α-Oxothiones, IV[‡]

Electrophilic Substitution of Phenols with α,α′-Dioxothiones and *ortho*-Thioquinones

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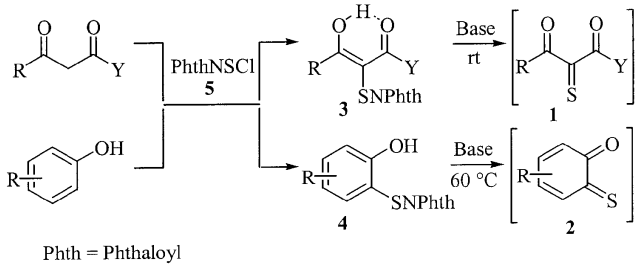
α,α′-Dioxothione **1a** and *ortho*-thioquinones **2a** and **2b** are able to react with several phenols and *N*,*N*-dimethylaniline to give the corresponding alkyl aryl or diaryl sulfides. The mechanism of this reaction was proved to be an electrophilic aromatic substitution undergone by the highly polarised carbon–sulfur double bond. Following this procedure, the atropoisomeric biphenyl compound **26** was also prepared.

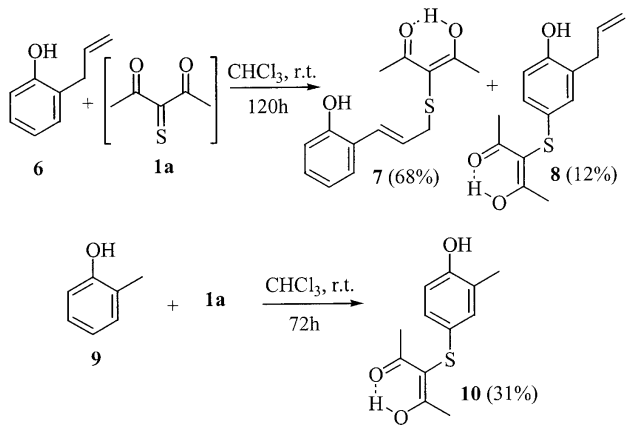
Over recent years we have demonstrated the utility in organic synthesis of α,α′-dioxothiones **1** and *ortho*-thioquinones **2**, thanks to their ability to act as enophiles,[1] electron-poor dienophiles[2] and heterodienes[3] in electrocyclic reactions. Derivatives **1** and **2** can be generated and trapped in situ by treating the corresponding *N*-thiophthalimides **3** and **4** with tertiary amines. Compounds **3** and **4** are, in turn, obtained by treating β-dicarbonyls[2] and phenols[4] with phthalimidesulfenyl chloride (**5**) (PhthNSCl, Phth = phthaloyl): the key reagent of this simple and efficient methodology for the generation of α-oxothiocarbonyl compounds (Scheme 1).



Scheme 1. Generation of α, α′-dioxothiones and *ortho*-thioquinones

In this paper we report that, in addition to their utility in cycloaddition reactions, thiones **1** and **2** also react with activated arenes, through an electrophilic aromatic substitution (S_EAr), affording alkyl aryl or diaryl sulfides.

During our study into the ene reaction[1] of thione **1a** (R = Y = Me) with *o*-allyl phenol **6**, we observed, together with the expected ene-adduct **7**, the unforeseen formation of sulfide **8**, isolated in 12% yield (Scheme 2). Compound **8** can be considered as the product of the S_EAr of thione **1a** on the *para* position of phenol **6**. Indeed, when we repeated the reaction using *o*-cresol **9**, we were able to isolate sulfide **10** in 31% yield (Scheme 2) after 72 h at room temperature.



Scheme 2. Reaction of thione **1a** with *o*-allyl phenol **6** and *o*-cresol **9**

Several examples of thiophilic attack by carbon nucleophiles are reported in the chemistry of thiocarbonyl compounds,[5] but to the best of our knowledge, no example of electrophilic thiones involved in S_EAr has been described. The formation of sulfide **10** could also be explained by invoking a direct attack of the *para* carbon of phenol **9**, or the corresponding phenolate, onto the sulfenamidic sulfur[6] of **3a** (Scheme 3, path a), without the effective intermediacy of thione **1a** (Scheme 3, path b).

