Tetrahedron 67 (2011) 5437–5443

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of sulfur containing analogues of the soluble guanylate cyclase inhibitor 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one NS2028

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ARTICLE INFO

Article history:
Received 14 March 2011
Received in revised form 6 May 2011
Accepted 16 May 2011
Available online 25 May 2011

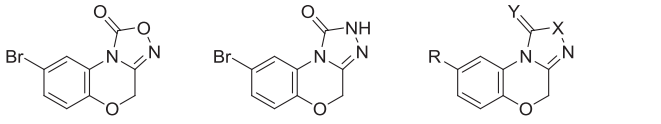
ABSTRACT

Sulfur analogues of the soluble guanylate cyclase (sGC) inhibitor NS2028 **1a** are synthesized. Treating 8-bromo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one oxime (**6**) with 1,1′-thiocarbonyldiimidazole (1.1 equiv) gave the carbamothioate 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazine-1-thione (**3a**) in 83% yield. Alternatively reacting NS2028 **1a** with P_2S_5 (0.5 equiv) affords the carbamothioate **3a** in 80% yield. Similar treatment of 8-aryl substituted NS2028 analogues **1b**–**d** with P_2S_5 gave the carbamothioates **3b**–**d** in 64–91% yields. Although quite stable, the carbamothioates **3a**–**d** could be thermally isomerized in the presence of Cu (10 mol %) to afford the thiocarbamates **4a**–**d** in high yields. Interestingly, in the case of carbamothioate **3a** Pd and In metals also facilitated the isomerization. Furthermore, treatment of the thiocarbamates **4a**–**d** with P_2S_5 (0.5 equiv) affords the carbamodithioates **5a**–**d** in 72–89% yields. All new compounds are fully characterized including single crystal X-ray data for carbamothioate **3a** and thiocarbamate **4a**. Finally, a mechanism is proposed for the carbamothioate to thiocarbamate isomerization.

1. Introduction

Soluble guanylate cyclase (sGC) is the only known physiological receptor for nitric oxide (NO). On binding to NO the activity of sGC increases 400-fold, promoting the conversion of guanosine 5′-triphospate (GTP) to the second messenger guanosine 3′,5′-cyclic monophosphate (cGMP) and pyrophosphate. cGMP acts to regulate various effector proteins, including protein kinases, phosphodiesterases and ion channels.[1] As such inhibitors of sGC can be used to regulate NO related signalling processes and to lower cGMP activity.[2]

8-Bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]-benzoxazin-1-one (NS2028) **1a** is a specific inhibitor of soluble guanylate cyclase (sGC). Recent applications of NS2028 **1a** include the development of inhibitors for lymphangiogenesis that can help prevent the metastasis of solid tumours,[3] for the treatment of dermatological diseases and in cosmetic skin care.[3,4] Furthermore, NS2028 has been used for neural thermoprotection against heat stroke or hyperthermia via inhibition of the PKG pathway,[5] and for the prevention and treatment of dental disorders.[6]



1a (NS2028) **2** **3** (X = O, Y = S) **4** (X = S, Y = O) **5** (X= Y = S)

Despite being known for approximately 15 years, the synthesis of NS2028 **1a** was only fully reported recently.[7] Not surprisingly, only a few analogues have been prepared and as such the pharmacophore structure of this compound remains unclear. Nevertheless, replacing the 8-bromo substituent by 4-methoxyphenyl or by 3-trifluoromethylphenyl gave analogues with interesting biological profiles, while replacing the 1,2,4-oxadiazolone ring with 1,2,4-triazolone to give 8-bromo-2,4-dihydro-1*H*-benzo[*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-1-one **2** led to a large decrease in activity demonstrating the importance of the former.[7a] Carbamides are far less electrophilic than carbamates and this indicated that introducing further structural modifications of the oxadiazole were warranted. The preparation of NS2028 analogues sporting carbamothioate **3**, thiocarbamate **4** and carbamodithioate **5** moieties would therefore be of interest.

We recently developed a non product specific synthesis of C-8 substituted analogues using Suzuki–Miyaura coupling reactions and NS2028 as a building block.[7b] Now we wish to report our

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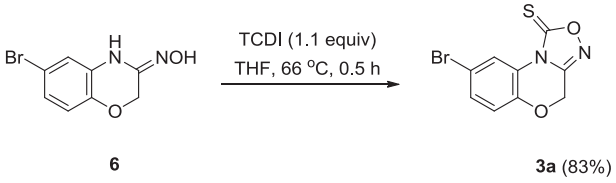
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.05.071

efforts to synthesize a library of 1,2,4-oxadiazole-5(4*H*)-thione (carbamothioate), 1,2,4-thiadiazol-5(4*H*)-one (thiocarbamate) and 1,2,4-thiadiazole-5(4*H*)-thione (carbamodithioate) analogues **3**–**5** of NS2028 that incorporate structural modifications at C-8.

