Nitrile Sulfides Part 16.\(^1\)\(^2\) Synthesis of 1,2-benzisothiazoles via nitrile sulfide cycloaddition reactions

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Abstract

The cycloaddition reactions of nitrile sulfides have been used to prepare benzisothiazole quinones and 1,2-benzisothiazole-5,6-dicarboxylates. The nitrile sulfides, generated by thermal decarboxylation of 1,3,4-oxathiazol-2-ones, reacted with 1,4-naphthoquinone to afford 3-substituted naphtho[2,3-\(d\)]isothiazole-4,9-diones (17), together with nitriles as by-products. The corresponding reactions with 1,4-benzoquinone yielded regioisomeric mixtures of 2:1 adducts. The 1,2-benzisothiazole-5,6-dicarboxylates were synthesised by a sequence involving both nitrile sulfide and Diels-Alder cycloaddition reactions. Dimethyl 3-phenylisothiazole-4,5-dicarboxylate (34), prepared from benzonitrile sulfide and dimethyl acetylenedicarboxylate (DMAD), was converted into the 4,5-bis(dibromomethyl) analogue 37 via the bis(dihydroxymethyl) compound 35. Treatment of 37 with sodium iodide in the presence of DMAD afforded dimethyl 3-phenyl-1,2-benzisothiazole-5,6-dicarboxylate (30) via the isothiazole \(o\)-quinodimethane 32.

Keywords: Nitrile sulfides, 1,3-dipolar cycloaddition, isothiazoles, heterocyclic 1,4-quinones, heterocyclic \(o\)-quinodimethanes

Introduction

Benzisothiazoles are an important class of heterocycles with a range of interesting properties and their synthesis has therefore attracted much attention.\(^3\) In this paper we describe the use of nitrile sulfide chemistry to prepare two groups of benzisothiazoles: \(viz\). benzisothiazole quinones and 1,2-benzisothiazole-5,6-dicarboxylates. Heterocyclic-fused 1,4-quinones possess a variety of
biological activities, most of which are associated with their redox properties.\textsuperscript{4-6} Recently there has been particular interest in isoxazole-fused 1,4-naphthoquinones (naphtho[2,3-d]isoxazole-4,9-diones) in view of their potential medicinal and agricultural applications.\textsuperscript{7,8} In contrast, little is known about the corresponding isothiazole-fused 1,4-quinones.

One of the key methods for synthesising the isoxazole quinones involves cycloaddition of nitrile oxides to 1,4-quinones. 1,4-Naphthoquinones have proved to be highly reactive dipolarophiles in cycloaddition reactions with various 1,3-dipoles.\textsuperscript{8-16} Nitrile oxides react at C(2)=C(3) of naphthoquinone (NQ) to afford isoxazoline cycloadduct 1, which readily undergo dehydrogenation to the naphtho[2,3-d]isoxazole-4,9-diones 2 (Scheme 1).\textsuperscript{10-13} Cycloaddition reactions of nitrile imides and nitrile ylides with NQs have also been reported.\textsuperscript{14,15} In contrast, much less attention\textsuperscript{16-18} has been paid to the corresponding reactions with nitrile sulfides (R-C≡N⁺−S⁻),\textsuperscript{19-21} yet these can provide access to naphtho[2,3-d]isothiazole-4,9-diones (3), a class of compounds for which there appears at present to be no alternative route. An additional incentive to develop this approach is the observation that the isothiazole-fused naphthoquinone aulosirazole (4), which has been isolated from the blue-green alga \textit{Aulosira fertilissima}, is a solid-tumour selective cytotoxin.\textsuperscript{22}

![Scheme 1](image)

Quinones such as NQ and 1,4-benzoquinone (BQ) are also of interest because they possess both alkene and carbonyl dipolarophiles. Nitrile sulfides are known to undergo 1,3-dipolar cycloaddition reactions with alkenes\textsuperscript{17,23-28} and with ketones,\textsuperscript{29,30} provided that the dipolarophiles are activated by electron-withdrawing substituents. For example, benzonitrile sulfide reacts with maleic anhydride\textsuperscript{23} and with hexachloroacetone\textsuperscript{29} to afford isothiazoline 7 and 1,3,4-oxathiazole 8, respectively (Scheme 2). In the present work we have explored the potential of nitrile sulfide chemistry for the preparation of novel isothiazole-fused quinones, and also examined the site selectivity of nitrile sulfide cycloadditions to the alkene and carbonyl dipolarophile units in NQ and BQ.\textsuperscript{18}
The first successful attempt to prepare naphtho[2,3-d]isothiazole-4,9-diones was reported by Sanders and Grunwell who isolated the trifluoromethyl derivative 5 from NQ and trifluoroacetonitrile sulfide, generated from (trifluoroethylimino)sulfur difluoride; 5-hydroxy-1,4-naphthoquinone (juglone) reacted similarly to afford 6. Both products were isolated in low yield, 11 and 14%, respectively. It has also been reported that acenaphthoquinone reacts with benzonitrile sulfide at one of the ketone groups to yield the 1,3,4-oxathiazole, thus demonstrating the activating effect of an adjacent carbonyl group. In the same paper the reaction of benzonitrile sulfide with o-pleiadienequinone (10), an α,β-unsaturated 1,2-dione, was reported to yield the bi(pleiadienylidene)dione 12. The proposed mechanism involved initial cycloaddition to the enone carbonyl and fragmentation of the resulting oxathiazole to generate the unstable thione 11; subsequent dimerisation to a 1,3-dithietane and desulfurization forms the observed pleiadienequinone.