To test these hypotheses, we carried out two different experiments. Firstly, *o*-cresol **9** was treated under the same conditions (i.e., chloroform, pyridine, room temperature) with sulfenamide **11**. No evidence was found for the formation of sulfide **12**, thus indicating that **9** is unable to attack the sulfur atom of similar *N*-thiophthalimido derivatives (Scheme 4, Equation 1).

[‡] Part III: Ref.[1]

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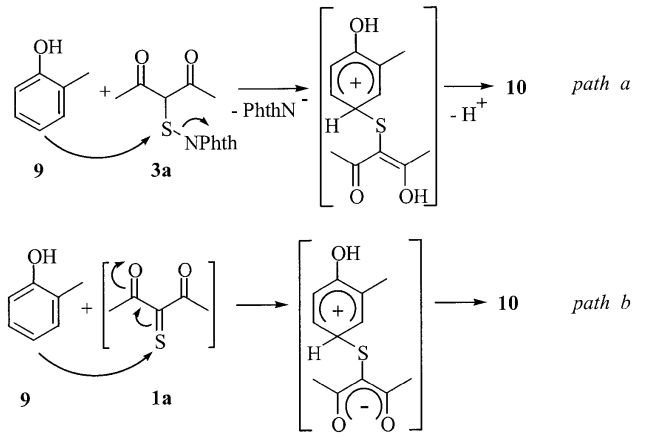
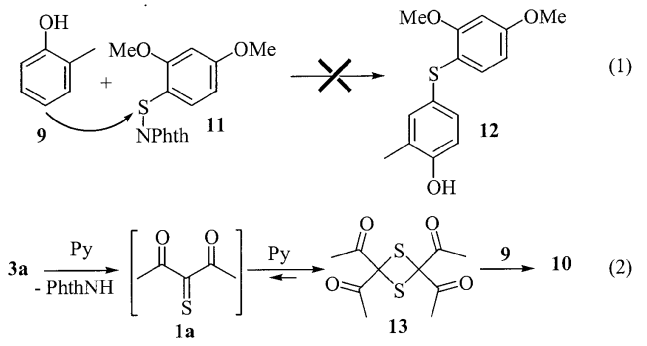


Scheme 3. Possible mechanisms for the formation of sulfide **10**



Scheme 4. Evidence for the actual mechanism operative in the formation of **10**

In the second experiment, we took advantage of the particular behaviour of thione **1a**, which, when generated in the absence of trapping reagents, dimerizes to give the 1,3-dithiacyclobutane **13**, which in turn undergoes a slow, base-catalysed retro-dimerization.[2] Thus, after treating **3a** with pyridine and filtering off the phthalimide formed, we had in solution mainly dimer **13** and pyridine. Addition of *o*-cresol (**9**) to this mixture resulted in the isolation of sulfide **10**, clearly formed through an electrophilic aromatic substitution process undergone by thione **1a** (Scheme 4, Equation 2).

We verified that this unusual reactivity of thione **1a** occurs with highly activated arenes, such as EDG-substituted phenols and *N*,*N*-dimethylaniline,[7] affording the corresponding alkyl aryl sulfides **14**–**19** as reported in Figure 1. Compounds **16**–**18** were obtained as mixtures of two regioisomers: tentative attribution[8] of the regiochemistry was carried out by examination of the spectroscopic data of minor and major isomers (see Experimental).