2. Results and discussion

2.1. Preparation of NS2028 thione

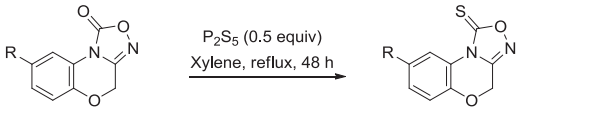
NS2028 **1a** can be prepared from 6-bromo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one oxime (**6**) on treatment with 1,1′-carbonyldiimidazole (CDI) in 95% yield.[7a] Similar treatment of the oxime **6** with 1,1′-thiocarbonyldiimidazole (TCDI) (1.1 equiv) in dry THF at ca. 66 °C for 0.5 h gave the carbamothioate 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazine-1-thione (**3a**) in 83% yield (Scheme 1).



6 **3a** (83%)

Scheme 1.

Alternatively, NS2028 **1a** can be reacted with diphosphorus pentasulfide (0.5 equiv) in refluxing xylene for 48 h to give the carbamothioate **3a** in 80% yield. The thionation worked equally well for 8-aryl substituted analogues bearing both electron withdrawing and donating substituents **1b** (R=4-MeOC$_6$H$_4$), **1c** (R=4-ClC$_6$H$_4$) and **1d** (R=3-O$_2$NC$_6$H$_4$) (Scheme 2).



1a (R = Br)
1b (R = 4-MeOC$_6$H$_4$)
1c (R = 4-ClC$_6$H$_4$)
1d (R = 3-O$_2$NC$_6$H$_4$)

3a (R = Br), 80%
3b (R = 4-MeOC$_6$H$_4$), 86%
3c (R = 4-ClC$_6$H$_4$), 91%
3d (R = 3-O$_2$NC$_6$H$_4$), 64%

Scheme 2.

The carbamothioate analogues of NS2028 **3a**–**d** were sufficiently stable to be recrystallized from $CHCl_3$ enabling full characterization, including elemental analysis and ^{13}C NMR spectroscopy. Since 1,2,4-oxadiazole-5(*H*)-thiones are known to thermally isomerize to give 1,2,4-thiadiazol-5(*H*)-ones,[8a–f] we also solved a single crystal X-ray structure for compound **3a**, to fully support the structural assignment (Fig. 1).

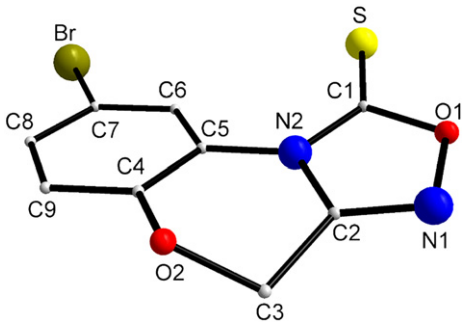


Fig. 1. Ball and stick representation of the crystal structure of 8-bromo-4*H*-[1,2,4]-oxadiazolo[3,4-*c*][1,4]benzoxazine-1-thione (**3a**) with crystallographic atom labelling. Hydrogen atoms are omitted for clarity.

2.2. Isomerization of NS2028 carbamothioates 3 to NS2028 thiocarbamates 4

Interestingly, prolonged heating (5 h) of the 6-bromo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one oxime (**6**) and 1,1′-thiocarbonyldiimidazole (TCDI) reaction mixture (Scheme 1) led to the formation of a side product that co-ran with the NS2028 **1a** on TLC. The product was isolated as pale yellow needles (mp 157–158 °C) and electron impact mass spectrometry gave a parent ion *m*/*z* (EI) 284 Da (98%) with an isotope pattern typical of one bromine atom. Elemental combustion analysis supported the formula $C_9H_5BrN_2O_2S$, which was isomeric with the carbamothioate **3a**. IR spectroscopy indicated the presence of a carbonyl stretch at ν(C=O) 1647 cm^{-1}, that was not present in the carbamothioate **3a**, while ^1H and ^{13}C NMR spectroscopy suggested the substitution pattern on the arene remained essentially the same, with only a noticeable change was observed in the most down field signals. As such we postulated that the new product was the isomeric thiocarbamate 8-bromobenzo[*b*][1,2,4]thiadiazolo-[4,3-*d*][1,4]-oxazin-1(4*H*)-one (**4a**).