Results and Discussion

Cycloaddition of a nitrile sulfide 15 to 1,4-naphthoquinone (NQ) could yield an isothiazoline 16 (and hence an isothiazole 17) by reaction at C(2)=C(3) and/or a spiro-oxathiazole 19 by reaction at one of the carbonyl groups (Scheme 3). To test the site selectivity of this process we examined the reactions of typical nitrile sulfides (15; R = Ph, 4-MeOC₆H₄, Me) with NQ and also with BQ (Table).
As nitrile sulfides are short-lived they are usually generated in situ in the presence of the dipolarophile. The most convenient sources are 1,3,4-oxathiazol-2-ones 14, which are readily prepared from the corresponding carboxamide and chlorocarbonylsulfonyl chloride; the nitrile sulfide can then be generated from the oxathiazolone by thermal decarboxylation at 120-160 °C. In an early study of nitrile sulfide chemistry Franz and Black had examined the reaction of NQ with an equimolar amount of the phenyloxathiazolone 14a as the source of benzonitrile sulfide (15a), but no cycloadducts were isolated and the main products were benzonitrile and the dibenzoanthrenetetrone 18. We adopted the same approach, except that an excess of NQ (3:1) was used. In a typical experiment a mixture of oxathiazolone 14a (56 mmol) and NQ (168 mmol) in xylene was heated at reflux (~138 °C) until HPLC analysis showed complete consumption of 14a (after 12 h). Filtration afforded an almost insoluble dark blue solid, which was recrystallised from nitrobenzene and identified as compound 18 (6%) by comparison with an authentic sample prepared from 2,3-dichloronaphthoquinone. Concentration of the filtrate, removal of the excess NQ by distillation/sublimation, and chromatography of the residue yielded 3-phenylnaphtho[2,3-d]isothiazole-4,9-dione (17a) as a yellow solid. The yields of 17a (36%) and benzonitrile (63%) were determined by HPLC and GC analysis, respectively. There was no evidence for the formation of the spiro-oxathiazole 19a. Structural assignment for 17a is based on its analytical and spectroscopic properties by comparison with those of 3-phenylnaphtho[2,3-d]isoxazole-4,9-diones and those of isothiazole-4,5-dicarboxylates. Of particular note are two C=O peaks in the 13C NMR spectrum at 178.1 and 176.7 ppm, and characteristic signals for the isothiazole ring carbons at 169.7, 167.0 and 134.4 ppm (Table). 

\[
\text{Scheme 3}
\]

The corresponding reaction of p-methoxynitrobenzonitrile sulfide (15b), generated from the oxathiazolone 14b, was complete in 5 h and yielded the naphtho[2,3-d]isothiazole-4,9-dione 17b (42%) together with p-methoxynitrobenzonitrile (52%). The 3-methyl analogue 17c (32%) was
prepared similarly (in 4 h) from oxathiazolone 14c. The shorter reaction times in these cases were not unexpected; it has previously been noted that electron-donating substituents increase the rate of reaction, an effect attributed to a partial positive charge developing at the 5-position of the oxathiazolone ring in the transition state for decarboxylation.\textsuperscript{31,37} The electronic spectra of the products (Table) show features expected of 2,3-disubstituted 1,4-naphthoquinones,\textsuperscript{38} including intense benzenoid and quinoid bands in the 240-290 nm region, a benzenoid band at 330-340 nm, and a quinoid band in the 330-450 nm region. In the mass spectra of products 17a-c there is a peak at \textit{m/z} 104, which is typical of 1,4-naphthoquinones and can be attributed to C\textsubscript{6}H\textsubscript{4}CO\textsuperscript{+} formed by cleavage adjacent to the carbonyl groups at C(3a)-C(4)/C(8a)-C(9) and/or C(4)-C(4a)/C(9)-C(9a);\textsuperscript{39,40} for the 3-methyl compound 17c there is also an M\textsuperscript{+}-28 peak corresponding to loss of CO and at M\textsuperscript{+}-41 peak due to loss of MeCN.

**Table. Benzisothiazole quinones**

<table>
<thead>
<tr>
<th>Cycloadduct (yield / %)</th>
<th>Reaction time / h</th>
<th>(\nu_{\text{max}} / \text{cm}^{-1})</th>
<th>Selected (^{13}\text{C} \text{NMR data}^a / \text{ppm})</th>
<th>(\lambda_{\text{max}} / \text{nm} (\varepsilon)^b)</th>
<th>Nitrile yield (yield/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17a (36)</td>
<td>12</td>
<td>1670</td>
<td>169.7  134.4  167.1  178.2  177.5</td>
<td>271 (24550)  343 (5820)</td>
<td>63</td>
</tr>
<tr>
<td>17b (42)</td>
<td>5</td>
<td>1673</td>
<td>169.5  134.5  167.2  178.2  177.6</td>
<td>268 (25170)  279 (24960) 298 (20630) 347 (5160) 394 (1670) 442 (1200)</td>
<td>52</td>
</tr>
<tr>
<td>17c (32)</td>
<td>4.5</td>
<td>1665</td>
<td>168.9  133.9  165.4  179.1  177.2</td>
<td>271 (11330)  277 (1140) 333 (5850)</td>
<td>c</td>
</tr>
<tr>
<td>24c (19)</td>
<td>4.5</td>
<td>1660</td>
<td>168.4  133.3  167.7  172.6</td>
<td>272 (13820) 278 (13490) 351 (8350)</td>
<td>c</td>
</tr>
<tr>
<td>24b (33)</td>
<td>5</td>
<td>1675</td>
<td>169.5  133.7  165.7  173.7</td>
<td>297 (17200) 458 (1410)</td>
<td>50</td>
</tr>
<tr>
<td>25b (1)</td>
<td></td>
<td>1670</td>
<td>c     c     c     c     c     c     c     c     c     c</td>
<td>278 (11080) 307 (13390) 470 (1740)</td>
<td>c</td>
</tr>
</tbody>
</table>

\(a\) In CDCl\textsubscript{3}; \(b\) in CHCl\textsubscript{3}; \(c\) not determined.