The long reaction time required for the synthesis of sulfides **14**–**19** is among the reasons for the moderate yields obtained. As a matter of fact, under these conditions the irreversible polymerization of thione **1a** becomes a competitive side reaction.[2] On the other hand, no improvement was achieved by using higher temperatures (60 and 80 °C), different solvents[9] or stronger bases.[10]

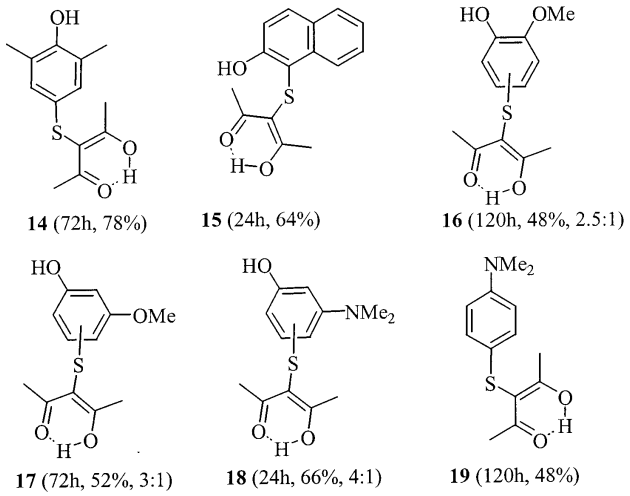
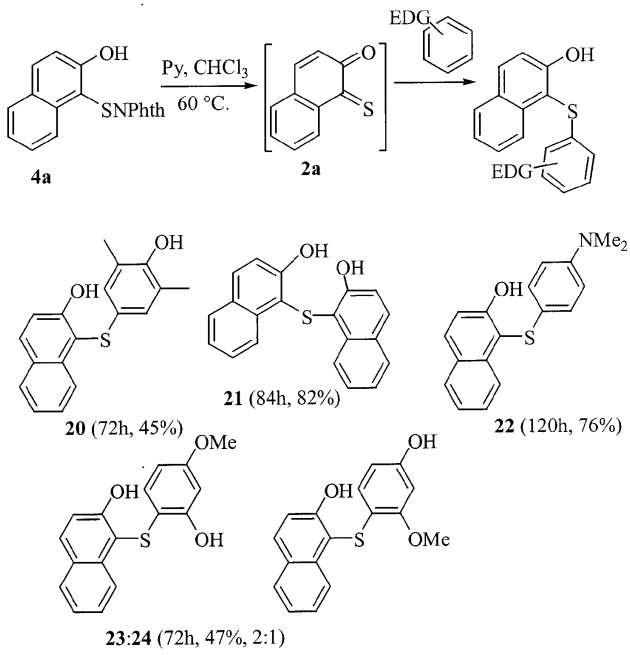


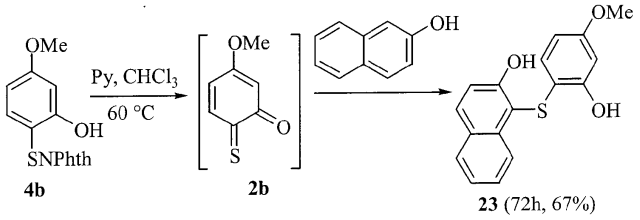
Figure 1. Aryl alkyl sulfides **14**–**19** obtained by treating thione **1a** with phenols and with *N*,*N*-dimethylaniline



Scheme 5. Diarylsulfides obtained from S_EAr of thioquinone **2a**

The next step was to verify whether such reactions could also take place with *ortho*-thioquinones. Thus, thioquinone **2a** was generated from thiophthalimide **4a** and pyridine in chloroform at 60 °C and treated with several activated arenes. As reported in Scheme 5, the S_EAr reaction also occurred with thioquinone **2a**, allowing us to isolate diaryl sulfides **20**–**24** in moderate to good yields (Scheme 5).

