

## A New Route to Naphtho[2,3-*b*]furan-4,9-diones from Thio-substituted 1,4-Naphthoquinones

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Reaction of 2-phenylthio- or 2-ethylthio-1,4-naphthoquinones (1) and (2) with lithium enolates or pyridinium ylides was found to give alkylated 1,4-naphthoquinones (3)–(6) in high yields. Alkylated 1,4-naphthoquinones (5) and (6) were then effectively cyclized to 2-substituted naphtho[2,3-*b*]furan-4,9-diones (8) by action of bromine in acetic acid.

Some naphtho[2,3-*b*]furan-4,9-dione derivatives isolated from various plants<sup>1–11</sup> have been reported to show cytotoxic activity to the KB cell and HeLa cells. For example, 2-acetyl-naphtho[2,3-*b*]furan-4,9-dione, isolated from root extracts of *Tabebuia cassinoides*,<sup>1</sup> reveals strong cytotoxic activity in the KB cell culture assay ( $ID_{50} = 1.0 \mu\text{g ml}^{-1}$ ). Consequently, several naphthofuran derivatives have been synthesized for their biological interest.<sup>12–14</sup> We have studied a new synthetic route to the naphtho[2,3-*b*]furan-4,9-dione ring system. In a preliminary report,<sup>15</sup> we reported the successful reaction of 2-thio-substituted 1,4-naphthoquinones with lithium enolates and an attempted transformation of one of the addition products to this ring system. We report here alkylations of 2-thio-substituted 1,4-naphthoquinones not only with lithium enolates but also with pyridinium ylides and transformation of the resulting alkylated 1,4-naphthoquinones to the 2-substituted naphtho[2,3-*b*]furan-4,9-diones (8).

We first examined the reactions of the parent 1,4-naphthoquinone, and its 2-methyl-, 2-methoxy-, 2-bromo-, and 2,3-dichloro- derivatives, with the lithium enolate generated from a ketone such as cyclohexanone by treatment with lithium dicyclohexylamide. According to the literature,<sup>16</sup> 2,3-dichloro-1,4-naphthoquinone reacted with the lithium enolate generated from *t*-butyl cyclohexanecarboxylate to give 3-chloro-2-(1-*t*-butoxycarbonylcyclohexyl)-1,4-naphthoquinone. In our hands, however, the desired alkylated 1,4-naphthoquinones were not obtained; messy products were formed or the starting material was recovered. In contrast, when 2-thio-substituted 1,4-naphthoquinone derivatives (1) and (2)<sup>17</sup> were treated with lithium enolates, we found that the conjugate addition occurred very smoothly and subsequent oxidation with air gave 2-alkylated 3-phenylthio- or 3-ethylthio-1,4-naphthoquinones (3)–(6) in 60–80% yields, without formation of any appreciable amounts of side products. The results are listed in Table 1. We also found that pyridinium ylides were effective in the conjugate addition to 2-thio-substituted 1,4-naphthoquinones (1) and (2). Pyridinium ylides were generated according to the literature<sup>18</sup> from pyridinium bromides by treatment with triethylamine in acetonitrile under argon, and used directly for the subsequent alkylation. Thus, the reaction of 2-ethylthio-1,4-naphthoquinone (2) with 1.2 mol equiv. of phenacylpyridinium ylide gave 2-ethylthio-3-phenacyl-1,4-naphthoquinone (6a) in 86% yield. The results of the reaction of thio-substituted 1,4-naphthoquinones (1) and (2) with various pyridinium ylides are summarized in Table 2.

We next studied the transformation of 2-phenacyl-3-phenylthio-1,4-naphthoquinone (5a) to 2-phenylnaphtho[2,3-*b*]furan-4,9-dione (8a) under various conditions. Treatment of (5a) with bases such as triethylamine or lithium di-isopropylamide or with acids such as acetic acid or acetic acid in the presence of

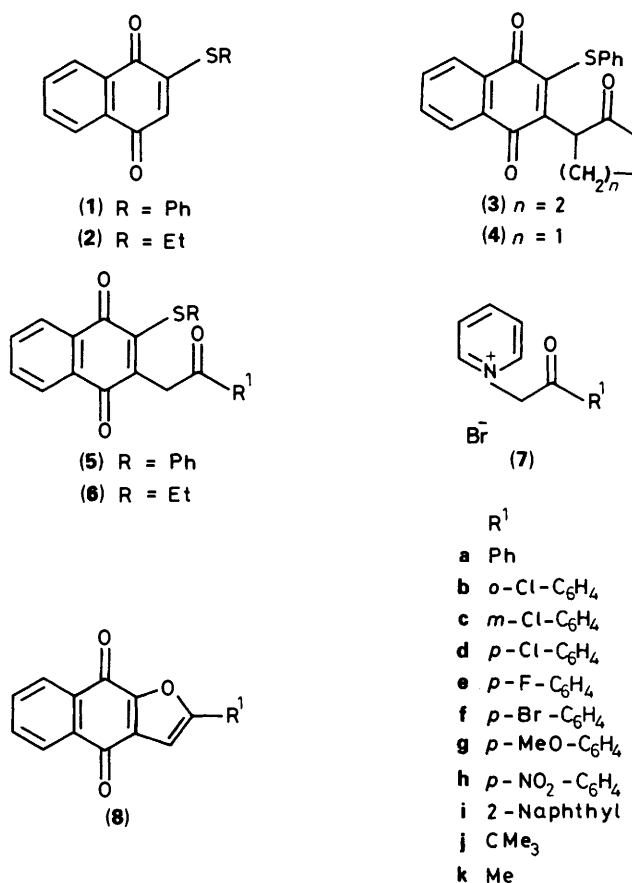


Table 1. Addition of lithium enolates to thio-substituted 1,4-naphthoquinones.

