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Microwave-induced generation and reactions of nitrile sulfides: an improved method for the synthesis of isothiazoles and 1,2,4-thiadiazoles

Euan A.F. Fordyce [a], Angus J. Morrison [b], Robert D. Sharp [a], R. Michael Paton [a,*]

[a] School of Chemistry, The University of Edinburgh, The King's Buildings, Edinburgh EH9 3JJ, UK
[b] MSD, Medicinal Chemistry Department, Newhouse, Lanarkshire ML1 5SH, UK

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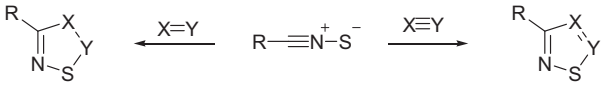
ABSTRACT

The 1,3-dipolar cycloaddition reactions of nitrile sulfides, generated by microwave-assisted decarboxylation of 1,3,4-oxathiazol-2-ones, have been investigated. By this approach ethyl 1,2,4-thiadiazole-5-carboxylates **3** were prepared in good yield by cycloaddition of the nitrile sulfides to ethyl cyanoformate. Similarly, reaction of benzonitrile sulfide with dimethyl acetylenedicarboxylate (DMAD) afforded dimethyl 3-phenylisothiazole-4,5-dicarboxylate (**5**). In contrast, *o*-hydroxybenzonitrile sulfide, generated from the corresponding oxathiazolone **2d**, reacted with DMAD to give methyl 4-oxo-4*H*-[1]benzopyrano[4,3-*c*]isothiazole-3-carboxylate (**8**) in high yield. A ca. 1:1 mixture of ethyl 3-phenylisothiazole-4- and 5-carboxylates (**6**,**7**) was formed from benzonitrile sulfide and ethyl propiolate. The corresponding reaction with diethyl fumarate gave diethyl *trans*-4,5-dihydro-3-phenylisothiazole-4,5-dicarboylate (**10**). 3-Arylisothiazoles, unsubstituted at both the 4- and 5-positions, were prepared from the reaction of 5-aryl-1,3,4-oxathiazolones with norbornadiene by a pathway involving cycloaddition of the nitrile sulfide to the norbornadiene, followed by retro-Diels–Alder extrusion of cyclopentadiene from the resulting isothiazoline cycloadduct **12**. In summary, the use of microwave irradiation, rather than conventional heating methods, allows nitrile sulfide generation and reactions to be carried out in shorter times, with easier work-up and, in some cases, in higher yields.

1. Introduction

The 1,3-dipolar cycloaddition reactions of nitrile ylides, nitrile imides and nitrile oxides (R–C≡N$^+$–X$^-$; X=CR$_2$, NR, O) are widely used for the preparation of five-membered heterocycles incorporating the C=N–X unit.[1] In contrast, less attention has been paid to the corresponding reactions of nitrile sulfides (R–C≡N$^+$–S$^-$).[2] Nitrile sulfides are uniquely well suited for the synthesis of the analogous C=N–S heterocycles via their cycloaddition reactions with double- and triple-bonded dipolarophiles (Scheme 1), and by this means various isothiazoles,[2,3] 2-isothiazolines,[2,4] 1,2,4-thiadiazoles,[2,3e,f,4a,5] 1,3,4-oxathiazoles,[2,6] 1,2,4-thiazaphospholes[7] and 1,4,2-dithiazoles[8] have been prepared. More general application of this chemistry is, however, limited both by the tendency of nitrile sulfides to decompose to the corresponding nitriles and the forcing conditions often required to generate these short-lived intermediates. One potential solution to this problem is the use of microwave technology.[9]



Scheme 1.

In recent years there has been rapid growth in the use of microwave irradiation to facilitate organic reactions.[9] Among the advantages of this method, compared with conventional heating, are reduced reaction times and the potential for improved product yields. A wide range of reactions have been shown to benefit from this technique. These include 1,3-dipolar cycloadditions[10] involving nitrile imides (R–C≡N$^+$–NR$^-$)[11] and nitrile oxides (R–C≡N$^+$–O$^-$).[11b,12] We now report on the application of microwave irradiation for the generation of nitrile sulfides.[13]

2. Results and discussion

The most efficient and commonly used method of generating nitrile sulfides (**1**) involves the thermal decarboxylation of 1,3,4-oxathiazol-2-ones (**2**),[2] which are usually prepared from the corresponding carboxamide by treatment with chlorocarbonylsulfenyl chloride, and this was the approach adopted for the current work (Scheme 2). To test the effectiveness of the microwave technique to promote the generation and reactions of nitrile sulfides we selected

* Corresponding author. Fax: +44 131 650 4743; e-mail address: r.m.paton@ed.ac.uk (R.M. Paton).