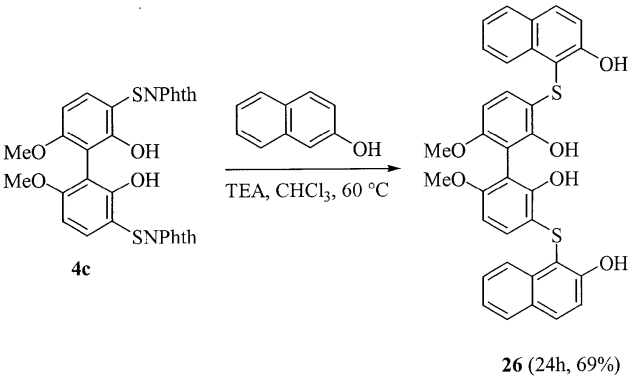
Structure assignment for regioisomers **23** and **24**, obtained by treatment of **2a** with *m*-methoxyphenol,[11] was unequivocally confirmed by comparison of derivative **23** with an authentic sample obtained by treating thioquinone **2b**, generated from the corresponding thiophthalimide **4b**,



Scheme 6. Reaction of thioquinone **2b** with β-naphthol

with β-naphthol (Scheme 6). As expected, in this case the electrophilic aromatic substitution afforded sulfide **23** in 67% yield, as the sole product (Scheme 6).

The generality of this approach to the synthesis of symmetrical and unsymmetrical polyhydroxylated diaryl sulfides[12] was further demonstrated by treating sulfenamide **4c**[14] with β-naphthol, which resulted in the isolation of biphenyl derivative **26** in 69% yield, as reported in Scheme 7.



Scheme 7. Synthesis of atropoisomeric biphenyl sulfide **26**

In conclusion, we have shown that dioxothiones and thioquinones are able to react with phenols to give polyhydroxylated alkyl aryl or diaryl sulfides, by an S_EAr mechanism, as a further demonstration of the synthetic versatility of these species. Incidentally, on treating di-*p*-tolylthioketone with β-naphthol in the presence of pyridine, we did not observe the formation of any product deriving from an S_EAr process, even after prolonged reaction time. Thus, this work represents the first example of such a reaction for thiocarbonyl compounds and strongly supports the conjecture of an unusually high polarizability in α-oxothiones (Figure 2).

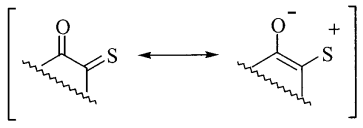


Figure 2. Polarizability of α-oxothiones

Further aspects of the chemistry of oxothiones **1** and **2**, including the extension of the S_EAr reaction to the preparation of synthetically valuable sulfides,[12] are currently under investigation in these groups.

Experimental Section

NMR: Varian Gemini-200 (200 and 50 MHz, for ^1H and ^{13}C, respectively). For ^1H and ^{13}C NMR, $CDCl_3$ as solvent $\delta_H = 7.26$; $\delta_C = 77.0$ respectively. − MS: Carlo Erba QMD100 (70 eV). − IR: Perkin−Elmer 4800. − Melting points are uncorrected. − $CHCl_3$, CH_2Cl_2 and pyridine were dried following standard procedures; all commercial reagents were used without further purification as obtained from freshly opened containers. Thiophthalimides **3a**,[2] **4a**,[4] **4b**,[4] **4c**,[14] and phthalimidesulfenyl chloride **5**[15] were prepared as described elsewhere.

General Procedure for the Synthesis of Sulfides 10, 14−25: Pyridine (2 mmol) was added to a solution of the phthalimide derivatives (1 mmol) and the required arene (1 mmol) in ethanol-free chloroform (3 mL), and the mixtures were kept at room temperature (or 60 °C for *ortho*-thioquinones) until the complete disappearance of the thiophthalimide, monitored by ^1H NMR and/or tlc. Evaporation of the solvent, followed by silica gel flash chromatography, gave the sulfides as pure compounds. Regioisomer ratios of derivatives **16−18** and **23** and **24** were obtained by ^1H NMR on the crude reaction mixtures. Yields, reaction times, and regioisomer ratios are as reported in the General Section.