Quinone	Ketone	Product	Yield (%)
(1)	cyclohexanone	(3)	76
(1)	cyclopentanone	(4)	75
(1)	acetophenone	(5a)	62
(1)	2'-chloroacetophenone	(5b)	80
(1)	3'-chloroacetophenone	(5c)	67
(2)	acetophenone	(6a)	60

hydrobromic acid failed to give any fruitful results. When (5a) was treated with bromine in dichloromethane, a trace amount of 2-phenylnaphtho[2,3-*b*]furan-4,9-dione (8a) could be isolated

**Table 2.** Addition of pyridinium ylides to thio-substituted 1,4-naphthoquinones

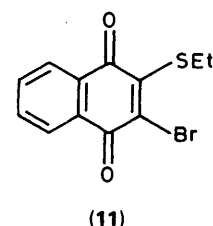
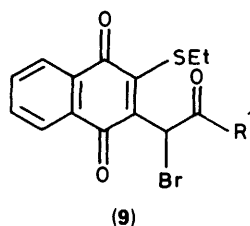
Quinone	Pyridinium Salt	Reaction time	Product	Yield (%)
(1)	(7a)	2 h	(5a)	85
(1)	(7b)	30 min	(5b)	87
(1)	(7c)	10 min	(5c)	94
(1)	(7d)	30 min	(5d)	94
(1)	(7e)	10 min	(5e)	82
(1)	(7f)	30 min	(5f)	88
(1)	(7g)	30 min	(5g)	89
(1)	(7h)	40 min	(5h)	58
(1)	(7i)	30 min	(5i)	86
(1)	(7j)	1 h	(5j)	83
(1)	(7k)	1.8 h	(5k)	85
(2)	(7a)	2 h	(6a)	92
(2)	(7b)	17 h	(6b)	71
(2)	(7c)	2 h	(6c)	88
(2)	(7d)	1.5 h	(6d)	88
(2)	(7e)	2 h	(6e)	89
(2)	(7f)	2 h	(6f)	83
(2)	(7g)	18 h	(6g)	85
(2)	(7h)	15 h	(6h)	84
(2)	(7i)	2 h	(6i)	93
(2)	(7j)	1 h	(6j)	83
(2)	(7k)	6 h	(6k)	96

**Table 3.** Transformation of 1,4-naphthoquinones (6) to substituted naphtho[2,3-*b*]furan-4,9-diones (8)

Quinone	Bromine	Time	Product	Yield (%)
(6a)	4 equiv.	3.5 h	(8a)	75
(6b)	2 equiv.	30 min	(8b)	51
(6c)	2 equiv.	40 min	(8c)	46
(6d)	3 equiv.	30 min	(8d)	86
(6e)	4 equiv.	30 min	(8e)	46
(6f)	3 equiv.	30 min	(8f)	46
(6g)	6 equiv.	10 min	(8g)	50
(6h)	5 equiv.	15 min	(8h)	46
(6i)	4 equiv.	1.5 h	(8i)	97
(6j)	2 equiv.	2 h	(8j)	64

(3% yield). When the reaction was carried out with bromine in acetic acid, (8a) was obtained in 45% yield together with several unidentified compounds. Furthermore, 2-ethylthio-3-phenacyl-1,4-naphthoquinone (6a) was found to be an excellent substrate for this transformation. The reaction of (6a) with 1 mol equiv. of bromine not only needed a long time to go to completion but also gave many side products besides (8a). In order to avoid these side reactions, an excess of bromine was used. Thus, treatment of compound (6a) with 4 mol equiv. of bromine for 3.5 h in acetic acid gave (8a) in 75% yield. Various 2-ethylthio-3-alkyl-1,4-naphthoquinones (6) could be efficiently converted into naphtho[2,3-*b*]furan-4,9-diones (8) by this method. The results are summarized in Table 3.

Although the precise mechanism of the transformation of (6) to (8) remains to be solved, this reaction apparently does not proceed *via* a bromoketone (9). Aldersley *et al.* have reported that treatment of 2-methyl-3-phenacyl-1,4-naphthoquinone with bromine in dichloromethane gives the  $\alpha$ -bromoketone, which was then converted into the naphtho[2,3-*c*]pyran-5,10-dione ring system by the action of triethylamine.<sup>19</sup> However, we observed that treatment of 2-methyl-3-phenacyl-1,4-naphthoquinone with 3 mol equiv. of bromine in acetic acid for 24 h resulted in the recovery of the starting quinone. This suggests that bromination  $\alpha$  to the carbonyl group of the 2-oxoalkyl



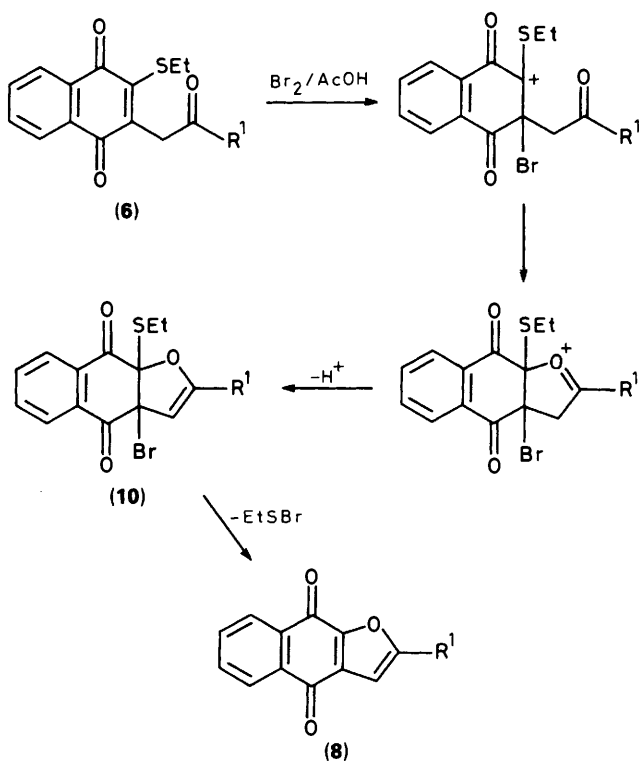
substituent of (6) would not occur under our reaction conditions using acetic acid as a solvent. Since treatment of (6) in acetic acid in the presence of hydrobromic acid gave only decomposition products without formation of naphtho[2,3-*b*]furan-4,9-diones (8), this cyclization reaction does not seem to occur *via* the simple proton-catalysed cyclization mechanism. The 2-ethylthio group in (6), which apparently plays an important role in the cyclization to the naphthofuran ring, may accelerate the bromination on the naphthoquinone ring since we found that treatment of 2-ethylthio-1,4-naphthoquinone (2) with an equimolar amount of bromine in acetic acid gave 2-bromo-3-ethylthio-1,4-naphthoquinone (11) in 97% yield. In addition, the reaction with an excess of bromine afforded 2,3-dibromo-1,4-naphthoquinone which was considered to be formed *via* the addition of bromine to the quinonoid ring and subsequent elimination of ethylsulphinyl bromide. From these results, it is proposed that the transformation of 2-ethylthio-3-alkyl-1,4-naphthoquinones (6) to 2-substituted naphtho[2,3-*b*]furan-4,9-diones (8) would start with the electrophilic attack of bromonium ion on the quinonoid ring of (6), followed by cyclization to the dihydrofuran (10). Elimination of ethylsulphinyl bromide then gives naphtho[2,3-*b*]furan-4,9-dione (8) as shown in the Scheme.