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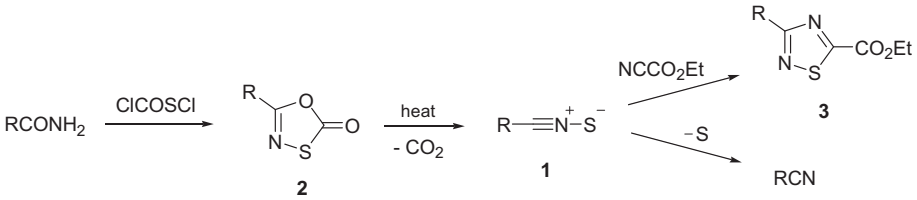


Scheme 2. [**1**–**3**: **a** R=Ph; **b** R=*p*-ClC_6H_4; **c** R=*m*-ClC_6H_4; **d** R=*o*-HOC_6H_4; **e** R=2-thienyl; **f** R=Me; **g** R=$ClCH_2$; **h** R=Cl_2CH; **i** R=EtO_2C].

for initial study the known reaction of benzonitrile sulfide (**1a**) and ethyl cyanoformate (ECF), which is a reactive dipolarophile towards nitrile sulfides.[14] An authentic sample of the cycloadduct (ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate, **3a**) was prepared by the conventional thermolysis method,[14] involving heating a solution of the oxathiazolone **1a** with excess ECF (~1:10 reactant ratio) in *p*-xylene at reflux for 18 h. Work-up of the reaction mixture afforded compound **3a** in 62% yield. The experiment was then repeated with the same solvent and reactant ratio, but using microwave irradiation (200 W, 10 min, 160 °C) (Table 1, entry 1). The crude product obtained after removal of the solvent and excess ECF was examined by ^{13}C NMR spectroscopy, which showed that the cycloadduct **3a** had been formed in near quantitative yield. The spectrum was indistinguishable from that of the authentic sample, with characteristic heterocyclic ring peaks at 178.8 (C-5) and 174.4 ppm (C-3), in addition to those of the phenyl and ethoxycarbonyl substituents. Neither the starting material **2a** nor benzonitrile, the expected by-product resulting from the competing desulfuration of the nitrile sulfide, could be detected. A pure sample of **2a** was isolated from the crude product in 83% yield by trituration with toluene and recrystallisation of the resulting solid from hexane. Similarly high yields were obtained at lower temperature (140 °C) and for a smaller excess of dipolarophile (1:3) (Table 1, entries 2 and 3). One of the advantages of the microwave technique is the ability to use low-boiling solvents, thus allowing easier work-up, and good yields of product were obtained for reactions carried out in THF (72%), chloroform (76%), ethyl acetate (94%) and 1,2-dichloroethane (96%) (Table 1, entries 4–7).

The *p*-chloro-, *m*-chloro- and *o*-hydroxy-phenyl oxathiazolones **2b**–**d** reacted similarly in ethyl acetate, affording the corresponding thiadiazoles **3b**–**d** in good yield (70–84%) (Table 1, entries 8–10). Likewise, the 2-thienyl thiadiazole **3e**, derived from thiophene-2-carbonitrile sulfide **1e**, was obtained from oxathiazolone **2e**. The methyl, chloromethyl and dichloromethyl oxathiazolones **2f**–**h** were also examined (Table 1, entries 12–14). All yielded the expected thiadiazoles **3f**–**h**, although the chloro-substituted precursors proved to be more stable and required higher temperatures and/or longer reaction times. In contrast, attempts to use ECF to trap ethoxycarbonylformonitrile sulfide (**1i**), generated from the oxathiazolone **2i**, were not successful.

Having established the advantages of the microwave method for nitrile sulfide cycloadditions to ECF, the corresponding reaction of benzonitrile sulfide with trichloroacetonitrile was examined. Using conventional heating this reaction is reported to afford 5-trichloromethyl-substitited 1,2,4-thiadiazoles in 45–65% yields, although reaction times are long (3–4 days).[15] Using microwave irradiation (300 W) a similar yield (61%) was achieved after 10 min in acetonitrile at 160 °C (Table 1, entry 17). As expected the nitrile