3-(4-Hydroxy-3-methylphenylthio)pentane-2,4-dione (10): Colourless oil (hexane/ethyl acetate, 6:1). − ^1H NMR: δ = 17.13 (s, 1 H, enolic OH), 6.89−6.68 (m, 3 H, arom), 5.19 (br. s, 1 H, phenolic OH), 2.37 (s, 6 H, CH_3−C=O), 2.22 (s, 3 H, CH_3). − ^{13}C NMR: δ = 198.2 (s, C=O), 152.3 (s, C−OH), 128.3 (d), 127.9 (s), 125.3 (s), 124.3 (d), 115.8 (d), 103.3 (s), 24.5 (q, CH_3−C=O), 15.9 (q). − MS; *m/z* (%): 238 (72) [M^+], 196 (10) [M^+ − 42], 162 (13), 138 (100). − $C_{12}H_{14}O_3S$ (238.3): calcd. C 60.48, H 5.92; found C 60.73, H 5.76.

3-(4-Hydroxy-3,5-dimethylphenylthio)pentane-2,4-dione (14): Pale yellow solid, m.p. 117−119 °C (hexane/ethyl acetate, 6:1) − ^1H NMR: δ = 17.17 (s, 1 H, enolic OH), 6.71 (s, 2 H, arom), 4.53 (s, 1 H, phenolic OH), 2.36 (s, 6 H, CH_3−C=O), 2.20 (s, 6 H, CH_3). − ^{13}C NMR: δ = 198.0 (s, C=O), 150.5 (s, C−OH), 134.8 (s), 128.1 (s), 125.6 (d), 103.3 (s), 24.4 (q, CH_3−C=O), 15.9 (q). − MS; *m/z* (%): 252 (40) [M^+], 154 (36), 122 (100). − $C_{13}H_{16}O_3S$ (252.3): calcd. C 61.88, H 6.39; found C 61.97, H 6.60.

3-(2-Hydroxynaphthylthio)pentane-2,4-dione (15): Colourless oil (hexane/ethyl acetate, 5:1). − ^1H NMR: δ = 17.96 (s, 1 H, enolic OH), 8.04 (d, *J* = 8.0 Hz, 1 H arom), 7.80−7.73 (m, 2 H arom.), 7.60−7.44 (m, 1 H arom), 7.41−7.32 (m, 1 H arom), 7.18 (d, *J* = 8.8 Hz, 1 H arom), 6.78 (br. s, 1 H, phenolic OH), 2.40 (s, 6 H, 2 CH_3−C=O). − MS; *m/z* (%): 274 (9) [M^+], 144 (100). − $C_{15}H_{14}O_3S$ (274.3): calcd. C 65.67, H 5.14; found C 65.51, H 5.03.

3-(4-Hydroxy-3-methoxyphenylthio)pentane-2,4-dione (16 major): Colourless oil (hexane/ethyl acetate, 6:1). − ^1H NMR: δ = 17.19 (s, 1 H, enolic OH), 6.85 (d, *J* = 8.4 Hz, 1 H arom), 6.65 (d, *J* = 2.2 Hz, 1 H arom), 6.57 (dd, *J* = 2.2, 8.4 Hz, 1 H arom), 5.48 (br. s, 1 H, phenolic OH), 3.86 (s, 3 H, CH_3−O), 2.36 (s, 6 H, CH_3−C=O). − MS; *m/z* (%): 254 (7) [M^+], 51 (100). − $C_{12}H_{14}O_4S$ (254.3): calcd. C 56.68, H 5.55; found C 56.50, H 5.48.

3-(3-Hydroxy-4-methoxyphenylthio)pentane-2,4-dione (16 minor): Colourless oil (hexane/ethyl acetate, 6:1). − ^1H NMR: δ = 17.28 (s, 1 H, enolic OH), 6.78 (d, *J* = 7.6 Hz, 1 H arom), 6.72 (d, *J* = 1.4 Hz, 1 H arom), 6.50 (dd, *J* = 1.4, 7.6 Hz, 1 H arom), 5.92 (br. s, 1 H, phenolic OH), 3.90 (s, 3 H, CH_3−O), 2.35 (s, 6 H, CH_3−C=O).**3-(2-Hydroxy-4-methoxyphenylthio)pentane-2,4-dione (17 major):** Colourless oil (hexane/ethyl acetate, 5:1). − ^1H NMR: δ =