The formation of the isothiazole-fused quinones 17 is believed to involve initial cycloaddition of the nitrile sulfide to the C(2)=C(3) double bond of NQ to form the isothiazoline
16 and hence its tautomer 20, as illustrated in Scheme 3, followed by in situ dehydrogenation under the reaction conditions, either by atmospheric oxygen or involving a second equivalent of NQ as oxidising agent. A similar mechanism has been established for the corresponding reactions of nitrile oxides. In the latter cases it is often possible to identify the initial isoxazoline cycloadducts 1, which then readily dehydrogenate to the isoxazoles 2. For example, it is reported12 that benzonitrile oxide reacts with NQs to afford isoxazolines that can be isolated, whereas the adducts from bromoformonitrile oxide dehydrogenate under the reaction conditions. In the present case attempts to identify the isothiazolines 16 were not successful. The reaction of oxathiazolone 14c with NQ was followed by 1H NMR spectroscopy; there were, however, no signals detectable in the region expected for an isothiazoline [δH 4.5-4.8 ppm (H-4), 4.8-5.2 ppm (H-5)],24,26 and the only signals observed were those of the starting materials and the isolated product 17c. The formation of nitriles and sulfur as by-products is a common feature of nitrile sulfide reactions and is attributed to desulfurization of the nitrile sulfide competing with the cycloaddition reaction.19-21

Sanders and Grunwell17 investigated the reaction of with 5-hydroxy-1,4-naphthoquinone with trifluoroacetonitrile sulfide (15, R = CF3), generated from (trifluoroethylimino)sulfur difluoride, and reported the isolation of a single cycloadduct in low yield. This was tentatively assigned the structure 6 on the basis of its mass spectrum. Such regioselectivity is remarkable and we therefore investigated the regioselectivity for nitrile sulfide cycloaddition to another asymmetrically substituted naphthoquinone, 5-acetamido-1,4-naphthoquinone (21). The naphthoquinone 21 was heated with two equivalents of the methyloxathiazolone 14c under reflux for 4.5 h. Work up afforded a three-component mixture comprising the two cycloadducts 22 and 23, together with unreacted 21. From this mixture a small amount (1.5%) of one of the cycloadducts was isolated pure as deep red crystals, but it did not prove possible to purify the other isomer (Scheme 4).

Scheme 4

The spectroscopic data for the purified product were consistent with both structures. In the 1H NMR spectrum there was a broad signal at 11.9 ppm for the amide NH and an ABC pattern in the range 9.1 to 7.8 ppm (JAB 8.3, JAC 1.5, JBC 7.5 Hz) for the benzo ring protons. The IR spectrum showed the characteristic absorptions for the amide group at 3270 and 1710 cm⁻¹, while in the electronic spectrum the extinction coefficient at wavelengths above 400 nm (λmax 437 nm, ε 7922) was increased compared with unsubstituted analogues 17a-c, as expected for the
introduction of the 5-NHAc group. HPLC analysis showed that the isomer ratio was ca 55:45, thus demonstrating that, as anticipated, cycloadditions to 5-substituted naphthoquinones show little regioselectivity. Similar low levels of regioselectivity have been reported for cycloaddition of nitrile oxides to 5-substituted-1,4-naphthoquinones.\(^{11}\)

Having established that naphtho[2,3-d]isothiazole-4,9-diones could be prepared from nitrile sulfides and 1,4-naphthoquinone, the corresponding reactions with 1,4-benzoquinone (BQ) were examined. BQ has two equivalent alkenic dipolarophiles [C(2)=C(3) and C(5)=C(6)], both of which are activated by adjacent electron-withdrawing carbonyl groups, and the carbonyl groups themselves are also potential dipolarophiles. Although BQ has proved to be an effective dipolarophile for cycloadditions to a variety of 1,3-dipoles,\(^9\)-\(^{11}\),\(^{41,42}\) there had been no reports of nitrile sulfides reacting with BQ prior to the present work.

The methyloxathiazolone 14c was heated with four equivalents of BQ at 138 °C in refluxing xylene for 4.5 h and after work up the novel benzodiisothiazole-4,8-dione 24c (19%) was isolated as the major product (Scheme 5) (Table). It showed one singlet at \(\delta_H 2.82\) ppm in the \(^1\)H NMR spectrum and a peak for \(M^+\) at \(m/z 250\) by mass spectrometry. These observations are consistent with both the trans and cis isomers 24c and 25c. The product was identified as the 2:1 trans-adduct 24c from its \(^{13}\)C NMR spectrum where only five individual carbon signals were detected [172.8 (C=O); 168.4, 167.7, 133.4 (isothiazole ring C); 19.4 (Me)]. The cis isomer 25c, which was not isolated, would be expected to show six distinct carbon signals: i.e. for two carbonyl carbons in addition to the Me substituents and carbons C(3), C(4) and C(5) of the isothiazole rings, whereas for compound 24c the two carbonyl carbons are equivalent.