Table 1
Microwave irradiation of 1,3,4-oxathiazol-2-ones

Entry	Oxathiazolone	Dipolarophile[a]	Reactant ratio	Solvent	Power/W	Time/min.	Temp/°C	Product (Yield/%)
1	**2a**	ECF	1:10	*p*-xylene	200	10	160	**3a** (83)
2	**2a**	ECF	1:10	*p*-xylene	200	10	140	**3a** (89)
3	**2a**	ECF	1:3	*p*-xylene	200	10	160	**3a** (82)
4	**2a**	ECF	1:10	THF	200	10	160	**3a** (72)
5	**2a**	ECF	1:10	$CHCl_3$	200	10	160	**3a** (76)
6	**2a**	ECF	1:10	EtOAc	200	10	160	**3a** (94)
7	**2a**	ECF	1:10	DCE	300	10	160	**3a** (96)
8	**2b**	ECF	1:10	EtOAc	300	10	160	**3b** (70)
9	**2c**	ECF	1:10	EtOAc	300	20	160	**3c** (80)
10	**2d**	ECF	1:10	EtOAc	300	10	160	**3d** (84)
11	**2e**	ECF	1:10	EtOAc	300	10	160	**3e** (85)
12	**2f**	ECF	1:10	DCE	300	10	160	**3f** (78)
13	**2g**	ECF	1:10	PhMe	300	10	190	**3g** (90)
14	**2h**	ECF	1:10	PhMe	300	30	200	**3h** (42)
15	**2i**	ECF	1:10	EtOAc	300	10	160	**3i** (0)
16	**2i**	ECF	1:10	PhMe	300	10	200	**3i** (0)
17	**2a**	Cl_3CCN	1:10	MeCN	300	10	160	**4** (61)
18	**2a**	DMAD	1:3	$CHCl_3$	200	10	160	**5** (56)
19	**2a**	EP	1:10	$CHCl_3$	200	10	160	**6,7** (48)
20	**2d**	DMAD	1:2	EtOAc	300	10	160	**8** (94)
21	**2a**	DEF	1:10	EtOAc	200	10	160	**10** ([b])
22	**2a**	NB	1:10	EtOAc	300	10	160	**11a** (47)
23	**2f**	NB	1:10	EtOAc	300	10	160	**11f** (16)
24	**2a**	NBD	1:10	EtOAc	300	30	170	**13a** (68)[c]
25	**2b**	NBD	1:10	EtOAc	200	30	170	**13b** (97)
26	**2d**	NBD	1:10	EtOAc	300	30	170	**13d** (32)[c]
27	**2e**	NBD	1:10	EtOAc	300	30	170	**13e** (68)[c]

[a] ECF=ethyl cyanoformate; DCE=1,2-dichloroethane; DMAD=dimethyl acetylenedicarboxylate; EP=ethyl propiolate; DEF=diethyl fumarate; NB=norbornene; NBD=norbornadiene.
[b] Not determined, isolated together with traces of DEF-derived side-products.
[c] Isolated together with traces of NBD-derived side-products.

sulfide reacts with the more reactive cyano group of trichloroacetonitrile rather than that of the acetonitrile solvent.[15] In summary, the cycloaddition reactions of nitrile sulfides with nitriles are uniquely well suited for the preparation of unsymmetrically substituted 1,2,4-thiadiazoles and the use of microwave irradiation provides a rapid means of preparing these compounds.

The cycloaddition reactions of nitrile sulfides are also well suited for the preparation of isothiazoles via their reactions with alkynes, provided that the dipolarophile is activated by electron-withdrawing groups. For example, dimethyl acetylenedicarboxylate (DMAD) was the first dipolarophile used to trap benzonitrile sulfide.[16] Microwave irradiation (Table 1, entry 18) of a solution of phenyloxathiazolone **2a** and DMAD (1:3) in chloroform afforded the isothiazole cycloadduct **5** (56%), which was identified by comparison of its spectroscopic properties with those previously reported.[17,18] In the ^{13}C NMR spectrum there are characteristic peaks for the isothiazole ring at 133.6 ppm (C-4), 155.4 (C-5) and 159.1 (C-3), and at 165.7, 164.8 (C=O) and 53.1, 53.0 (OMe) for the methoxycarbonyl substituents. In this case the use of microwave irradiation, rather than conventional heating, avoids the long reaction times which can sometimes lead to contamination of the product by DMAD-derived by-products. The corresponding reaction of **2a** with ethyl propiolate (1:10) afforded a mixture of regioisomeric isothiazoles **6** and **7** in 48% combined yield. The isomer ratio (**6**:**7**=13:14) was measured by comparison of the characteristic signals in the ^{1}H NMR spectrum for H-4 (8.04 ppm) of isomer **7** and H-5 (9.26 ppm) of isomer **6**. Similar low levels of regioselectivity with alkyl propiolates have been reported previously for various nitrile sulfides,[3e,17–19b] and are in marked contrast to the corresponding reactions with nitrile oxides, which afford predominantly the isoxazole-5-carboxylates.[20] This effect has been attributed to a greater degree of HOMO-dipole control for the nitrile sulfide reactions.[17,18]

by chromatography afforded only compound **8**, for which the OMe peak is at 4.00 ppm. The peaks at 3.94 and 3.90 ppm were therefore attributed to the intermediate isothiazole **9**. Such values are typical of dimethyl isothiazole-4,5-dicarboxylates.[17] The signals for the protons of the arene ring of compound **9** were also very similar to those of the corresponding 1,2,4-thiadiazole (**3d**), vide supra.

