New reductive addition of hard nucleophiles to 6,7-bis(methylsulfanyl)-1,4-dihydro-1,4-methanonaphthalene-5,8-dione

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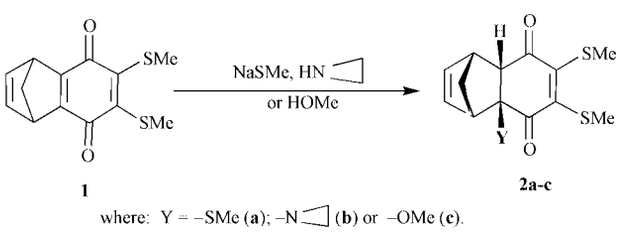
A new reaction mode of 6,7-bis(methylsulfanyl)-1,4-dihydro-1,4-methanonaphthalene-5,8-dione **1** with the hard nucleophiles sodium benzene- or methane-sulfinate and cyanide, in DMSO, at room temperature, leads to the unexpected hydroquinonoid products **3a**–**c**. All the data are in agreement with a mechanistic pathway involving the initial attack of the hard nucleophile onto the hard carbonyl group, followed by a symbiotic re-attack of the oxygen on the incoming group. In the case of soft nucleophiles, reaction on the olefinic carbon of the enedione system is preferential.

Introduction

Some of our previous reports[1,2] were devoted to the study of the reactivity of nucleophiles with potentially quinonoid systems. Thus, we showed that the tetrachlorobenzoquinone–cyclopentadiene adduct, when treated with excess of sodium methyl sulfide, furnishes the tris(methylsulfanyl) derivative containing the new sulfurated group in an *exo* configuration at the ring junction. We have put forward the suggestion that this reaction proceeds through initial attack of sulfide onto the ring junction chlorine atoms, leading to chlorine elimination, followed by addition of sulfide to the quinonoid system thus formed. Regarding the behavior of nitrogen, oxygen and sulfur nucleophiles in the presence of 6,7-bis(methylsulfanyl)-1,4-dihydro-1,4-methanonaphthalene-5,8-dione **1**, in protic solvents like methanol, we similarly observed exclusive formation of the corresponding *cis-endo* trisubstituted adducts **2a**–**c**, containing the new substituent at the ring junction (Scheme 1).



Scheme 1

Results and discussion

In order to extend this conjugate addition to a wider number of nucleophiles and obtain, after pyrolysis,[3] new potentially bioactive quinonoid compounds, we have submitted quinone **1** to reaction with the sodium salts of benzene- and methane-sulfinic acids and also with sodium cyanide, in DMSO. Unexpectedly, the resulting products exhibited a strong hydroxy absorption but no carbonyl absorption in the IR spectra, suggesting that a reductive process had occurred. On the basis of ^{1}H and ^{13}C NMR spectroscopic data, together with X-ray crystallographic analysis (Fig. 1), we were able to establish the structure of these new compounds as being **3a**–**c**, as depicted in Scheme 2.

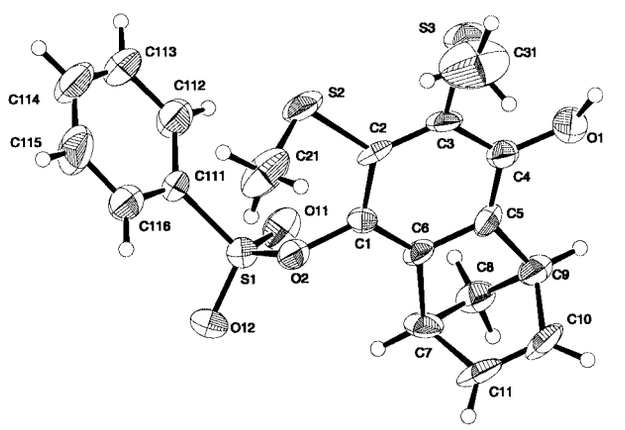
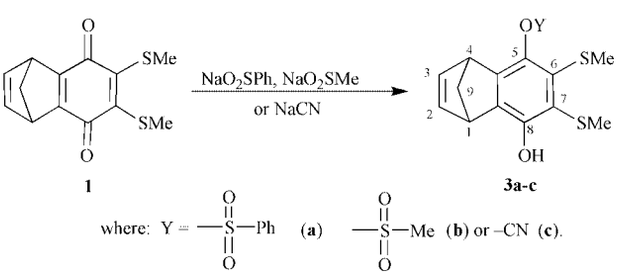


Fig. 1 Crystal structure of compound **3a**.