17.05 (s, 1 H, enolic OH), 7.03 (d, J = 12.0 Hz, 1 H arom), 6.49−6.40 (m, 2 H arom), 5.96 (br. s, 1 H, phenolic OH), 3.78 (s, 3 H, CH_3−O), 2.41 (s, 6 H, CH_3−C=O). − MS; *m/z* (%): 254 (46) [M^+], 124 (100). − $C_{12}H_{14}O_4S$ (254.3): calcd. C 56.68, H 5.55; found C 56.99, H 5.49.

3-(4-Hydroxy-2-methoxyphenylthio)pentane-2,4-dione (17 minor): Pale yellow oil, (hexane/ethyl acetate, 5:1). − ^{1}H NMR: δ = 17.22 (s, 1 H, enolic OH), 6.72 (d, J = 8.4 Hz, 1 H arom), 6.45 (d, J = 2.2 Hz, 1 H arom), 6.38 (dd, J = 2.2, 8.4 Hz, 1 H arom), 5.27 (br. s, 1 H, phenolic OH), 3.86 (s, 3 H, CH_3−O), 2.34 (s, 6 H, CH_3−C=O).

3-[4-(Dimethylamino)-2-hydroxyphenylthio]pentane-2,4-dione (18 major) and 3-[2-(dimethylamino)-4-hydroxyphenylthio]pentane-2,4-dione (18 minor): In this case separation of the two isomers by flash chromatography was not possible. Data for the mixture of major (*M*) and minor (*m*) isomer are as follows: Colourless oil (CH_2Cl_2/methanol, 50:1). − ^{1}H NMR: δ = 17.00 (s, 1 H, enolic OH), 7.18 (d, J = 8.8 Hz, 1 H arom, *m*), 7.04 (s, 1 H, phenolic OH, *m*), 7.03 (d, J = 9.2 Hz, 1 H arom, *M*), 6.33−6.23 (m, 3 H arom, *M* + *m*), 6.19 (dd, J = 3.0, 8.8 Hz, 1 H arom, *m*), 6.10 (br. s, 1 H, phenolic OH, *M*), 2.93 (s, 12 H, CH_3−N, *M* + *m*), 2.44 (s, 6 H, CH_3−C=O, *M*), 2.32 (s, 6 H, CH_3−C=O, *m*). − MS; *m/z* (%): 267 (40) [M^+], 168 (73), 137 (100). − $C_{13}H_{17}NO_3S$ (267.3): calcd. C 58.40, H 6.41, N 5.24; found C 58.24, H 6.58, N 5.17.

3-[4-(Dimethylamino)phenylthio]pentane-2,4-dione (19): Yellow oil (hexane/ethyl acetate, 15:1). − ^{1}H NMR: δ = 17.05 (s, 1 H, enolic OH), 7.08−6.98 (m, 2 H arom), 6.72−6.62 (m, 2 H arom), 2.91 (s, 6 H, CH_3−N), 2.37 (s, 6 H, CH_3−C=O). − MS; *m/z* (%): 251 (37) [M^+], 121 (100). − $C_{13}H_{17}NO_2S$ (251.3): calcd. C 62.12, H 6.82, N 5.57; found C 61.93, H 6.74, N 5.82.

1-(4-Hydroxy-3,5-dimethylphenylthio)naphthalen-2-ol (20): Colourless oil (hexane/ethyl acetate, 4:1). − ^{1}H NMR: δ = 8.28 (d, J = 8.4 Hz, 1 H arom), 7.87 (d, J = 8.8 Hz, 1 H arom), 7.80 (s, 1 H, phenolic OH), 7.54−7.29 (m, 4 H arom), 6.76 (s, 2 H arom), 4.48 (s, 1 H, phenolic OH), 2.10 (s, 6 H, CH_3). − MS; *m/z* (%): 296 (27) [M^+], 122 (100). − $C_{18}H_{16}O_2S$ (296.4): calcd. C 72.94, H 5.44; found C 73.11, H 5.82.