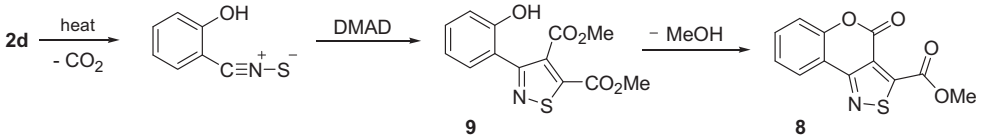
Electron-poor alkenes are also reported to undergo cycloaddition to nitrile sulfides affording 2-isothiazolines (4,5-dihydroisothiazoles).[2,4] Thus irradiation of phenyloxathiazolone **2a** with diethyl fumarate (1:10) in ethyl acetate yielded diethyl *trans*-2-isothiazoline-4,5-dicarboxylate (**10**) (Table 1, entry 21). The trans configuration of the product was deduced from the ^{1}H NMR spectrum in which there was a ^3J coupling of 3.4 Hz for H-4/H-5. Whereas most simple alkenes are unreactive towards nitrile sulfides, cycloadducts are formed with norbornene-type dipolarophiles, although reaction times are long and yields low;[14,22] for example, benzonitrile sulfide and norbornene are reported to afford isothiazoline **11a** in 19% yield.[22] The use of microwave irradiation instead of conventional heating lead to an improved yield (47%) after 10 min at 160 °C (Table 1, entry 22). Acetonitrile sulfide, generated from methyl oxathiazolone **2f**, reacted similarly to yield isothiazoline **11f**.

The corresponding reaction of aryl nitrile sulfides with norbornadiene (NBD) has been shown to lead directly to 3-arylisothiazoles,[22] a process which is believed to involve initial cycloaddition of the nitrile sulfide to one of the alkene units in NBD to form the isothiazoline **12** (presumably as a mixture of *exo* and *endo* isomers), which under the reaction conditions (~100 h, ~130 °C) undergoes a Diels–Alder cycloreversion to form the isothiazole **13** with expulsion of cyclopentadiene, as shown in Scheme 4. With microwave irradiation the reactions were complete in 30–60 min at 170 °C (Table 1, entries 24–27). For the 3-(*p*-chlorophenyl)isothiazole **13b** the yield was near quantitative (98%). The products were readily identified from their characteristic NMR spectra. In addition to the expected ^{13}C peaks for C-3 (161–168), CH-4 (120–121) and CH-5

4 **5** $R^1 = R^2 = CO_2Me$; **6** $R^1 = CO_2Et$, $R^2 = H$; **7** $R^1 = H$; $R^2 = CO_2Et$ **10** **11a** R = Ph; **11f** R = Me

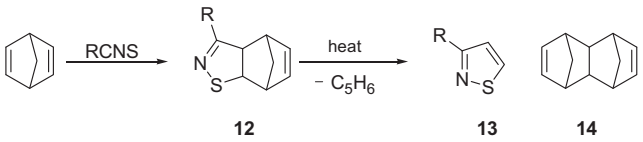
Under similar conditions the reaction of the *o*-hydroxyphenyloxathiazolone **2d** with DMAD (1:2) in ethyl acetate afforded the known[21] benzopyrano[4,3-*c*]isothiazole **8** in excellent yield (94%) (Scheme 3). The isolation of compound **8**, rather than the usual isothiazoledicarboxylate **9**, can be attributed to facile intramolecular elimination of methanol between the phenolic hydroxyl group and the methyl ester at the 4-position in the first-formed adduct **9**,[21] as illustrated in Scheme 3. Evidence in support of this pathway was provided from the NMR and mass spectra of the crude product before chromatography, which showed the presence of both **9** and **8** in a ca. 4:1 ratio. In the ^{1}H NMR spectrum of the mixture there were three OMe signals at 4.00, 3.94 and 3.90 ppm with relative intensities 1:4:4. Attempts to separate these products

(147–149 ppm),[13] there were characteristic ^{1}H signals for H-4 (7.4–7.6) and H-5 (8.6 ppm) with a mutual coupling of 4.7 Hz. The isothiazolines **12** were not isolated and could not be detected spectroscopically. A common by-product was observed for all of the NBD reactions; on the basis of its spectroscopic properties this was tentatively assigned as compound **14**[23] resulting from Diels–Alder cycloaddition of NBD, acting as the dienophile, with the cyclopentadiene generated on fragmentation of the isothiazoline **12**. This process, in which NBD is acting as an acetylene equivalent, thus offers a short and efficient route to isothiazoles unsubstituted at both 4- and 5-positions. A similar approach has previously been reported[24] for the corresponding reactions of NBD with nitrile oxides and nitrile imides, leading to isoxazoles and pyrazoles, respectively.



9 **8**

Scheme 3.



12 13 14

Scheme 4. [**12**–**13**: **a** R=Ph; **b** R=*p*-ClC_6H_4; **d** R=*o*-HOC_6H_4; **e** R=2-thienyl].

In conclusion, these results show that the use of microwave irradiation, rather than conventional heating methods, allows nitrile sulfide generation and reactions to be carried out in shorter times, with easier work-up and, in some cases, in higher yields.

