7.92 (m, 2 H Phth).

^{13}C NMR: δ = 15.7 (q), 123.8 (d), 124.0 (d), 124.4 (s), 132.0 (s), 134.4 (d), 135.3 (s), 154.5 (s), 168.0 (s).

MS: *m/z* (%) = 299 ($M^{+\cdot}$, 5), 147 (39), 76 (100). Anal. $C_{16}H_{13}NO_3S$: Calcd. C, 64.20; H, 4.38; N, 4.68. Found C, 64.00; H, 4.60; N, 4.20.

***N*-(3,5-Di-*tert*-butyl-4-hydroxyphenylthio)phthalimide (14b)**

Pale yellow solid; mp 215–217 °C.

^{1}H NMR: δ = 1.41 (s, 18 H), 5.50 (s, 1 H, OH), 7.67–7.82 (m, 4 H), 7.84–7.96 (m, 2 H).

^{13}C NMR: δ = 30.0 (q), 34.3 (s), 123.8 (d), 124.2 (s), 132.2 (s), 132.8 (d), 134.3 (d), 136.8 (s), 156.3 (s), 168.0 (s).

MS: *m/z* (%) = 383 ($M^{+\cdot}$, 16), 236 (16), 147 (100). Anal. $C_{22}H_{25}NO_3S$: Calcd. C, 68.90; H, 6.57; N, 3.65. Found C, 68.73; H, 6.80; N, 3.28.

Thiophthalimide 21

Pale yellow solid; mp 149–151°C.

IR (KBr pellet): ν = 2923 (CH), 1784, 1740 (amide C=O), 1714 (C=O), 1667 cm^{-1} (C=C).

^{1}H NMR: δ = 1.72 (s, 3 H), 6.09 (d, 1 H, AB system, *J* = 9.6 Hz), 6.75 (d, 1 H, AB system, *J* = 9.6 Hz), 7.10–7.15 (m, 1 H), 7.40–7.56 (m, 2 H), 7.73–7.78 (m, 2 H, Phth), 7.84–7.89 (m, 2 H, Phth), 8.02–8.15 (m, 1 H).

^{13}C NMR: δ = 20.2 (q), 59.6 (s), 124.0 (d), 127.5, 128.3, 129.2, 129.3, 130.8, 134.1 (d), 129.6 (s), 131.6 (d), 134.6 (d), 136.1 (s), 167.6 (s), 194.1 (s). MS: *mz* (%) = 335 ($M^{+\cdot}$, 5), 188 (23), 157 (100), 147 (27).

Anal. $C_{19}H_{13}NO_3S$: Calcd. C, 68.04; H, 3.91; N, 4.18. Found C, 68.33; H, 3.78; N, 4.02.

Spiro Cycloadducts 6, 15a, 15b, 17, 18 and 23: General Procedure

To a solution of *N*-thiophthalimide in anhyd $CHCl_3$ were added succesively the appropriate diene (2 equiv) and Et_3N (1 equiv). The mixture was kept at r.t. until the complete disappearance of the thiophthalimide, monitored by TLC and/or ^{1}H NMR spectroscopy. Evaporation of the solvent and flash chromatography allowed the isolation of cycloadducts **6**,[4] **15a, 15b, 17, 18** and **23**. Spectroscopic data are reported in Table 2. Derivatives **15a, 15b, 17, 18** and **23** gave satisfactory microanalyses (± 0.4%) (Table 2).

Desulfurization of Cycloadducts 15a and 23: General Procedure

To a solution of the spirocycloadduct **15a** or **23** (0.1 mmol) in anhyd THF (1 mL) was added activated Raney Nickel[15] (0.3 mL) and the mixture stirred at r.t. for 30 min. The crude mixture was diluted with CH_2Cl_2 (20 mL) filtered through Celite and evaporated to dryness. Purification of the phenols **25** and **26** was achieved by flash chromatography.

4-(2,3-Dimethylbut-2-enyl)-2,6-dimethylphenol (25)

Petroleum ether/EtOAc (5:1); yield: 48%; orange oil.

^{1}H NMR: δ = 1.58 (br s, 3 H), 1.72 (br s, 3 H), 1.79 (br s, 3 H), 2.22 (s, 6 H), 3.26 (s, 2 H), 4.50 (br s, 1 H, OH), 6.75 (s, 2 H).

^{13}C NMR: δ = 18.2 (q), 20.6 (q, 3 CH_3), 39.1 (t), 109.0 (s), 122.7 (s), 125.2 (s), 128.5 (d), 132.5 (s), 150.2 (s).

MS: *m/z* (%) = 204 ($M^{+\cdot}$, 28), 122 (22), 84 (100). Anal. $C_{14}H_{20}O$: Calcd. C, 82.30; H, 9.87. Found C, 82.47; H, 9.69.

4-(2,3-Dimethylbut-2-enyl)-2-methylnaphthol (26)

Petroleum ether/EtOAc 10:1 (53%); red glassy solid.

^{1}H NMR: δ = 1.60 (br s, 6 H), 1.80 (br s, 3 H), 2.38 (s, 3 H), 3.73 (br s, 2 H), 4.95 (s, 1 H, OH), 6.95 (s, 1 H), 7.43–7.51 (m, 2 H), 7.91–7.97 (m, 1 H), 8.16–8.19 (m, 1 H).

MS: *m/z* (%) = 240 ($M^{+\cdot}$, 12), 225 (7), 158 (32), 41 (100).

Anal. $C_{17}H_{20}O$: Calcd. C, 84.96; H, 8.39. Found C, 85.11; H, 8.22.

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