\(p\)-Methoxybenzonitrile sulfide 15b reacted similarly with BQ, but in this case both the possible 2:1 benzodiisothiazole-4,8-diones 24b and 25b were isolated. The trans 2:1 product 24b (33%) was the major product, formed together with traces (1%) of the cis 2:1 product 25b and \(p\)-methoxybenzonitrile (50%); the last is the expected by-product resulting the competing desulfurisation of the nitrile sulfide. A similar preference for trans 2:1 adducts has been reported for the corresponding reactions of nitrile oxides with BQ.\(^{10,43}\)
[a, R = Ph; b, R = 4-MeOC₆H₄; c, R = Me]

**Scheme 5**

A characteristic feature of the mass spectra of the 2:1 adducts is a peak for fragment 28, corresponding to cleavage at C(1)-C(2) and C(4)-C(5) of the 1,4-quinone. For methyl-substituted compound 23c there are also peaks at m/z 222, 209 and 181, corresponding to loss of CO, MeCN and CO + MeCN, respectively; there is also a significant peak at 84 consistent with SC₂C≡O⁺, formed by loss of MeCN from fragment 28c.

The reaction pathway is believed to involve initial formation of the 1:1 isothiazoline adduct 26, its oxidation to the isothiazole 27, followed by a second addition of the nitrile sulfide to form the 2:1 adducts, as illustrated in Scheme 5. It is noteworthy that in neither case was the 1:1 product 27 isolated even though excess of BQ was used. This indicates that the remaining enedione unit in 27, like that in NQ, is a reactive dipolarophile towards nitrile sulfides.

In all the cases investigated the nitrile sulfide reacted exclusively at C(2)=C(3) of the 1,4-quinone to yield isothiazole-fused quinones and there was no evidence for competing formation of spiro-oxathiazoles, e.g. 19. For example, heating the phenyloxathiazolone 14a with NQ yielded 36% of adduct 17a and 63% of benzonitrile (Scheme 3), thus accounting for 99% of the oxathiazolone and hence of the benzonitrile sulfide. It is known that 1,3,4-oxathiazoles, e.g. 8, can undergo cycloreversion to regenerate the nitrile sulfide and carbonyl compound. The possibility that such a cycloreversion was occurring in the present case, as illustrated in Scheme 6, was therefore considered. While such a reaction pathway cannot be ruled out, it is regarded as unlikely since oxathiazoles such as 6 are stable under the reaction conditions (~138 °C) and the cycloreversion requires temperatures >160 °C.

These results are in contrast to those reported for o-pheadienequinone 10, which reacts with benzonitrile sulfide at the α,β-unsaturated carbonyl group to form oxathiazole 13, and not at the activated alkene moiety. Of the other nitrilium betaines, nitrile oxides can react at both the alkene and carbonyl group. With NQ the first reaction usually takes place at the alkene unit, followed by addition to the carbonyl; with BQ both reactions can occur depending on the substitution pattern and the reaction conditions. Likewise, for nitrile ylides cycloaddition can take place at both alkene and carbonyl groups.

**Scheme 6**
The route used to synthesise the 3-phenyl-1,2-benzisothiazole-5,6-dicarboxylate 30 was prompted by a report by Mitkidou and Stephanidou-Stephanatou, who had prepared the corresponding benzisoxazole 29 from dimethyl 3-phenylisoxazole-4,5-dicarboxylate (33) using the Diels-Alder cycloaddition reaction of the isoxazole-based \( o \)-quinodimethane 31 with DMAD (Scheme 7). Heterocyclic \( o \)-quinodimethanes have been widely used in synthesis, and we hoped that a similar approach should be possible for the benzisothiazole analogue 30 via the isothiazole \( o \)-quinodimethane 32, and using the readily accessible isothiazole dicarboxylate 34 as the starting material.

Scheme 7

Our route, which is outlined in Scheme 8, uses the previously unknown 4,5-bis(bromo-methyl)-3-phenylisothiazole (37) as the precursor of the required isothiazole \( o \)-quinodimethane (4,5-dihydro-4,5-dimethylene-3-phenylisothiazole 32). The starting material (dimethyl 3-phenylisoxazole-4,5-dicarboxylate 34) was prepared in 78% yield as previously reported, by the cycloaddition reaction between dimethyl acetylenedicarboxylate (DMAD) and benzonitrile sulfide (15a), which was generated by thermal decarboxylation of the corresponding oxathiazolone 14a. Reduction with sodium borohydride then yielded the bis-hydroxymethyl compound 35 (75%), which was converted into the bis-bromomethyl analogue 37 (55%) by treatment with phosphorus tribromide. Heating the product with sodium iodide in DMF in the presence of DMAD afforded dimethyl 3-phenyl-1,2-benzisothiazole dicarboxylate (30) in 45% yield. The reaction is believed to involve an initial iodide-induced 1,4-halogen elimination to generate the short-lived isothiazole \( o \)-quinodimethane 32, which is trapped by DMAD as its Diels-Alder adduct 36. Dehydrogenation of this 4,7-dihydrobenzisothiazole under the reaction conditions then yields the required product.
Scheme 8

Compound 30 was identified from its spectroscopic properties. In the NMR spectra there are characteristic signals for the two methoxycarbonyl groups [$\delta_H 3.90, 3.86$ ppm; $\delta_C 167.7, 167.3$ ppm] in addition to those expected for the isothiazole ring [$\delta_C 164.9$ ppm (C=N)] and the phenyl substituent. There are also distinctive signals for the CHs at the 4- and 7-positions [$\delta_H 8.48, 8.24$ ppm; $\delta_C 126.4, 121.0$ ppm]. The product was thus prepared in five steps from benzamide using readily available reagents. Both [3+2] and [4+2] cycloaddition reactions are involved; the isothiazole is formed by a 1,3-dipolar cycloaddition of a nitrile sulfide, and the fused arene ring via a Diels-Alder cycloaddition.