In summary, introduction of a phenylthio or alkylthio group at the 2-position of 1,4-naphthoquinone permitted not only the conjugate alkylation of lithium enolates or pyridinium ylides to 1,4-naphthoquinones, but also the one-pot transformation of 3-alkyl-2-thio-1,4-naphthoquinones (5) and (6) into substituted naphtho[2,3-*b*]furan-4,9-diones (8) *via* the bromocyclization and subsequent elimination of ethylsulphinyl bromide. Furthermore, this characteristic feature of the phenylthio or ethylthio group allowed us to develop a novel and convenient synthesis of naphtho[2,3-*b*]furan-4,9-diones. A further study on the bioactivities of the naphthofurans prepared is under progress.

### Experimental

M.p.s were recorded on a Yanaco micro-melting point apparatus and are uncorrected. IR spectra were measured on KBr discs on a JASCO A-102 spectrometer. NMR spectra were determined using a Varian XL-200 spectrometer for solutions in deuteriochloroform or [<sup>2</sup>H<sub>6</sub>]-DMSO with TMS as internal standard. Mass spectra were obtained with a Hitachi M-52 spectrometer. Column chromatography was carried out with Merck Kieselgel 60 silica gel using toluene-hexane as the eluant.

*General Procedure for Conjugate Addition of Thio-1,4-naphthoquinones (1) and (2) with Lithium Enolates.*—Butyllithium (2 mmol, 15% hexane solution) was added dropwise over 5 min to a stirred solution of dicyclohexylamine (2 mmol) in THF (8 ml) at -45 °C under argon. After the addition, the mixture was cooled to -78 °C and a solution of ketone (2 mmol) in THF (1 ml) was slowly added. The mixture was stirred until it became a clear solution (10–15 min), then HMPA (1 ml) was added. After stirring for 10 min at the same temperature, the resulting solution was added to 1,4-naphthoquinone (1) or



Scheme.

(2) (2 mmol) in THF (15 ml) and HMPA (1 ml) at  $-78^{\circ}\text{C}$ . The reaction mixture was stirred for 15 min and then 5% aqueous hydrochloric acid (10 ml) was added. Extraction of the reaction mixture with toluene and evaporation of the solvent gave a residue which was purified on a column (silica gel, toluene-hexane, 1:1) to give the alkylated thio-1,4-naphthoquinone in the yields shown in Table 1.

**General Procedure for Conjugate Addition of Thio-1,4-naphthoquinone with Pyridinium Ylides.**—The pyridinium salt (7) (1.2 mmol) was suspended at room temperature in acetonitrile (20 ml) containing 2-thio-1,4-naphthoquinone (1) or (2) (1 mmol) under argon, then a solution of triethylamine (1.2 mmol) in acetonitrile (5 ml) was added. The mixture was stirred for 1 h, extracted with toluene, and the organic layer was washed with dilute hydrochloric acid and brine successively. Evaporation of the solvent followed by column chromatography on silica gel with toluene or toluene-hexane (3:1) as eluant gave the substituted 1,4-naphthoquinone (5) or (6) in the yields shown in Table 2.

**2-(2-Oxocyclohexyl)-3-phenylthio-1,4-naphthoquinone (3).** M.p.  $146\text{--}148^{\circ}\text{C}$  (from methanol) (Found: C, 72.75; H, 5.0.  $\text{C}_{22}\text{H}_{18}\text{O}_3\text{S}$  requires C, 72.91; H, 5.01%);  $\nu_{\text{max}}$  1 700 and 1 600  $\text{cm}^{-1}$ ;  $\delta(\text{CDCl}_3)$  1.90–2.48 (6 H, m), 2.60–2.80 (2 H, d), 4.26–4.42 (1 H, m), 7.16–7.30 (5 H, m), 7.62–7.82 (2 H, m), 7.92–8.04 (1 H), and 8.06–8.18 (1 H);  $m/z$  362 ( $M^+$ , 45%), 253 (100), and 237 (42).

**2-(2-Oxocyclopentyl)-3-phenylthio-1,4-naphthoquinone (4).** M.p.  $163\text{--}164^{\circ}\text{C}$  (from methanol) (Found: C, 72.5; H, 4.6.  $\text{C}_{21}\text{H}_{16}\text{O}_3\text{S}$  requires C, 72.39; H, 4.63%);  $\nu_{\text{max}}$  1 680 and 1 655  $\text{cm}^{-1}$ ;  $\delta(\text{CDCl}_3)$  1.20–1.82 (3 H, m), 1.88–2.47 (3 H, m), 2.60–2.79 (1 H, q), 3.11 (1 H, t), 4.36 (1 H), 7.23–7.37 (3 H, m), 7.39–7.54 (2 H, m), 7.62–7.78 (2 H, m), and 7.92–8.11 (2 H, m);  $m/z$  348 ( $M^+$ , 40%) and 238 (100).