3. Experimental

3.1. General

Melting points were measured on a Gallenkamp capillary apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded with Brucker WP200SY, AX250 or WH360 spectrometers on solutions in $CDCl_3$ with Me_4Si as an internal standard. Positive-ion FAB and high resolution mass spectra were obtained on a Kratos MS50TC instrument using either glycerol or thioglycerol matrices. Merck aluminium-backed plates coated with Kieselgel GF_{254} (0.2 mm) were used for analytical TLC, with detection by UV or sulfuric acid charring. Preparative chromatography was carried out, either using Kieselgel GF_{254} and eluting under water pump vacuum, or with Isolute or Strata pre-packed silica columns. Solvents and reagents were standard laboratory grade and used as supplied, unless otherwise stated. THF was dried over calcium hydride and distilled before use.

Microwave irradiation experiments were conducted in a CEM Discoverer microwave with ramp times of between 5 and 15 min, and with 20 min cooling. The reaction mixture was contained in a sealed tube in the microwave oven and irradiated at the power specified in Table 1, which also gives the solvent, reactant ratio and the reaction time. The products were purified by crystallisation and/or dry-flash chromatography, and identified from their NMR and mass spectra and by comparison with those previously reported.

3.2. 1,3,4-Oxathiazol-2-ones

The following oxathiazolones were prepared from the corresponding carboxamides by treatment with chlorocarbonylsulfenyl chloride as previously reported. 5-Phenyl-1,3,4-oxathiazol-2-one (**2a**),[17] 5-(4-chlorophenyl)-1,3,4-oxathiazol-2-one (**2b**),[17] 5-(3-chlorophenyl)-1,3,4-oxathiazol-2-one (**2c**),[17] 5-(2-hydroxyphenyl)-1,3,4-oxathiazol-2-one (**2d**),[21] 5-(2-thienyl)-1,3,4-oxathiazol-2-one (**2e**).[4a] 5-methyl-1,3,4-oxathiazol-2-one (**2f**),[17] 5-chloromethyl-1,3,4-oxathiazol-2-one (**2g**),[17] 5-dichloromethyl-1,3,4-oxathiazol-2-one (**2h**), 5-ethoxycarbonyl-1,3,4-oxathiazol-2-one (**2i**).[17]

3.3. 1,2,4-Thiadiazoles

*3.3.1. Ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate (**3a**)*[25]*. Conventional thermolysis*. A solution of oxathiazolone **2a** (193 mg, 1.08 mmol) and ethyl cyanoformate (ECF) (1.0 mL, ~10.1 mmol) in *p*-xylene (6 mL) was heated at reflux for 16 h. After removal of the excess ECF and the solvent under reduced pressure the residue was recrystallised from hexane to afford the compound **3a** as white crystals (156 mg, 62%); mp 67 °C (lit.[25] 70–71 °C); δ_H (200 MHz, $CDCl_3$) 1.41 ppm (3H, t, *J* 7.1 Hz, CH_3), 4.46 (2H, q, *J* 7.1 Hz, CH_2), 7.35–7.45 (3H, m, PhH), 8.30 (2H, m, PhH); δ_C (50 MHz, $CDCl_3$) 14.0 (CH_3), 63.1 (CH_2), 128.3, 128.6, 130.7 (PhCH), 131.8 (PhC), 158.3 (C=O), 174.4 (C-3), 178.8 (C-5); *m*/*z* (FAB) found: M^++1, 235.0547. $C_{11}H_{10}NO_2S$ requires 235.0544.

Microwave irradiation. A solution of oxathiazolone **2a** (100 mg, 0.56 mmol) and ethyl cyanoformate (ECF) (0.5 mL, ~5.0 mmol) in *p*-xylene (3 mL) was heated in the microwave at 160 °C and with a 200 W power input for 10 min. After cooling the excess ECF and the solvent were removed under reduced pressure and the residue examined by ^1H and ^{13}C NMR spectroscopy. The resulting spectra were indistinguishable from those of the authentic sample of compound **3a**, indicating that it had been formed in near quantitative yield.

*3.3.2. Ethyl 3-(4-chlorophenyl)-1,2,4-thiadiazole-5-carboxylate (**3b**)*[25]. Yield 69%; white needles (from hexane); mp 78–80 °C (lit.[25] 82–84 °C); δ_H (360 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.1 Hz, CH_3), 4.48 (2H, q, *J* 7.1 Hz, CH_2), 7.39 (2H, d, *J* 8.7 Hz, H-2′), 8.23 (2H, d, *J* 8.7 Hz, H-3′); δ_C (91 MHz, $CDCl_3$) 14.0 (CH_3), 63.3 (CH_2), 128.9, 129.7, 130.4, 137.0 (ArC), 158.3 (C=O), 173.5 (C-3), 179.1 (C-5).