Under similar conditions the isothiazole quinodimethane 32 reacted with diethyl fumarate to afford the adduct 38 as a mixture of $5R,6R$ and $5S,6S$ isomers. In contrast, attempts to prepare the anhydride 39, the imide 40, and the dihydropyridazine 41, by reaction with maleic anhydride, N-phenylmaleimide and diethyl azodicarboxylate, respectively, were not successful.

Conclusions

In conclusion, these results show that isothiazole-fused 1,4-quinones, a class of compounds to which there is currently no alternative synthetic approach, can be synthesised from readily accessible oxathiazolones using nitrile sulfide cycloaddition chemistry. It is also concluded that nitrile sulfides, like nitrile oxides, react preferentially at C(2)=C(3) of 1,4-quinones, rather than at the carbonyl groups. 3-Substituted-1,2-benzisothiazoles can be prepared by a short route involving both nitrile sulfide and Diels-Alder cycloaddition reactions.
Experimental Section

General. Melting points were measured on a Gallenkamp capillary apparatus. The $^1$H and $^{13}$C NMR spectra were recorded with Bruker Avance 300, WP200 and AC250 or Varian HA100 and CFT20 spectrometers on solutions in CDCl$_3$ (unless otherwise stated) with Me$_4$Si as internal standard. IR spectra were obtained using Perkin-Elmer 257 and BioRad SPC 3200 spectrophotometers. EI and FAB mass spectra were recorded on a Kratos MS902 or MS50TC spectrometers. Kieselgel GF$_{254}$ (0.2 mm) was used for analytical TLC; detection was by UV or KMnO$_4$ staining. Dry flash chromatography was carried out with Kieselgel GF$_{254}$ and eluted under water pump vacuum. HPLC analysis used alumina columns (25% water deactivated) with 80% hexane–20% CH$_2$Cl$_2$ (25% water deactivated) as eluant. The 1,3,4-oxathiazol-2-ones 14a-c were prepared by treatment of the corresponding carboxamides with chlorocarbonylsulfenyl chloride using established literature procedures. 31 Dibenzo[b,i]thianthrene-5,7,12,14-tetrone 18 was prepared (90%) from 2,3-dichloro-1,4-naphthoquinone and sodium sulfide, as described by Brass and Kohler. 32

Preparation of naphtho[2,3-d]isothiazole-4,9-diones 17

3-Phenylnaphtho[2,3-d]isothiazole-4,9-dione (17a). To a suspension of NQ (26.5 g, 168 mmol) in dry xylene (250 mL) was added 5-phenyl-1,3,4-oxathiazol-2-one (14a) (10.0 g, 56 mmol) and the mixture heated at reflux (138 °C) until HPLC analysis indicated complete consumption of 14a (after 12 h). Filtration of the reaction mixture yielded an almost insoluble dark blue solid which was crystallised and recrystallised from hot nitrobenzene to give dibenzo[b,i]thianthrene-5,7,12,14-tetraone (18) (0.6 g, 6%); m.p. and mixed m.p. 309-311 °C (lit. 302 °C); MS (EI): m/z 376 (M$^+$). The filtrate was concentrated under vacuum, then subjected to distillation at reduced pressure (100 °C at 1.0 mm Hg) to remove most of the excess NQ, and the residue chromatographed on silica. Elution with chloroform yielded an orange solid which was recrystallised from toluene to give 3-phenylnaphtho[2,3-d]isothiazole-4,9-dione (16a). M.p. 217–219 °C; IR (Nujol) $\nu_{max}$ 1670 cm$^{-1}$ (C=O); $^1$H NMR (100 MHz, CDCl$_3$): $\delta$: 8.1–8.3 (2H, m, ArH), 7.7–7.9 (4H, m, ArH), 7.4–7.6 (3H, m, ArH); $^{13}$C NMR (20 MHz, CDCl$_3$): $\delta$: 178.0, 177.5 (C=O), 169.7, 167.0, 134.4 (isothiazole ring C), 135.0, 133.8, 127.9, 127.7 (benzo ring CH), 134.2 (PhC), 133.1, 132.7 (benzo ring C), 130.0, 129.4, 127.9 (5 PhCH); MS (El): m/z (%) 291 (M$^+$, 100%), 290 (97), 132 (13), 104 (15). Anal. Calcd. for C$_{17}$H$_8$NO$_2$S: C, 70.1; H, 3.1; N, 4.8. Found: C, 70.1; H, 3.1; N, 4.7. The yields of 17a (36%) and benzonitrile (63%) were determined by HPLC and GLC (2.5% OV1, 60 °C).