1-(2-Hydroxynaphthylthio)naphthalen-2-ol (21): White solid; m.p. 217−219 °C (CH_2Cl_2); ref.[13a] m.p. 215 °C. − ^{1}H NMR: δ = 8.46−8.38 (m, 2H arom), 7.75 (br. d, J = 8.4 Hz, 4 H arom), 7.56−7.47 (m, 2 H arom), 7.38−7.30 (m, 2 H arom), 7.17 (d, J = 9.2 Hz, 2 H arom), 6.83 (s, 2 H, phenolic OH). − ^{13}C NMR: δ = 155.8 (s), 134.7 (s), 131.7 (d), 129.6 (s), 128.7 (s), 128.9 (d), 128.0 (d), 123.9 (d), 123.7 (d), 117.4 (d). − MS; *m/z* (%): 318 (16) [M^+], 145 (100). − $C_{20}H_{14}O_2S$ (318.1): calcd. C 75.45, H 4.43; found C 75.62, H 4.31.

1-[4-(Dimethylamino)phenylthio]naphthalen-2-ol (22): Yellow oil. − ^{1}H NMR: δ = 8.36 (d, J = 8.0 Hz, 1 H arom), 7.87−7.76 (m, 2 H arom), 7.55−7.47 (m, 1 H arom), 7.42 (s, 1 H, phenolic OH), 7.38−7.29 (m, 2 H arom), 7.13−7.04 (m, 2 H arom), 6.60−6.51 (m, 2 H arom), 2.86 (s, 6 H, CH_3−N). − MS; *m/z* (%): 295 (34) [M^+], 121 (100). − $C_{18}H_{17}NOS$ (295.4): calcd. C 73.19, H 5.80, N 4.74; found C 73.02, H 5.68, N 4.73.

1-(2-Hydroxy-4-methoxyphenylthio)naphthalen-2-ol (23): White solid, m.p. 128−130 °C (hexane/ethyl acetate, 10:1) − ^{1}H NMR: δ = 8.39 (d, J = 8.4 Hz, 1 H arom), 7.83−7.73 (m, 2 H, 1 H arom + 1 OH), 7.60−7.52 (m, 2 H arom), 7.40−7.33 (m, 2 H arom), 7.25 (d, J = 8.8 Hz, 1 H arom), 7.17 (d, J = 8.8 Hz, 1 H arom), 6.43 (d, J = 2.6 Hz, 1 H arom), 6.33 (dd, J = 2.6, 8.8 Hz, 1 H arom), 6.26 (br. s, 1 H, OH), 3.68 (s, 3 H, CH_3−O). − ^{13}C NMR: δ = 161.2 (s), 156.2 (s, 2 C), 135.0 (s), 133.8 (d), 132.1 (d), 129.6 (s), 128.7 (d), 127.9 (d), 124.3 (d), 123.8 (d), 117.0 (d), 110.9 (s), 110.6 (s), 108.0 (d), 101.4 (d), 55.3 (q). − MS; *m/z* (%): 298 (26) [M^+], 124 (100). − $C_{17}H_{14}O_3S$ (298.4): calcd. C 68.44, H 4.73 found C 68.29, H 4.67.