**2-Phenacyl-3-phenylthio-1,4-naphthoquinone (5a).** M.p.  $158\text{--}159^{\circ}\text{C}$  (from methanol) (Found: C, 75.7; H, 4.0.  $\text{C}_{24}\text{H}_{16}\text{O}_3\text{S}$  requires C, 74.87; H, 4.20%);  $\nu_{\text{max}}$  1 672, 1 654, and 1 584  $\text{cm}^{-1}$ ;

$\delta(\text{CDCl}_3)$  4.73 (2 H, s,  $\text{CH}_2$ ), 7.18–7.33 (4 H, m), 7.36–7.78 (6 H, m), and 7.98–8.15 (4 H, m);  $m/z$  384 ( $M^+$ , 100%), 368 (10), 275 (88), and 263 (57).

**2-(2'-Chlorophenacyl)-3-phenylthio-1,4-naphthoquinone (5b).** M.p.  $139\text{--}140.5^{\circ}\text{C}$  (from methanol) (Found: C, 68.9; H, 3.6.  $\text{C}_{24}\text{H}_{15}\text{O}_3\text{SCl}$  requires C, 68.81; H, 3.61%);  $\nu_{\text{max}}$  1 674 (phenacyl C=O), 1 648, and 1 580  $\text{cm}^{-1}$  (naphthoquinone system);  $\delta(\text{CDCl}_3)$  4.70 (2 H, s,  $\text{CH}_2$ ), 7.12–7.62 (8 H, m), 7.64–7.83 (3 H, m), and 7.98–8.18 (2 H, m);  $m/z$  418 ( $M^+$ ,  $^{35}\text{Cl}$ , 81%) and 309 (100).

**2-(3'-Chlorophenacyl)-3-phenylthio-1,4-naphthoquinone (5c).** M.p.  $158.5\text{--}159.5^{\circ}\text{C}$  (from methanol) (Found: C, 68.65; H, 3.4.  $\text{C}_{24}\text{H}_{15}\text{O}_3\text{SCl}$  requires C, 68.81; H, 3.61%);  $\nu_{\text{max}}$  1 690 (phenacyl C=O), 1 660, and 1 592  $\text{cm}^{-1}$  (naphthoquinone system);  $\delta(\text{CDCl}_3)$  4.69 (2 H, s,  $\text{CH}_2$ ), 7.19–7.39 (2 H, m), and 7.39–8.19 (11 H, m);  $m/z$  418 ( $M^+$ ,  $^{35}\text{Cl}$ , 8%), 309 (6), 279 (8), 139 (100), and 111 (38).

**2-(4'-Chlorophenacyl)-3-phenylthio-1,4-naphthoquinone (5d).** M.p.  $171.5\text{--}172.5^{\circ}\text{C}$  (from methanol) (Found: C, 68.65; H, 3.3.  $\text{C}_{24}\text{H}_{15}\text{O}_3\text{SCl}$  requires C, 68.81; H, 3.61%);  $\nu_{\text{max}}$  1 672 (phenacyl C=O), 1 652, and 1 586  $\text{cm}^{-1}$  (naphthoquinone system);  $\delta(\text{CDCl}_3)$  4.62 (2 H, s,  $\text{CH}_2$ ), 7.22–7.60 (7 H, m), 7.67–7.85 (2 H, m), and 7.94–8.19 (4 H, m);  $m/z$  420 ( $M^+$ ,  $^{37}\text{Cl}$ , 67%), 418 ( $M^+$ ,  $^{35}\text{Cl}$ , 100), 309 (100), and 279 (64).

**2-(4'-Fluorophenacyl)-3-phenylthio-1,4-naphthoquinone (5e).** M.p.  $137\text{--}138^{\circ}\text{C}$  (from methanol) (Found: C, 71.85; H, 3.7.  $\text{C}_{24}\text{H}_{15}\text{O}_3\text{SF}$  requires C, 71.63; H, 3.76%);  $\nu_{\text{max}}$  1 660 (phenacyl C=O), 1 642, and 1 586  $\text{cm}^{-1}$  (naphthoquinone system);  $\delta(\text{CDCl}_3)$  4.70 (2 H, s,  $\text{CH}_2$ ), 7.08–7.54 (7 H, m), 7.65–7.86 (2 H, m), and 8.00–8.20 (4 H, m);  $m/z$  402 ( $M^+$ , 71%) and 293 (100).

**2-(4'-Bromophenacyl)-3-phenylthio-1,4-naphthoquinone (5f).** M.p.  $171\text{--}171.5^{\circ}\text{C}$  (from methanol) (Found: C, 62.35; H, 3.35.  $\text{C}_{24}\text{H}_{15}\text{O}_3\text{SBr}$  requires C, 62.21; H, 3.26%);  $\nu_{\text{max}}$  1 666, 1 652, and 1 582  $\text{cm}^{-1}$ ;  $\delta(\text{CDCl}_3)$  4.63 (2 H, s,  $\text{CH}_2$ ), 7.22–7.50 (5 H, m), and 7.62–8.20 (8 H, m);  $m/z$  464 ( $M^+$ ,  $^{81}\text{Br}$ , 100%) and 462 ( $M^+$ ,  $^{79}\text{Br}$ , 80).

**2-(4'-Methoxyphenacyl)-3-phenylthio-1,4-naphthoquinone (5g).** M.p.  $185.5\text{--}186.5^{\circ}\text{C}$  (from methanol) (Found: C, 72.6; H, 4.2.  $\text{C}_{25}\text{H}_{18}\text{O}_4\text{S}$  requires C, 72.45; H, 4.38%);  $\nu_{\text{max}}$  1 646 and 1 584  $\text{cm}^{-1}$ ;  $\delta(\text{CDCl}_3)$  3.88 (3 H, s,  $\text{OCH}_3$ ), 4.68 (2 H, s,  $\text{CH}_2$ ), 6.95–7.08 (2 H, m), 7.21–7.51 (5 H, m), 7.67–7.81 (2 H, m), and 7.99–8.19 (4 H, m);  $m/z$  414 ( $M^+$ , 8%) and 305 (100).