3-(p-Methoxyphenyl)naphtho[2,3-d]isothiazole-4,9-dione (17b). The reaction was carried out as described above for 17a using 5-(p-methoxyphenyl)-1,3,4-oxathiazol-2-one (14b) and NQ (reaction time 5 h). Chromatography (silica, CHCl$_3$) of the concentrated reaction mixture yielded p-methoxybenzonitrile (52%) as a colourless solid (from hexane); IR (Nujol): $\nu_{max}$ 2210 cm$^{-1}$ (C≡N); MS (El) m/z: 133 (M$^+$). Further elution with CHCl$_3$ gave an orange solid which
crystallised from EtOH/CHCl₃ (1:1) to afford 3-(p-methoxyphenyl)naphtho[2,3-d]isothiazole-4,9-dione (17b) (42%) as fine orange needles (from EtOH/CHCl₃). M.p. 228–229 °C, IR (Nujol): νmax 1673 cm⁻¹ (C=O); ¹H NMR (100 MHz, CDCl₃): δ 8.1–8.3 (2H, m, ArH), 7.7–7.9 (4H, m, ArH), 6.97 (2H, d, J 9 Hz, half of AB system, ArH), 3.85 (3H, s, OCH₃); ¹³C NMR (20 MHz, CDCl₃): δC 178.1, 177.6 (C=O), 169.5, 167.2, 134.5 (isothiazole ring C), 161.6, 126.7 (anisyl ring C), 135.0, 133.7, 127.9, 127.7 (benzo ring CH), 132.7, 132.6 (benzo ring C), 131.1, 113.4 (4 anisyl ring CH), 55.3 (OMe); MS (EI) m/z (%): 231 (M⁺, 100%), 290(12), 278(15), 104(17), 76(19). Anal. Calcd. for C₁₈H₁₁NO₃S: C, 67.3; H, 3.4; N, 4.4. Found: C, 67.1; H, 3.4; N, 4.3.

3-Methylnaphtho[2,3-d]isothiazole-4,9-dione (17c). The reaction was carried out as described above for 17a using 5-methyl-1,3,4-oxathiazol-2-one (14c) and NQ (reaction time 4 h). Chromatography (silica, CHCl₃) of the concentrated reaction mixture yielded a grey-brown solid which crystallised from EtOH to afford 3-methylnaphtho[2,3-d]isothiazole-4,9-dione (17c) (32%) in the form of pale yellow crystals (from EtOH). M.p. 147–149 °C, IR (Nujol): νmax 1665 cm⁻¹ (C=O); ¹H NMR (100 MHz, CDCl₃): δ 8.1–8.3 (2H, m, ArH), 7.6–7.9 (2H, m, ArH), 2.83 (3H, s, CH₃); ¹³C NMR (20 MHz, CDCl₃): δC 179.1, 177.3 (C=O), 168.9, 165.4, 133.9 (isothiazole ring C), 134.7, 133.7, 127.5, 127.2 (benzo ring CH), 133.6, 133.1 (benzo ring C), 19.6 (CH₃); MS (EI) m/z (%): 229 (M⁺, 100%), 201(18), 188(32), 160(30), 158(28), 104(66). Anal. Calcd. for C₁₈H₁₂NO₃S: C, 62.6; H, 3.1; N, 6.1. Found: C, 62.9; H, 3.1 N, 6.1.

5/8-Acetamido-3-methylnaphtho[2,3-d]isothiazole-4,9-diones (22/23). To a suspension of 5-acetamido-1,4-naphthoquinone (21) (2.0 g, 9.4 mmol) in dry xylene (30 mL) was added 5-methyl-1,3,4-oxathiazol-2-one (14c) (2.2 g, 18.8 mmol) and the mixture was heated at reflux (138 °C) until HPLC analysis indicated complete consumption of 14c (after 4.5 h). The mixture was concentrated and subjected to MPLC on silica. Elution with hexane/CH₂Cl₂ (3:2) yielded a red solid which crystallised from EtOH to give 5- or 8-acetamido-3-methylnaphtho[2,3-d]isothiazole-4,9-dione (22/23) (0.04 g, 1.5%) as deep red needles (from EtOH). M.p. 211 °C; IR (Nujol): νmax 3270 (N-H), 1710 (C=O) cm⁻¹; ¹H NMR (100 MHz, CDCl₃): δ 11.90 (1H, brs, NH), 9.11 (1H, dd, J 8.3 & 1.5 Hz, Hₐ), 8.00 (1H, dd, J 7.5 & 1.5 Hz, Hₐ), 7.82 (1H, dd, J 7.9 & 8.3 Hz, Hₐ), 2.87 (3H, s, CH₃), 2.32 (3H, s, NHAc); UV (EtOH): λmax / nm (ε) 266 (25974), 331 (6494), 437 (7922). HRMS (EI) m/z: Calcd. for C₁₆H₁₀N₂O₃S: 286.04121. Found: 286.04021. Further elution with the same solvent mixture gave mixed fractions containing both 5- and 8-acetamido-3-methylnaphtho[2,3-d]isothiazole-4,9-diones, together with unreacted 21. Further MPLC afforded fractions rich in the second more polar cycloadduct.