*3.3.3. Ethyl 3-(3-chlorophenyl)-1,2,4-thiadiazole-5-carboxylate (**3c**)*. Yield 80%; yellow needles; mp 86–88 °C; δ_H (360 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.1 Hz, CH_3), 4.47 (2H, q, *J* 7.1 Hz, CH_2), 7.36 (2H, m, H-5′, H-6′), 8.16 (1H, d, *J* 7.3 Hz, H-4′), 8.28 (1H, s, H-2′); δ_C (91 MHz, $CDCl_3$) 14.0 (CH_3), 63.3 (CH_2), 126.4, 128.3, 129.9, 130.8, 133.3, 134.7 (ArC), 158.2 (C=O), 173.1 (C-3), 179.1 (C-5); *m*/*z* (EI) found: M^+ 268.0074. $C_{11}H_9N_2{}^{35}ClO_2S$ requires 268.0073.

*3.3.4. Ethyl 3-(2-hydroxyphenyl)-1,2,4-thiadiazole-5-carboxylate (**3d**)*[21]. Yield 84%; pale yellow solid; mp 93–95 °C (lit.[21] 93–95 °C); δ_H (360 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.1 Hz, CH_3), 4.48 (2H, q, *J* 7.1 Hz, CH_2), 6.92 (1H, m, H-4′), 7.00 (1H, dd, *J* 8.0, 1.1 Hz, H-6′), 7.33 (1H, m, H-5′), 8.27 (1H, dd, *J* 7.9, 1.7 Hz, H-3′), 10.51 (1H, s, OH); δ_C (91 MHz, $CDCl_3$) 14.0 (CH_3), 63.5 (CH_2), 115.9, 117.6, 119.7, 129.7, 133.0 (ArC), 157.6 (COH), 157.8 (C=O), 173.8 (C-3), 177.8 (C-5).

*3.3.5. Ethyl 3-(2-thienyl)-1,2,4-thiadiazole-5-carboxylate (**3e**)*. Yield 85%; pale yellow solid; mp 72–74 °C; δ_H (360 MHz, $CDCl_3$) 1.39 (3H, t, *J* 7.1 Hz, CH_3), 4.47 (2H, q, *J* 7.1 Hz, CH_2), 7.07 (1H, t, *J* 5.0, 3.7 Hz, H-3′), 7.41 (1H, dd, *J* 5.0, 1.2 Hz, H-2′), 7.90 (1H, dd, *J* 3.7, 1.2 Hz, H-4′); δ_C (91 MHz, $CDCl_3$) 14.0 (CH_3), 63.3 (CH_2), 127.9, 129.4, 129.8, 135.3 (*C*-thiophene), 158.1 (C=O), 169.7 (C-3), 178.8 (C-5); *m*/*z* (EI) found: M^+ 240.0027. $C_9H_8N_2O_2S$ requires 240.0027.

*3.3.6. Ethyl 3-methyl-1,2,4-thiadiazole-5-carboxylate (**3f**)*[19]. Yield 78%; pale yellow oil; δ_H (250 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, CH_3), 2.70 (3H, s, CH_3), 4.45 (2H, q, *J* 7.1 Hz, CH_2); δ_C (63 MHz, $CDCl_3$) 13.9 (CH_3), 18.8 (CH_3), 63.0 (CH_2), 158.2 (C=O), 174.8 (C-3), 178.5 (C-5).

*3.3.7. Ethyl 3-chloromethyl-1,2,4-thiadiazole-5-carboxylate (**3g**)*. Yield 90%; pale yellow oil; δ_H (360 MHz, $CDCl_3$) 1.39 (3H, t, *J* 7.1 Hz, CH_3), 4.47 (2H, q, *J* 7.1 Hz, CH_2), 4.81 (2H, s, CH_2Cl); δ_C (91 MHz, $CDCl_3$) 13.9 (CH_3), 39.7 (CH_2Cl), 63.4 (CH_2), 157.8 (C=O), 172.6 (C-3), 179.9 (C-5).

*3.3.8. Ethyl 3-dichloromethyl-1,2,4-thiadiazole-5-carboxylate (**3h**)*. Yield 42%; yellow oil; δ_H (250 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.1 Hz, CH_3), 4.48 (2H, q, *J* 7.1 Hz, CH_2), 6.91 (1H, s, $CHCl_2$); δ_C (63 MHz, $CDCl_3$) 14.0 (CH_3), 63.7, 63.9 (CH_2O, $CHCl_2$), 157.6 (C=O), 172.3 (C-3), 180.9 (C-5).

*3.3.9. 3-Phenyl-5-trichloromethyl-1,2,4-thiadiazole (**4**)*[15]. Yield 61%; pale yellow solid; mp 70–72 °C (lit.[15] 74–75 °C); δ_H (250 MHz, $CDCl_3$) 7.37–7.62 ppm (3H, m, PhH), 8.25 (2H, m, PhH); δ_C (63 MHz, $CDCl_3$) 88.1 (CCl_3), 131.8 (PhC), 128.3, 128.7, 130.9 (PhCH), 174.0 (C-3), 190.6 (C-5); *m*/*z* (FAB) found: M^++1, 280.9282. $C_9H_6N_2{}^{37}Cl^{35}Cl_2S$ requires 1 280.9309; found: M^++1, 278.9374. $C_9H_6N_2{}^{35}Cl_3S$ requires 278.9317.