**2-(4'-Nitrophenacyl)-3-phenylthio-1,4-naphthoquinone (5h).** M.p.  $165.5\text{--}167^{\circ}\text{C}$  (from methanol) (Found: C, 67.3; H, 3.3.  $\text{C}_{24}\text{H}_{15}\text{NO}_5\text{S}$  requires C, 67.12; H, 3.52%);  $\nu_{\text{max}}$  1 680, 1 650, and 1 586  $\text{cm}^{-1}$ ;  $\delta(\text{CDCl}_3)$  4.72 (2 H, s,  $\text{CH}_2$ ), 7.16–7.53 (5 H, m), 7.66–7.86 (2 H, m), and 8.08–8.48 (6 H, m);  $m/z$  429 ( $M^+$ , 50%) and 398 (100).

**2-[2-Oxo-2-(2-naphthyl)ethyl]-3-phenylthio-1,4-naphthoquinone (5i).** M.p.  $165.5\text{--}166.5^{\circ}\text{C}$  (from methanol) (Found: C, 77.65; H, 3.95.  $\text{C}_{28}\text{H}_{18}\text{O}_3\text{S}$  requires C, 77.40; H, 4.18%);  $\nu_{\text{max}}$  1 632, 1 620, and 1 584  $\text{cm}^{-1}$ ;  $\delta(\text{CDCl}_3)$  4.89 (2 H, s,  $\text{CH}_2$ ), 7.21–8.21 (15 H, m), and 8.41 (1 H, s);  $m/z$  434 ( $M^+$ , 63%) and 325 (100).

**2-(3-Dimethyl-2-oxobutyl)-3-phenylthio-1,4-naphthoquinone (5j).** M.p.  $139.5\text{--}140.5^{\circ}\text{C}$  (from methanol) (Found: C, 72.3; H, 5.4.  $\text{C}_{22}\text{H}_{20}\text{O}_3\text{S}$  requires C, 72.50; H, 5.53%);  $\nu_{\text{max}}$  2 960, 1 632, 1 620, and 1 586  $\text{cm}^{-1}$ ;  $\delta(\text{CDCl}_3)$  1.28 (9 H, s,  $3 \times \text{CH}_3$ ), 4.29 (2 H, s,  $\text{CH}_2$ ), 7.25–7.79 (7 H, m), and 7.99–8.18 (2 H, m);  $m/z$  364 ( $M^+$ , 25%) and 279 (100).

**2-Acetyl-3-phenylthio-1,4-naphthoquinone (5k).** M.p.  $148\text{--}148.5^{\circ}\text{C}$  (from methanol) (Found: C, 70.7; H, 4.2.  $\text{C}_{19}\text{H}_{14}\text{O}_3\text{S}$  requires C, 70.79; H, 4.38%);  $\nu_{\text{max}}$  1 706 (acetyl C=O), 1 654, and 1 586  $\text{cm}^{-1}$  (naphthoquinone system);  $\delta(\text{CDCl}_3)$  2.31 (3 H, s,  $\text{CH}_3$ ), 4.17 (2 H, s,  $\text{CH}_2$ ), 7.22–7.32 (2 H, m), 7.36–7.46 (3 H, m), 7.63–7.77 (2 H, m), and 7.95–8.13 (2 H, m);  $m/z$  322 ( $M^+$ , 57%), 281 (100), and 263 (30).

**2-Ethylthio-3-phenacyl-1,4-naphthoquinone (6a).** M.p.  $97\text{--}$

98 °C (from methanol) (Found: C, 71.5; H, 4.75. C<sub>20</sub>H<sub>16</sub>O<sub>3</sub>S requires C, 71.41; H, 4.79%);  $\nu_{\max}$  1 688 (phenacyl C=O), 1 648, and 1 594 cm<sup>-1</sup> (naphthoquinone system);  $\delta$ (CDCl<sub>3</sub>) 2.26 (3 H, t, *J* 7 Hz, CH<sub>3</sub>), 3.22 (2 H, q, *J* 7 Hz, CH<sub>2</sub>), 4.67 (2 H, s, CH<sub>2</sub>), 7.49–7.82 (5 H, m), and 8.05–8.22 (4 H, m); *m/z* 336 (*M*<sup>+</sup>, 7%) and 105 (100).

**2-(2'-Chlorophenacyl)-3-ethylthio-1,4-naphthoquinone (6b).** An oil (Found: C, 64.6; H, 4.15. C<sub>20</sub>H<sub>15</sub>O<sub>3</sub>SCl requires C, 64.77; H, 4.08%);  $\nu_{\max}$  1 690, 1 660, and 1 584 cm<sup>-1</sup>;  $\delta$ (CDCl<sub>3</sub>) 1.31 (3 H, t, *J* 7 Hz, CH<sub>3</sub>), 3.28 (2 H, q, *J* 7 Hz, CH<sub>2</sub>), 4.65 (2 H, s, CH<sub>2</sub>), 7.36–7.56 (3 H, m), 7.69–7.84 (3 H, m), and 8.08–8.20 (2 H, m); *m/z* 370 (*M*<sup>+</sup>, 3%) and 139 (100).

**2-(3'-Chlorophenacyl)-3-ethylthio-1,4-naphthoquinone (6c).** M.p. 112–113 °C (from methanol) (Found: C, 64.75; H, 4.05. C<sub>20</sub>H<sub>15</sub>O<sub>3</sub>SCl requires C, 64.77; H, 4.08%);  $\nu_{\max}$  1 664, 1 638, and 1 584 cm<sup>-1</sup>;  $\delta$ (CDCl<sub>3</sub>) 1.28 (3 H, t, *J* 7 Hz, CH<sub>3</sub>), 3.22 (2 H, q, *J* 7 Hz, CH<sub>2</sub>), 4.63 (2 H, s, CH<sub>2</sub>), and 7.44–8.12 (8 H, m); *m/z* 372 (*M*<sup>+</sup>, <sup>37</sup>Cl, 8%), 370 (*M*<sup>+</sup>, <sup>35</sup>Cl, 16), 139 (100), and 111 (31).