Preparation of benzodiisothiazole-4,8-diones (24,25) 3,7-Bis-(p-methoxyphenyl)benzo[1,2-d;4,5-d]diisothiazole-4,8-dione (24b) and 3,5-bis-(p-methoxyphenyl)benzo[1,2-d;5,4-d]diisothiazole-4,8-dione (25b). To a suspension of BQ (10.4 g, 96 mmol) in dry xylene was added 5-(p-methoxyphenyl)-1,3,4-oxathiazol-2-one (14b) (5.0 g, 24 mmol) and the mixture heated at reflux until HPLC analysis indicated complete consumption of 14b (after 5 h). The mixture was concentrated under vacuum and distilled at reduced pressure (90 °C at 1.0 mmHg) to remove excess BQ. The dark residue was dissolved in chloroform and
diluted with an equal volume of toluene to give a red crystalline precipitate of 3,5-bis(p-methoxyphenyl)benzo[1,2-\textit{d};5,4-\textit{d}']diisothiazole-4,8-dione (25b) (1%). M.p. 269-271 °C; IR (Nujol): ν\textsubscript{max} 1670 cm\textsuperscript{-1} (C=O); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δH 7.86 (4H, d, J 9 Hz, half of AB system, ArH), 6.94 (4H, d, J 9 Hz, half of AB system, ArH), 3.89 (6H, s, OCH\textsubscript{3}); MS (El): m/z (%) 434 (M\textsuperscript{+}, 100%), 419 (4), 403 (7), 217 (13), 174 (8). Calcd. for C\textsubscript{22}H\textsubscript{14}N\textsubscript{2}O\textsubscript{4}S: 434.03951. Found: 434.03871. The remaining reaction mixture was further chromatographed on alumina; elution with toluene gave 3,7-bis(p-methoxyphenyl)benzo[1,2-\textit{d};4,5-\textit{d}']diisothiazole-4,8-dione (24b) (36%). M.p. 214–215 °C (from EtOH); IR (Nujol): ν\textsubscript{max} 1675 cm\textsuperscript{-1} (C=O); \textsuperscript{1}H NMR (199 MHz, CDCl\textsubscript{3}): δH 7.69 (4H, d, J 9 Hz, half of AB system, ArH), 6.92 (4H, d, J 9 Hz, half of AB system, ArH), 3.81 (6H, s, OCH\textsubscript{3}); \textsuperscript{13}C NMR (20 MHz, CDCl\textsubscript{3}): δC 173.7 (C=O), 169.5, 165.7, 133.6 (isothiazole ring C), 161.0, 126.1 (anisyl ring C), 131.0, 113.4 (anisyl ring CH), 55.2 (OCH\textsubscript{3}); MS (El): m/z (%) 434 (M\textsuperscript{+}, 100%), 419 (13), 403 (52), 217 (20), 174 (12), 135 (10); Calcd. for C\textsubscript{22}H\textsubscript{14}N\textsubscript{2}O\textsubscript{4}S: C, 60.8; H, 3.2; N, 6.4. Found: C, 60.6; H, 3.4 N, 6.1. The yields of 24b (33%) and p-methoxybenzonitrile (50%) were determined by HPLC analysis using benzonitrile as internal standard.

3,7-Dimethylbenzo[1,2-\textit{d};4,5-\textit{d}']diisothiazole-4,8-dione (24c). The reaction was carried out as described above for 24b using 5-methyl-1,3,4-oxathiazol-2-one (14c) and BQ (reaction time 4.5 h). Chromatography (alumina, toluene) of the concentrated reaction mixture yielded a purple solid which was treated with decolorising charcoal and recrystallised from cold EtOH to afford 3,7-dimethylbenzo[1,2-\textit{d};4,5-\textit{d}']diisothiazole-4,8-dione (24c) (13%) as pale yellow needles (from EtOH), mp. 221-222 °C. IR (Nujol) ν\textsubscript{max}: 1660 cm\textsuperscript{-1} (C=O); \textsuperscript{1}H NMR (100 MHz, CDCl\textsubscript{3}): δH 2.82 (6H, s, CH\textsubscript{3}); \textsuperscript{13}C NMR (20 MHz, CDCl\textsubscript{3}): δC 178.2 (C=O), 168.4, 167.7, 133.4 (isothiazole ring C), 19.4 (CH\textsubscript{3}); MS (El) m/z (%): 254 (M\textsuperscript{+}, 100%), 222 (23), 209 (13), 181 (38), 125 (8), 112 (112), 84 (39). Anal. Calcd. for C\textsubscript{10}H\textsubscript{6}N\textsubscript{2}O\textsubscript{4}S: C, 48.0; H, 2.4; N, 11.2. Found: C, 48.2; H, 2.4 N, 11.2. The yield of 24c (19%) was also determined by HPLC analysis using benzonitrile as internal standard.

Dimethyl 3-phenylisothiazole-4,5-dicarboxylate (34). A solution of 5-phenyl-1,3,4-oxathiazol-2-one (14a) (2.71 g, 15.1 mmol) and DMAD (3.7 mL, 30.2 mmol) in dry xylene (50 mL) was heated at reflux for 17 h. The excess DMAD and the solvent were removed under reduced pressure and the residual oil triturated with EtOH. The resulting solid was treated with activated charcoal in refluxing CH\textsubscript{2}Cl\textsubscript{2} for 1 h Filtration and evaporation of the solvent afforded the product as a colourless crystals. M.p. 72-74 °C (from EtOH) (lit.\textsuperscript{16} 72-73 °C).