1-(4-Hydroxy-2-methoxyphenylthio)naphthalen-2-ol (24): White solid, m.p. 149−151 °C (hexane/ethyl acetate, 10:1). − ^{1}H NMR: δ = 8.44 (d, J = 8.4 Hz, 1 H arom), 7.90−7.84 (m, 2 H, 1 H arom + 1 OH), 7.55−7.48 (m, 1 H arom), 7.38−7.30 (m, 2 H arom), 7.27 (d, J = 11.4 Hz, 1 H arom), 6.86 (d, J = 8.4 Hz, 1 H arom), 6.41 (d, J = 2.6 Hz, 1 H arom), 6.21 (dd, J = 2.6, 8.4 Hz, 1 H arom), 5.10 (s, 1 H, OH), 3.90 (s, 3 H, CH_3−O) − ^{13}C NMR: δ = 158.7 (s), 156.9 (s), 156.5 (s), 135.7 (s), 132.1 (d), 132.0 (d), 129.4 (s), 128.5 (d), 127.5 (d), 124.8 (d), 123.5 (d), 117.0 (d), 113.9 (s), 110.0 (s), 108.1 (d), 99.5 (d), 56.0 (q)

1-[4-Hydroxy-5-(2-hydroxynaphthylthio)-2-methoxyphenylthio]-naphthalen-2-ol (25): Glassy solid, (hexane/ethyl acetate, 10:1). − ^{1}H NMR: δ = 8.12−8.00 (m, 4 H arom), 7.82−7.45 (m, 6 H arom), 7.42 (s, 1 H, OH), 7.16 (d, J = 8.0 Hz, 1 H arom), 7.11 (s, 1 H, OH), 7.07 (d, J = 8.0 Hz, 1 H arom), 6.82 (s, 1 H arom), 6.56 (br. s, 1 H, OH), 6.38 (s, 1 H arom), 3.75 (s, 3 H, CH_3−O). − MS; *m/z* (%): 472 (6) [M^+], 298 (34), 144 (100).

2,2′-Dihydroxy-3,3′-bis(α-thio-β-naphthyl)-6,6′-dimethoxy-1,1′-biphenyl (26): White solid, m.p. 195−196 °C (hexane/ethyl acetate/CH_2Cl_2, 4:1:1). − ^{1}H NMR (DMSO d_6): δ = 8.59 (d, J = 8.4 Hz, 2 H), 7.91 (d, J = 8.8 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H), 7.59 (t, J = 7.4 Hz, 2 H), 7.38 (t, J = 7.4 Hz, 2 H), 7.30 (d, J = 8.8 Hz, 2 H), 7.10 (d, J = 8.8 Hz, 2 H), 6.40 (d, J = 8.8 Hz, 2 H), 3.50 (s, 6 H, CH_3−O). − ^{13}C NMR (DMSO d_6): δ = 158.2 (s, C−OH), 157.1 (s, C−OCH_3), 154.7 (s, C−OH *b*), 136.0 (d), 131.7 (d), 131.5 (s, CH−C−CS), 128.9 (d), 128.6 (s), 127.6 (d), 124.6 (d), 123.4 (d), 118.2 (s), 113.4 (d), 110.7 (s, C−S), 110.5 (s, C−S), 103.4 (s), 55.4 (q). − MS (ESI-Finnigan LCQ ion trap); *m/z* 595 [MH^+].

Acknowledgments

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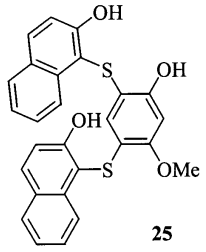
[7] Several other electron-rich arenes tested − such as, among others, 1,3-dimethoxybenzene, anthracene, and aniline − were unreactive towards thione **1a**.

[8] In the case of sulfide **17**, the attribution of the relative regiochemistry was also achieved by comparison with the result observed in the same reaction with *ortho*-thioquinone **2a** (vide infra).

[9] Chloroform and dichloromethane are the best solvents for these reactions. Benzene, THF, acetone, acetonitrile, and DMSO cause a remarkable decrease in the reaction rate, while with DMF we observed only polymerization of the thione **1a**.

[10] Generation of thione **1a** with TEA or DBU in the presence of phenol **9**, resulted in a drastic decrease in the reaction yield.

[11] In the reaction of **2a** with *m*-methoxyphenol, we also isolated the corresponding bis-substituted derivative **25** (6%).



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[12] Polyhydroxylated diaryl sulfides have found several applications as stabilisers against oxidation (see ref.[13]).

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