**2-(4'-Chlorophenacyl)-3-ethylthio-1,4-naphthoquinone (6d).** M.p. 144.5–145.5 °C (from methanol) (Found: C, 64.8; H, 3.95. C<sub>20</sub>H<sub>15</sub>O<sub>3</sub>SCl requires C, 64.77; H, 4.08%);  $\nu_{\max}$  1 678 (phenacyl C=O), 1 664, 1 640, and 1 584 cm<sup>-1</sup> (naphthoquinone system);  $\delta$ (CDCl<sub>3</sub>) 1.27 (3 H, t, *J* 7 Hz, CH<sub>3</sub>), 3.23 (2 H, q, *J* 7 Hz, CH<sub>2</sub>), 4.63 (2 H, s, CH<sub>2</sub>), 7.47–7.57 (2 H, m), 7.70–7.84 (2 H, m), and 7.79–8.21 (4 H, m); *m/z* 372 (*M*<sup>+</sup>, <sup>37</sup>Cl, 4%), 370 (*M*<sup>+</sup>, <sup>35</sup>Cl, 8), 139 (100), and 111 (28).

**2-Ethylthio-3-(4'-fluorophenacyl)-1,4-naphthoquinone (6e).** M.p. 108.5–109 °C (from methanol) (Found: C, 67.9; H, 4.2. C<sub>20</sub>H<sub>15</sub>O<sub>3</sub>SF requires C, 67.78; H, 4.27%);  $\nu_{\max}$  1 660, 1 640, and 1 586 cm<sup>-1</sup>;  $\delta$ (CDCl<sub>3</sub>) 1.27 (3 H, t, *J* 7 Hz, CH<sub>3</sub>), 3.23 (2 H, q, *J* 7 Hz, CH<sub>2</sub>), 4.64 (2 H, s, CH<sub>2</sub>), 7.17–7.30 (2 H, m), 7.70–7.81 (2 H, m), and 8.05–8.19 (4 H, m); *m/z* 354 (*M*<sup>+</sup>, 14), 123 (100), and 95 (33).

**2-(4'-Bromophenacyl)-3-ethylthio-1,4-naphthoquinone (6f).** M.p. 151–152 °C (from methanol) (Found: C, 57.55; H, 3.4. C<sub>20</sub>H<sub>15</sub>O<sub>3</sub>SBr requires C, 57.84; H, 3.64%);  $\nu_{\max}$  1 680 (phenacyl C=O), 1 666, 1 640, and 1 580 cm<sup>-1</sup> (naphthoquinone system);  $\delta$ (CDCl<sub>3</sub>) 1.27 (3 H, t, *J* 7 Hz, CH<sub>3</sub>), 3.24 (2 H, q, *J* 7 Hz, CH<sub>2</sub>), 4.62 (2 H, s, CH<sub>2</sub>), 7.64–7.85 (4 H, m), and 7.92–8.26 (4 H, m); *m/z* 416 (*M*<sup>+</sup>, <sup>81</sup>Br, 11%), 414 (*M*<sup>+</sup>, <sup>79</sup>Br, 10), 231 (7), 183 (100), and 155 (25).

**2-Ethylthio-3-(4'-methoxyphenacyl)-1,4-naphthoquinone (6g).** M.p. 131–132 °C (from methanol) (Found: C, 68.6; H, 4.75. C<sub>21</sub>H<sub>18</sub>O<sub>4</sub>S requires C, 68.83; H, 4.95%);  $\nu_{\max}$  1 622 (phenacyl C=O), 1 646 and 1 598 cm<sup>-1</sup> (naphthoquinone system);  $\delta$ (CDCl<sub>3</sub>) 1.26 (3 H, t, *J* 7 Hz, CH<sub>3</sub>), 3.22 (2 H, q, *J* 7 Hz, CH<sub>2</sub>), 3.91 (3 H, s, OCH<sub>3</sub>), 4.64 (2 H, s, CH<sub>2</sub>), 6.97–7.09 (2 H, m), 7.69–7.83 (2 H, m), and 8.03–8.21 (4 H, m); *m/z* 366 (*M*<sup>+</sup>, 1%), 135 (100), and 107 (7).

**2-Ethylthio-3-(4'-nitrophenacyl)-1,4-naphthoquinone (6h).** M.p. 125.5–127 °C (from methanol) (Found: C, 62.95; H, 3.7. C<sub>20</sub>H<sub>15</sub>NO<sub>3</sub>S requires C, 62.98; H, 3.96%);  $\nu_{\max}$  1 684 (phenacyl C=O), 1 664, 1 640, and 1 588 cm<sup>-1</sup> (naphthoquinone system);  $\delta$ (CDCl<sub>3</sub>) 1.27 (3 H, t, *J* 7 Hz, CH<sub>3</sub>), 3.26 (2 H, q, *J* 7 Hz, CH<sub>2</sub>), 4.67 (2 H, s, CH<sub>2</sub>), 7.71–7.86 (2 H, m), and 8.05–8.49 (6 H, m); *m/z* 381 (*M*<sup>+</sup>, 19%), 231 (19), 150 (100), 120 (52), and 104 (50).

**2-Ethylthio-3-[2-oxo-2-(2-naphthylethyl)-1,4-naphthoquinone (6i).** M.p. 138.5–139.5 °C (from methanol) (Found: C, 74.55; H, 4.45. C<sub>26</sub>H<sub>18</sub>O<sub>3</sub>S requires C, 74.59; H, 4.69%);  $\nu_{\max}$  1 672 (C=O), 1 656, and 1 588 cm<sup>-1</sup> (naphthoquinone system);  $\delta$ (CDCl<sub>3</sub>) 1.27 (3 H, t, *J* 7 Hz, CH<sub>3</sub>), 3.23 (2 H, q, *J* 7 Hz, CH<sub>2</sub>), 4.82 (2 H, s, CH<sub>2</sub>), 7.53–8.27 (10 H, m), and 8.65 (1 H, s); *m/z* 386 (*M*<sup>+</sup>, 4%), 155 (100), and 111 (43).