3.4. Isothiazoles

*3.4.1. Dimethyl 3-phenylisothiazole-4,5-dicarboxylate (**5**)*[17]. Yield 56%; white solid (from hexane); mp 69–71 °C (lit.[17] 72–73 °C); δ_H

(250 MHz, $CDCl_3$) 4.01 (3H, s, CH_3), 4.05 (3H, s, CH_3), 7.30–7.48 (3H, m, PhH) 7.62 (2H, m, PhH); δ_C (63 MHz, $CDCl_3$) 53.1, 53.0 (CH_3), 127.5, 128.6, 129.7 (PhCH), 132.7, 133.6, 155.4, 159.1 (PhC, C-3, C-4, C-5), 164.8, 165.7 (C=O); *m*/*z* (FAB) found: M^++1, 278.0486. $C_{13}H_{11}NO_4S$ requires 278.0487.

*3.4.2. Ethyl 3-phenylisothiazole-4- and 5-carboxylates (**6**,**7**)*[17]. Yield 48% combined yield; pale yellow solid (from hexane); mp 66–67 °C (lit.[17] 63–65 °C); δ_H (250 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz, CH_3 of **6**), 1.33 (3H, t, *J* 7.1 Hz, CH_3 of **7**), 4.16 (2H, q, *J* 7.1 Hz, CH_2 of **6**), 4.35 (2H, q, *J* 7.1 Hz, CH_2 of **7**), 9.26 (1H, s, H-5 of **6**) 8.04 (1H, s, H-4 of **7**), 7.22–7.40 (3H, m, PhH), 7.90 (2H, m, PhH); δ_C (63 MHz, $CDCl_3$) 13.2, 13.3 (CH_3), 29.0, 30.2 (CH_2), 124.1 (CH-4 of **7**), 126.7, 127.1, 128.2, 128.6, 128.9 (PhCH), 133.3, 134.3, 159.4, 161.4 (PhC, C-3, C-4 of **6**, C-5 of **7**), 155.1 (CH-5 of **6**), 159.4, 161.4 (C-4 of **6**, C-5 of **7**), 167.3, 167.9 (C=O); *m*/*z* (FAB) found: M^++1, 234.0579. $C_{12}H_{11}NO_2S$ requires 234.0589.

*3.4.3. 3-Phenylisothiazole (**13a**)*[22,26]. Yield 68%, yellow oil, together with norbornadiene derived side-products; δ_H (250 MHz, $CDCl_3$) 7.35 (3H, m, PhH), 7.53 (1H, d, *J* 4.7 Hz, H-4), 7.89 (2H, m, PhH), 8.60 (1H, d, *J* 4.7 Hz, H-5); δ_C (63 MHz, $CDCl_3$) 121.1 (CH-4), 126.8, 128.7, 129.0, 134.5 (PhC), 148.8 (CH-5), 167.5 (C-3).

*3.4.4. 3-(4-Chlorophenyl)isothiazole (**13b**)*[22]. Yield 97%; pale yellow solid; δ_H (360 MHz, $CDCl_3$) 7.34 (2H, d, *J* 8.8 Hz, H-2′), 7.49 (1H, d, *J* 4.7 Hz, H-4), 7.81 (2H, d, *J* 8.8 Hz, H-3′), 8.62 (1H, d, *J* 4.7 Hz, H-5); δ_C (91 MHz, $CDCl_3$) 120.9 (CH-4), 128.0, 128.8, 133.2, 134.9 (ArC), 149.2 (CH-5), 166.2 (C-3); *m*/*z* (EI) found: M^+ 194.9911. C_9H_6NClS requires 194.9910.

*3.4.5. 3-(2-Hydroxyphenyl)isothiazole (**13d**).* Yield 32%, yellow oil, together with norbornadiene derived side-products; δ_H (250 MHz, $CDCl_3$) 6.88 (1H, m, H-4′), 7.01 (1H, m, H-6′), 7.23 (1H, m, H-5′), 7.64 (2H, m, H-3′+H-4), 8.63 (1H, d, *J* 4.9 Hz, H-5), 11.75 (1H, br s, OH); δ_C (63 MHz, $CDCl_3$) 117.7, 119.1 (ArC), 120.5 (CH-4), 127.5, 131.1 (ArC), 147.3 (CH-5), 157.5 (COH), 168.2 (C-3).