4,5-Bis(hydroxymethyl)-3-phenylisothiazole (35) To a stirred solution of dimethyl 3-phenylisothiazole-4,5-dicarboxylate (34) (100 mg, 0.36 mmol) in THF (15 mL) was added sodium borohydride (140 mg, 3.7 mmol) in EtOH (3 mL). After stirring for 17 h at room temperature the mixture was added to water (50 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 10 mL). The extracts were dried (MgSO\textsubscript{4}), filtered, and the solvent removed under reduced pressure to afford the product (75%) as colourless needles (from CHCl\textsubscript{3}). M.p. 114 °C (lit.\textsuperscript{51} 111-113 °C); IR (Nujol) ν\textsubscript{max}: 3534 cm\textsuperscript{-1} (OH); \textsuperscript{1}H NMR (200 MHz, CD\textsubscript{3}COCD\textsubscript{3}): δH 7.84–7.79 (2H, m, PhH), 7.51–7.43 (3H, m, PhH), 4.64–4.62 (4H, m, CH\textsubscript{2}), 3.03–2.99 (2H,
m, OH); $^{13}$C NMR (50 MHz, CD$_3$COCD$_3$): $\delta$: 169.6, 167.4, 135.2 (isothiazole ring C), 132.6 (PhC), 130.6, 127.7, 127.4 (PhCH), 56.9, 54.4 (CH$_2$); MS (FAB) m/z (%): 222 (MH$^+$).

4,5-Bis(bromomethyl)-3-phenylisothiazole (37). A solution of phosphorus tribromide (0.69 mL, 7.2 mmol) in dry CH$_2$Cl$_2$ (5 mL) was added dropwise with stirring to an ice-cold solution of 4,5-bis(hydroxymethyl)-3-phenylisothiazole (35) (800 mg, 3.6 mmol) and dry pyridine (0.16 mL) in CH$_2$Cl$_2$ (10 mL). The mixture was stirred for 16 h and then poured onto water and extracted with CH$_2$Cl$_2$. The extracts were dried (MgSO$_4$), filtered, and the solvent removed under reduced pressure to afford a brown oil. Chromatography (silica, 4:1 hexane-EtOAc) afforded the product (55%) as a colourless crystalline solid, mp. 114 °C; $^1$H NMR (200 MHz, CD$_3$COCD$_3$): $\delta$: 7.89–7.75 (2H, m, PhH), 7.61–7.53 (3H, m, PhH), 4.47–4.26 (4H, m, CH$_2$); $^{13}$C NMR (50 MHz, CD$_3$COCD$_3$): $\delta$: 167.2, 163.5, 136.3 (isothiazole ring C), 132.6 (PhC), 131.1, 129.0, 127.0 (PhCH), 56.2, 57.4 (CH$_2$); MS (FAB) m/z (%): 350, 348, 346 (MH$^+$).

Generation of 4,5-dihydro-4,5-dimethylene-3-phenylisothiazole (32) and its reactions with dienophiles: General procedure

Sodium iodide (4.0 mmol) was added to a stirred solution of 4,5-bis(bromomethyl)-3-phenylisothiazole (37) (2.0 mmol) and the dienophile (2.0 mmol) in DMF (20 mL). After heating the mixture for at 90 °C for 2 h, the solvent was removed under reduced pressure. The resulting brown oil was dissolved in CH$_2$Cl$_2$, washed with aq. sodium metabisulfite and then with water. The organic phase was dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. The products were purified by chromatography (silica; 9:1 hexane-EtOAc).

Dimethyl 3-phenyl-1,2-benzisothiazole-5,6-dicarboxylate (30). 48%; m.p. 165 °C; IR (Nujol) $\nu$ max: 1722 cm$^{-1}$ (C=O); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$: 8.48 (1H, s, 7-H), 8248 (1H, s, 4-H), 7.78–7.75 (2H, m, ArH), 7.50–7.48 (3H, m, ArH), 3.90 (3H, s, CH$_3$), 3.86 (3H, s, CH$_3$); $^{13}$C NMR (60 MHz, CDCl$_3$): $\delta$: 167.8, 167.3 (C=O), 164.9 (C=N), 155.5 (C=7a), 134.5, 134.2, 131.1, 128.6 (PhC, C=3a, C=5, C=6), 129.9, 129.1, 128.7 (PhCH), 126.4 (C=7), 121.0 (C=4), 53.1, 53.0 (CH$_3$); MS (EI) m/z (%): 327 (M$^+$); HRMS (EI): Calcd. for C$_{17}$H$_{13}$NO$_4$S; [M] 327.0560. Found: m/z 327.0561.

Diethyl (E)-4,5,6,7-tetrahydro-3-phenyl-1,2-benzisothiazole-5,6-dicarboxylate (38) 25%; yellow oil; IR (film) $\nu$ max: 1720 cm$^{-1}$ (C=O); $^1$H NMR (200 MHz, CDCl$_3$): $\delta$: 7.70–7.61 (2H, m, PhH), 7.50–7.40 (3H, m, PhH), 4.24–4.12 (4H, 2 × q, OCH$_2$), 3.45–2.93 (6H, m, 4-H, 5-H, 6-H, 7-H), 1.30–1.21 (6H, 2 × t, CH$_3$); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$: 173.7, 173.2 (C=O), 166.1 (C=N), 157.7 (C=7a), 135.1 (C=3a), 133.7 (PhC), 129.0, 128.7, 127.8 (PhCH), 61.1, 61.0 (OCH$_2$), 42.0, 41.5 (CH), 27.5, 26.1 (CH), 14.1, 14.0 (CH$_3$); HRMS (EI): Calcd. for C$_{19}$H$_{21}$NO$_4$S; [M] 359.1191. Found: m/z: 359.1204.

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