**2-Ethylthio-3-(3,3-dimethyl-2-oxobutyl)-1,4-naphthoquinone (6j).** An oil (Found: C, 68.05; H, 6.6. C<sub>18</sub>H<sub>20</sub>O<sub>3</sub>S requires C, 68.33; H, 6.37%);  $\nu_{\max}$  1 704 (C=O), 1 660, and 1 592 cm<sup>-1</sup> (naphthoquinone system);  $\delta$ (CDCl<sub>3</sub>) 1.27 (3 H, t, *J* 7 Hz, CH<sub>3</sub>),

1.30 (9 H, s, 3 × CH<sub>3</sub>), 3.20 (2 H, q, *J* 7 Hz, CH<sub>2</sub>), 4.20 (2 H, s, CH<sub>2</sub>), 7.70–7.89 (2 H, m), and 8.06–8.17 (2 H, m); *m/z* 316 (*M*<sup>+</sup>, 74%) and 232 (100).

**2-Acetylthio-3-ethylthio-1,4-naphthoquinone (6k).** M.p. 72–73 °C (from hexane) (Found: C, 65.5; H, 4.9. C<sub>15</sub>H<sub>14</sub>O<sub>3</sub>S requires C, 65.69; H, 5.11%);  $\nu_{\max}$  1 715 (acetylthio), 1 665, and 1 650 cm<sup>-1</sup> (naphthoquinone system);  $\delta$ (CDCl<sub>3</sub>) 1.30 (3 H, t, CH<sub>3</sub>CH<sub>2</sub>), 2.35 (3 H, s, COCH<sub>3</sub>), 3.24 (2 H, q, CH<sub>2</sub>CH<sub>3</sub>), 4.12 (2 H, s, COCH<sub>2</sub>), 7.70–7.85 (2 H, m), and 8.08–8.24 (2 H, m); *m/z* 274 (*M*<sup>+</sup>, 100%) and 232 (93).

**Preparation of Naphtho[2,3-*b*]furan-4,9-diones (8).**—To a solution of thio-substituted 1,4-naphthoquinone (5) or (6) (1 mmol) in acetic acid (10 ml) in the dark was added bromine (quantity as shown in Table 3) with stirring. On completion of the bromination, the reaction mixture was extracted with benzene and washed with aqueous sodium bisulphite then water and dried with anhydrous sodium sulphate. Evaporation of the solvent and column chromatography on silica gel with toluene-hexane as eluant gave the 2-substituted naphtho[2,3-*b*]furan-4,9-dione (8).

**2-Phenylnaphtho[2,3-*b*]furan-4,9-dione (8a).** M.p. 249.5–250.5 °C (from toluene) (lit.,<sup>20</sup> m.p. 246.5–247.5 °C);  $\nu_{\max}$  1 660 and 1 580 cm<sup>-1</sup>;  $\delta$ (CDCl<sub>3</sub>) 7.24 (1 H, s, 3-H), 7.42–7.63 (3 H, m), 7.72–8.01 (4 H, m), and 8.18–8.34 (2 H, m); *m/z* 274 (*M*<sup>+</sup>, 100%).

**2-(2'-Chlorophenyl)naphtho[2,3-*b*]furan-4,9-dione (8b).** M.p. 185–186 °C (from ethyl acetate) (Found: C, 70.15; H, 2.8. C<sub>18</sub>H<sub>9</sub>O<sub>3</sub>Cl requires C, 70.03; H, 2.94%);  $\nu_{\max}$  1 664, 1 592, and 1 580 cm<sup>-1</sup>;  $\delta$ ([<sup>2</sup>H<sub>6</sub>]-DMSO, 90 °C) 7.52–7.62 (3 H, m), 7.64–7.74 (1 H, m), 7.86–7.95 (2 H, m), 7.97–8.06 (1 H, m), and 8.10–8.21 (2 H, m); *m/z* 310 (*M*<sup>+</sup>, <sup>37</sup>Cl, 34%), 308 (*M*<sup>+</sup>, <sup>35</sup>Cl, 100), and 280 (28).

**2-(3'-Chlorophenyl)naphtho[2,3-*b*]furan-4,9-dione (8c).** M.p. 300–301 °C (from ethyl acetate) (Found: C, 69.75; H, 2.8. C<sub>18</sub>H<sub>9</sub>O<sub>3</sub>Cl requires C, 70.03; H, 2.94%);  $\nu_{\max}$  1 662 and 1 582 cm<sup>-1</sup>;  $\delta$ ([<sup>2</sup>H<sub>6</sub>]-DMSO, 90 °C) 7.50–7.67 (2 H, m), 7.73 (1 H, s), 7.84–8.00 (3 H, m), 8.03 (1 H, s), and 8.10–8.25 (2 H, m); *m/z* 310 (*M*<sup>+</sup>, <sup>37</sup>Cl, 42%), 308 (*M*<sup>+</sup>, <sup>35</sup>Cl, 100), and 280 (25).

**2-(4'-Chlorophenyl)naphtho[2,3-*b*]furan-4,9-dione (8d).** M.p. 276–277.5 °C (from methanol-toluene) (Found: C, 69.75; H, 2.7. C<sub>18</sub>H<sub>9</sub>O<sub>3</sub>Cl requires C, 70.03; H, 2.94%);  $\nu_{\max}$  1 660 cm<sup>-1</sup>;  $\delta$ ([<sup>2</sup>H<sub>6</sub>]-DMSO, 90 °C) 7.56–7.71 (3 H, m), 7.86–7.96 (2 H, m), 8.01 (2 H, d), and 8.10–8.23 (2 H, m); *m/z* 310 (*M*<sup>+</sup>, <sup>37</sup>Cl, 39%), 308 (*M*<sup>+</sup>, <sup>35</sup>Cl, 100), and 280 (30).