*3.4.6. 3-(2-Thienyl)isothiazole (**13e**).* Yield 68%, yellow oil, together with norbornadiene derived side-products; δ_H (250 MHz, $CDCl_3$) 7.01 (1H, m, H-2′), 7.28 (1H, m, H-1′), 7.40 (2H, m, H-4+H-3′), 8.54 (1H, d, *J* 4.7 Hz, H-5); δ_C (91 MHz, $CDCl_3$) 120.6 (C-4), 125.6, 126.9, 127.5, 138.6 (*C*-thiophene), 148.8 (C-5), 161.9 (C-3); *m*/*z* (EI) M^+ found 166.9864. $C_7H_5NS_2$ requires M^+ 166.9863. In the ^1H NMR spectrum additional signals at 0.9–1.4, 2.4–2.7 and 6.0–6.2 ppm were attributed to the aliphatic and olefinic protons of compound **14**.[23b]

*3.4.7. Methyl 4-oxo-4H-[1]benzopyrano[4,3,-c]isothiazole-3-carboxylate (**8**)*[21]. Yield 96%; white crystals (from EtOAc); mp 160–163 °C (lit.[21] 158–160 °C); δ_H (360 MHz, $CDCl_3$) 4.00 (3H, s, CH_3), 7.26–7.30 (2H, m, H-7, H-9), 7.50 (1H, m, H-8), 8.17 (1H, dd, *J* 6.7, 1.7 Hz, H-6); δ_C (91 MHz, $CDCl_3$) 53.8 (CH_3), 116.3 (C-9a), 117.1, 124.2, 124.9, 132.4 (C-6–C-9), 120.8 (C-3a), 152.4 (C-5a), 154.1 (C-4), 158.9 (C=O), 162.3 (C-9b), 163.4 (C-3); *m*/*z* (EI) found: M^+ 261.0094. $C_{12}H_7NO_4S$ requires 261.0096. The crude product also contained *dimethyl 3-(2-hydroxyphenyl) isothiazole-4,5-dicarboxylate* (**9**). δ_H (360 MHz, $CDCl_3$) 3.90 (3H, s, CH_3), 4.94 (3H, s, CH_3), 6.84 (1H, m, H-4′), 7.01 (1H, dd, *J* 8.3, 1.2 Hz, H-6′), 7.20–7.50 (1H, m, H-5′), 8.22 (1H, dd, *J* 8.7, 1.7 Hz, H-3′), 10.50 (1H, s, OH).

3.5. 4,5-Dihydroisothiazoles (2-isothiazolines)

*3.5.1. Diethyl trans-3-phenyl-2-isothiazoline-4,5-dicarboxylate (**10**)*[4b]. Clear oil, isolated as a mixture with unreacted diethyl fumarate; δ_H (250 MHz, $CDCl_3$) 1.07 (3H, t, *J* 7.0 Hz, CH_3), 1.24 (3H, t, *J* 7.0 Hz, CH_3), 4.73 (1H, d, *J* 4.1 Hz, H-4), (1H, d, *J* 4.1 Hz, H-5), 7.26–7.37 (3H, m, PhH), 7.7 (2H, m, PhH), the expected quartets for CH_2 were masked by diethyl fumarate peaks; *m*/*z* (FAB) found: M^++1, 308.0958. $C_{15}H_{17}NO_4S$ requires 308.0957.

*3.5.2. exo-3a,7a-4,5,6,7-Hexahydro-4,7-methano-3-phenyl-1,2-benzisothiazole (**11a**)*[22]. Yield 47%; pale yellow oil; δ_H (360 MHz, $CDCl_3$) 1.13–1.62 (6H, m, H-5, H-6, H-8), 2.34 (1H, m, H-4), 2.57 (1H, s, H-7), 3.72 (1H, d, *J* 9.6 Hz, H-3a), 3.87 (1H, dd, *J* 9.6, 1.8 Hz, H-7a) 7.29 (3H, m, Ph), 7.66 (2H, m, Ph); δ_C (91 MHz, $CDCl_3$) 27.2 (C-5), 28.5 (C-6), 33.2 (C-8), 42.2 (C-4), 44.8 (C-7), 56.7 (C-3a), 63.1 (C-7a), 127.3, 128.3, 129.2, 133.6 (PhC), 166.7 (C-3).

*3.5.3. exo-3a,7a-4,5,6,7-Hexahydro-4,7-methano-3-methyl-1,2-benzisothiazole (**11b**).* Yield 16%; pale yellow oil; δ_H (360 MHz, $CDCl_3$) 1.16–1.33, 1.45–1.62 (6H, m, H-5, H-6, H-8), 1.93 (3H, s, CH_3), 2.28 (1H, m, H-4), 2.46 (1H, d, *J* 1.7 Hz, H-7a), 3.11 (1H, d, *J* 9.4 Hz, H-3a), 3.69 (1H, dd, *J* 9.4, 1.7 Hz, H-7a); δ_C (91 MHz, $CDCl_3$) 19.2 (CH_3), 27.1 (C-5), 28.3 (C-6), 33.0 (C-8), 40.8 (C-4), 44.8 (C-7), 55.4 (C-3a), 67.5 (C-7a), 168.3 (C-3); *m*/*z* (EI) found: M^+ 167.0768. $C_9H_{13}NS$ requires 167.0769.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.06.068.

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