Scheme 2

In view of this interesting new result, we propose that structures of type 3 are formed through initial attack of the nucleophile onto the carbonyl group, followed by a symbiotically[4] favoured re-attack from the negative oxygen thus formed on the entering group. This re-attack might not necessarily occur on the same atom which has just bonded to the carbonyl carbon in the initial step. Therefore, in the case of **3a** and **3b** attack occurs onto the sulfur, whereas in the case of **3c**, carbon should

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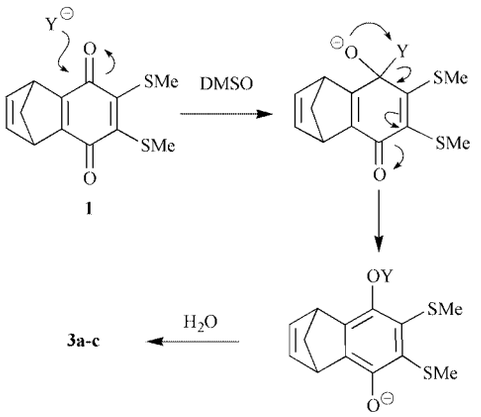
act as an electrophile. It should be emphasized that the most conspicuous characteristic of the nucleophiles used herein, as compared to those we have previously employed,[1,2] in spite of their hardness, is their ability to act also as electron acceptors, due to their –R resonance effect[5] (Scheme 3).



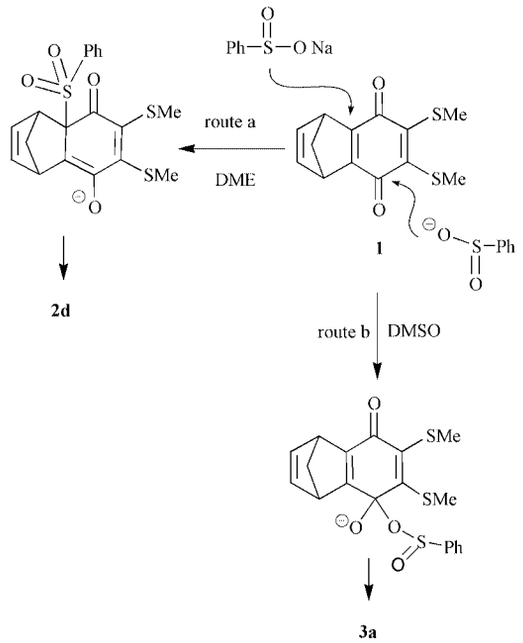
Scheme 3

The role of the solvent in determining the course of the addition is noteworthy. When DMSO was replaced by 1,2-dimethoxyethane (DME), using sodium benzenesulfinate as nucleophile, only the "normal" 1,4-addition product **2d** was obtained. (Scheme 4).

Scheme 4

A rationalization of the facts reported above can be formulated according to Pearson's hard and soft acids and bases principle[6] (HSAB). The carbonyl group has a hard donor oxygen and a fairly hard acceptor carbon. α,β-Unsaturated ketones are assumed to react with soft nucleophiles at the softer C-4 conjugate enedione system.[7] Saville's rule[8] describes satisfactorily the course of our previously reported multicentered reactions involving the sulfur, oxygen and nitrogen nucleophiles in methanol.[2] According to this rule, the exclusive formation of the conjugate addition products **2a**–**c** may be explained if we consider a precoordination of the hard carbonyl oxygen atom, *via* a hydrogen bond, with the hard hydrogen hydroxy acceptor moiety in methanol. In a concomitant step, the soft nucleophilic entity attacks the soft C-4 enedione carbon, leading to the isolated 1,4-addition products shown in Scheme 1.

In the case of the ambident sulfurated nucleophiles employed in this work, we believe that the HSAB principle also explains our results quite well. Accordingly, in analogy to studies regarding carbon and oxygen alkylation of ambident nucleophiles like the β-naphthoxide ion[9] or enolates,[10] we propose that in the case of sodium benzenesulfinate in 1,2-dimethoxyethane (a B-class, weakly polar solvent[11]), ion-pair aggregates should be present. This aggregation ought to hinder the negative charge at the oxygen atom, which then becomes less available for reaction with electrophiles. Consequently, the sulfur atom, which has an electron pair, can act as a soft nucleophile. On the other hand, the use of DMSO (a C-class, polar aprotic solvent[11]) should favour a strong countercation solvation, making the sulfinate a hard nucleophile at the oxygen atom, which accommodates the negative charge better. These reasonings are corroborated by the obtention of sulfone **2d** from the reaction of quinone **1** with sodium benzenesulfinate in 1,2-dimethoxyethane (Scheme 4), due to the preferential attack of the soft sulfur nucleophile on the soft C-4 (route a in Scheme 5). For the analogous reaction