**2-(4'-Fluorophenyl)naphtho[2,3-*b*]furan-4,9-dione (8e).** M.p. > 300 °C (from ethyl acetate) (Found: C, 74.15; H, 2.85. C<sub>18</sub>H<sub>9</sub>O<sub>3</sub>F requires C, 73.97; H, 3.10%);  $\nu_{\max}$  1 680 cm<sup>-1</sup>;  $\delta$ ([<sup>2</sup>H<sub>6</sub>]-DMSO, 90 °C) 7.30–7.46 (2 H, m), 7.57 (1 H, s, 3-H), 7.83–8.09 (4 H, m), and 8.14–8.23 (2 H, m); *m/z* 292 (*M*<sup>+</sup>, 100%) and 274 (39).

**2-(4'-Bromophenyl)naphtho[2,3-*b*]furan-4,9-dione (8f).** M.p. 267–268 °C (from ethyl acetate) (Found: C, 61.3; H, 2.45. C<sub>18</sub>H<sub>9</sub>O<sub>3</sub>Br requires C, 61.22; H, 2.57%);  $\nu_{\max}$  1 658 cm<sup>-1</sup>;  $\delta$ ([<sup>2</sup>H<sub>6</sub>]-DMSO, 90 °C) 7.64 (1 H, s), 7.75 (2 H, dd, *J* 8 Hz), 7.84–8.00 (4 H, m), and 8.08–8.22 (2 H, m); *m/z* 354 (*M*<sup>+</sup>, <sup>81</sup>Br, 100%) and 352 (*M*<sup>+</sup>, <sup>79</sup>Br, 90).

**2-(4'-Methoxyphenyl)naphtho[2,3-*b*]furan-4,9-dione (8g).** M.p. 226.5–227 °C (from ethyl acetate) (Found: C, 74.8; H, 3.7. C<sub>19</sub>H<sub>12</sub>O<sub>4</sub> requires C, 74.99; H, 3.98%);  $\nu_{\max}$  1 658 and 1 604 cm<sup>-1</sup>;  $\delta$ ([<sup>2</sup>H<sub>6</sub>]-DMSO, 90 °C) 3.86 (3 H, s, OCH<sub>3</sub>), 7.12 (2 H, d, *J* 8 Hz), 7.83 (1 H, s), 7.82–8.00 (4 H, m), and 8.08–8.21 (2 H, m); *m/z* 304 (*M*<sup>+</sup>, 100%), 289 (19), 276 (10), 261 (36), 233 (16), and 205 (13).

**2-(4'-Nitrophenyl)naphtho[2,3-*b*]furan-4,9-dione (8h).** M.p. 215.5–217 °C (from ethyl acetate) (Found: C, 74.8; H, 4.05. C<sub>18</sub>H<sub>9</sub>NO<sub>3</sub> requires C, 74.99; H, 3.98%);  $\nu_{\max}$  1 670 and 1 590 cm<sup>-1</sup>;  $\delta$ ([<sup>2</sup>H<sub>6</sub>]-DMSO, 90 °C) 7.87–8.02 (3 H, m), 8.12–8.32 (4

H, m), and 8.34–8.45 (2 H, m);  $m/z$  319 ( $M^+$ , 100%), and 289 (35).

2-(2-Naphthyl)naphtho[2,3-b]furan-4,9-dione (**8i**). M.p. 301–302 °C (from ethyl acetate) (Found: C, 81.45; H, 3.45.  $C_{22}H_{12}O_3$  requires C, 81.24; H, 3.44%);  $\nu_{\max}$  1 652 and 1 588  $cm^{-1}$ ;  $\delta([^2H_6]-DMSO, 90\text{ }^\circ C)$  7.56–7.67 (2 H, m), 7.72 (1 H, s), 7.86–8.03 (3 H, m), 8.05–8.24 (5 H, m), and 8.56 (1 H, s);  $m/z$  324 ( $M^+$ , 100%) and 296 (13).

2-*t*-Butylnaphtho[2,3-b]furan-4,9-dione (**8j**). M.p. 131.5–132.5 °C (from methanol) (Found: C, 75.4; H, 5.45.  $C_{16}H_{14}O_3$  requires C, 75.58; H, 5.55%);  $\nu_{\max}$  1 660 and 1 580  $cm^{-1}$ ;  $\delta(CDCl_3)$  1.41 (9 H, s, 3  $\times$   $CH_3$ ), 6.63 (1 H, s), 7.73–7.78 (2 H, m), and 8.16–8.27 (2 H, m);  $m/z$  254 ( $M^+$ , 22%), 239 (100), and 211 (10).

**Reaction of 2-Ethylthio-1,4-naphthoquinone (2) with Bromine.**—To a solution of (**2**) (2 mmol) in acetic acid (10 ml) at room temperature was added in the dark a solution of bromine (2.1 mmol) in acetic acid (2 ml) and the mixture was stirred for 2 h. The mixture was poured into water and extracted with toluene, then the combined extracts were washed successively with aqueous sodium bisulphite and water, and dried with anhydrous sodium sulphate. Evaporation of the solvent and column chromatography on silica gel, eluting with toluene–hexane (1:1), gave 2-bromo-3-ethylthio-1,4-naphthoquinone (**11**) in 97% yield. Compound (**11**) showed m.p. 140–141.5 °C (from methanol) (Found: C, 48.6; H, 3.3.  $C_{12}H_9O_2SBr$  requires C, 48.50; H, 3.05%);  $\nu_{\max}$  1 662 and 1 655, 1 582, and 1 500  $cm^{-1}$ ;  $\delta(CDCl_3)$  1.25–1.55 (3 H, t,  $CH_3$ ), 3.25–3.68 (2 H, q,  $CH_2$ ), 7.55–7.82 (2 H, m), and 7.92–8.18 (2 H, m);  $m/z$  298 ( $M^+$ ,  $^{81}Br$ , 100%), 296 ( $M^+$ ,  $^{79}Br$ , 95). Further treatment of (**11**) with 20 mol equiv. of bromine at room temperature in the dark for 24 h gave 2,3-dibromo-1,4-naphthoquinone in 88% yield, identical with an authentic sample.<sup>21</sup>

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