Scheme 5

in DMSO, the isolation of the sulfonic ester **3a** led us to propose that the sulfinic oxygen acts as a hard nucleophile onto the fairly hard carbonyl group (route b in Scheme 5). In the subsequent step, the nucleophilic oxygen thus generated can play the symbiotic[4] role previously depicted in Scheme 3, in analogy to the initial step proposed for decomposition of α-(methylthio)benzyl sulfones leading to phenyl alkyl ketones,[12] *i.e.* attack at sulfur leading to an intermediate sulfurane[13] which collapses to the sulfonate ester *via* elimination at oxygen.[14]

In conclusion, we have reported an interesting new addition mode of nucleophiles to a quinonoid system, in DMSO, corresponding formally to a reduction process. We have also proposed that by using HSAB one can explain all known facts relating to the system under study.

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 7.05 T with a Bruker DPX-300 instrument. *J* Values are given in Hz. IR spectra were obtained on a Nicolet Infrared Spectrometer FT-IR 510. Elemental analyses were performed on a Perkin-Elmer Elemental Analyzer PE 2400 CHN.

Carbon assignments use the numbering systems shown in Schemes 2 and 4 and were established by combining information from DEPT and HETCOR experiments.

Reaction of 6,7-bis(methylsulfanyl)-1,4-dihydro-1,4-methanonaphthalene-5,8-dione with sodium benzenesulfinate—general procedure

8-Hydroxy-6,7-bis(methylsulfanyl)-1,4-dihydro-1,4-methanonaphthalen-5-yl benzenesulfonate 3a. A solution of quinone **1** (0.39 g, 1.5 mmol) in DMSO (5 mL) was treated portionwise with solid sodium benzenesulfinate (0.26 g, 1.6 mmol) at room temperature, under nitrogen and stirring until the color faded (1 h). The mixture was poured into water (25 mL), extracted with dichoromethane and dried over magnesium sulfate. The solvent was removed in vacuum and the hydroquinonoid compound **3a** (0.48 g, 79%) was isolated as a white solid, after column chromatography using benzene as eluant; mp 116–117 °C (from EtOH) (Found: C, 56.1; H, 4.6. $C_{19}H_{18}O_4S_3$ requires C,

56.1; H, 4.5%); ν_{max} (KBr)/cm^{-1} 3365 (OH), 1390, 1367 (SO_2, asym.), 1189, 1154 (SO_2, sym.); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.16 (d, *J* 5.5, 1H), 2.21 (s, 3H), 2.24 (s, 3H), 2.29 (d, *J* 5.5, 1H), 4.14 (m, 1H), 4.18 (m, 1H), 6.83 (m, 2H), 7.04 (s, 1H), 7.51 (t, *J* 4.9, 2H), 7.66 (t, *J* 5.0, 1H), 7.93 (d, *J* 5.2, 2H); δ_C (80 MHz; $CDCl_3$; Me_4Si) 19.63 (SMe), 19.72 (SMe), 47.47 (1 or 4), 49.86 (1 or 4), 68.98 (9), 123.94 (4a or 8a), 128.60 (Ph), 128.77 (Ph), 133.18 (4a or 8a), 134.02 (Ph), 136.16 (Ph), 138.20 (6 or 7), 138.57 (6 or 7), 142.43 (2 or 3), 142.65 (2 or 3), 149.26 (5 or 8), 149.77 (5 or 8).

8-Hydroxy-6,7-bis(methylsulfanyl)-1,4-dihydro-1,4-methanonaphthalen-5-yl methanesulfonate 3b. (73%); mp 113–115 °C (Found: C, 48.6; H, 4.7 $C_{14}H_{16}O_4S_3$ requires C, 48.8; H, 4.7%); ν_{max} (KBr)/cm^{-1} 3380 (OH), 1391, 1363 (SO_2 asym.), 1183, 1158 (SO_2 sym.); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.19 (m, 2H), 2.26 (s, 3H), 2.40 (s, 3H), 3.30 (s, 3H), 4.13 (m, 1H), 4.21 (m, 1H), 6.78 (m, 2H), 7.00 (s, 1H); δ_C (80 MHz; $CDCl_3$; Me_4Si) 19.83 (SMe), 20.05 (SMe), 39.24 (SO_2Me), 47.69 (1 or 4), 49.94 (1 or 4), 69.13 (9), 124.37 (4a or 8a), 131.71 (4a or 8a), 138.86 (6 or 7), 139.95 (6 or 7), 142.50 (2 or 3), 142.74 (2 or 3), 149.57 (5 or 8), 150.24 (5 or 8).

8-Hydroxy-6,7-bis(methylsulfanyl)-1,4-dihydro-1,4-methanonaphth-5-yl cyanate 3c. (79%); mp 133–135 °C (Found: C, 57.9; H, 4.5; N, 4.9. $C_{14}H_{13}NO_2S_2$ requires C, 57.7; H, 4.5; N, 4.8%); ν_{max} (KBr)/cm^{-1} 3353 (OH), 2224 (OCN); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.24 (m, 1H), 2.29 (m, 1H), 2.31 (s, 3H), 2.49 (s, 3H), 3.84 (m, 1H), 5.33 (m, 1H), 5.79 (m, 1H), 6.50 (m, 1H), 7.32 (s, 1H); δ_C (80 MHz; $CDCl_3$; Me_4Si) 18.31 (SMe), 19.18 (SMe), 35.58 (9), 40.11 (1), 80.34 (4), 95.73 (4a), 114.54 (8a), 122.84 (CN), 125.04 (3), 132.09 (6 or 7), 136.69 (6 or 7), 140.44 (2), 146.11 (8), 152.26 (5).

4a,8a-*endo-cis*-6,7-Bis(methylsulfanyl)-8a-phenylsulfonyl-1,4-dihydro-1,4-methanonaphthalene-5,8-dione 2d. (67%); mp 110–112 °C (from ethanol) (Found: C, 56.0; H, 4.5. $C_{19}H_{18}O_4S_3$ requires C, 56.1; H, 4.5%); ν_{max} (KBr)/cm^{-1} 1662 (CO), 1308 (SO_2 asym.), 1142 (SO_2 sym.); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.46 (dt, *J* 8.8 and 2.2, 1H), 2.22 (d, *J* 8.8, 1H), 2.52 (s, 3H), 2.64 (s, 3H), 3.13 (dd, *J* 2.9 and 1.5, 1H), 3.65 (m, 1H), 4.18 (d, *J* 3.5, 1H), 5.92 (dd, *J* 5.1 and 2.9, 1H), 6.24 (dd, *J* 5.1 and 2.9, 1H), 7.62–7.82 (m, 5H); δ_C (80 MHz; $CDCl_3$; Me_4Si) 15.98 (SMe), 16.88 (SMe), 43.93 (9), 46.01 (4), 51.03 (1), 52.81 (4a), 80.28 (8a), 128.94 (Ph), 129.73 (Ph), 134.40 (Ph), 135.85 (Ph), 137.12 (2 or 3), 139.99 (2 or 3), 149.44 (6 or 7), 150.11 (6 or 7), 183.91 (C=O), 188.36 (C=O).

Crystal data for 3a

$C_{19}H_{18}O_4S_3$, $M = 406.51$, monoclinic, space group *C*c, $a = 20.672(2)$, $b = 10.8482(9)$, $c = 8.7192(9)$ Å, $\beta = 104.683(7)°$, $V = 11891.4(3)$ Å^3, $Z = 4$, $D_x = 1.428$ Mg m^{-3}, λ(Mo-Kα) = 0.71073 Å, $\mu = 0.414$ mm^{-1}, $R = 0.0550$. X-ray diffraction data were collected on a CAD4 Mach3 diffractometer with θ–2θ scan technique at 293 K. Solution by direct methods (SIR92).[15] Full matrix least squares refinement on F^2. 1816 Measured reflections ($2\theta_{max} = 51°$) and 1174 with $F_o^2 \geq 4\sigma F_o^2$. Anisotropic displacement parameters for all non-H atoms were applied. H atoms were located on stereochemical grounds and refined with fixed geometry, each riding on a carrier atom, with an isotropic displacement parameter amounting to 1.5 (for methyl H atoms) or 1.2 (for the other H atoms) times the value of the equivalent isotropic displacement parameter of the atom they are attached. 237 parameters were refined and the final conventional *R* was 0.0550. Structure refinement, final geometrical calculations were carried out with SHELXL97,[16] PARST-95[17] and WinGX.[18] Fig. 1 was produced using ZORTEP.[19]

CCDC reference number 207/481. See http://www.rsc.org/suppdata/p1/b0/b000575o/ for crystallographic files in .cif format.

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