The structure of the thiocarbamate **4a** was also confirmed by single crystal X-ray crystallography, thus providing supporting structure assignments for both carbamothioates and thiocarbamates (Fig. 2). A close comparison of the spectroscopic data revealed useful handles for identifying between the two isomers. The thione carbon resonance in the ^{13}C NMR spectra of the carbamothioates **3a**–**d** fell in a narrow range $\delta_{C=S}$ 179.2–181.0 ppm, while that of the carbonyl of the thiocarbamates **4a**–**d** fell in the narrow range $\delta_{C=O}$ 174.3–174.9 ppm. Similarly, the H-9 resonance in the ^1H NMR spectra was distinctly different for both sets of compounds with the thione functionality deshielding the H-9 hydrogen greater than the carbonyl, $\delta_{H\text{-}9}$ 9.32–9.51 ppm (carbamothioates **3a**–**d**) versus $\delta_{H\text{-}9}$ 8.53–8.73 ppm (thiocarbamates **4a**–**d**).

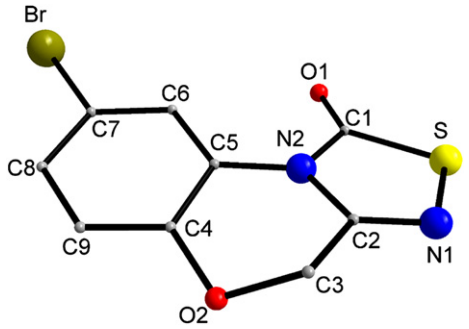
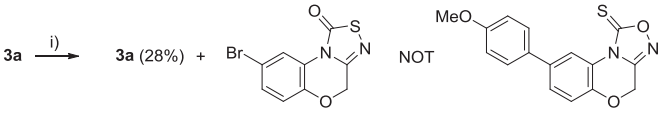


Fig. 2. Ball and stick representation of the crystal structure of 8-bromo-4*H*-[1,2,4]thiadiazolo-[3,4-*c*][1,4]benzoxazin-1-one (**4a**) with crystallographic atom labelling. Hydrogen atoms are omitted for clarity.

More surprisingly, isomerization was also observed when carbamothioate **3a** was subjected to Suzuki–Miyaura coupling conditions. As such, treating carbamothioate **3a** with 4-methoxyphenylboronic acid (1.5 equiv), Pd(OAc)$_2$ (5 mol %) and Hünig's base (3 equiv) in dioxane/H$_2$O (4:1) at ca. 110 °C for 2.5 h gave not the expected C-8 arylated analogue **3b** but the thiocarbamate **4a** in a moderate 54% yield together with recovered carbamothioate **3a** (28%) (Scheme 3).

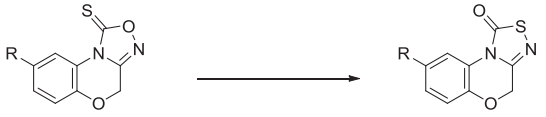


4a (54%) **3b**

Scheme 3. Reagent and conditions: (i) 4-MeOC$_6$H$_4$B(OH)$_2$ (1.5 equiv), Pd(OAc)$_2$ (5 mol %), *i*-Pr$_2$NEt (3 equiv), dioxane/H$_2$O (4:1), 110 °C, 2.5 h.

The isomerization of carbamothioates into thiocarbamates is known to proceed either photochemically, or thermally and in the latter cases copper was found to be an effective catalyst.[8] In light of this, we isomerized a pure sample of carbamothioate **3a** by heating a toluene solution of the carbamothioate with Cu powder (10 mol %) at ca. 110 °C for 1 h (Table 1). The isomerization also occurred when the Cu catalyst was replaced by $Pd(OAc)_2$, which partly explained the failure of the Suzuki–Miyaura reaction of the carbamothioate **3a**. In fact, the use of either heterogeneous or homogeneous Pd(0) sources, Pd/C (5 mol %) or $Pd(OAc)_2$ (5 mol %), respectively, also led to isomerization but the palladium catalyzed reactions were less clean than those using catalytic Cu powder. ^{1}H NMR spectroscopy of the products mixtures from the $Pd(OAc)_2$ catalyzed isomerization tentatively identified one of the contaminates to be NS2028 **1a**. Fortunately recrystallization of these mixtures gave pure thiocarbamate **4a**. Switching to In powder (1 equiv) in dioxane at reflux led to a clean and quantitative isomerization but the reaction failed when either catalytic In (10 mol %) was used or when dioxane was replaced by toluene. Owing to the relative costs of In, Pd and Cu we carried out all subsequent isomerizations of carbamothioates **3b**–**d** using catalytic Cu powder (Table 1).

Table 1
Metal catalyzed isomerization of the carbamothioates **3** into the thiocarbamates **4**



3a-d **4a-d**

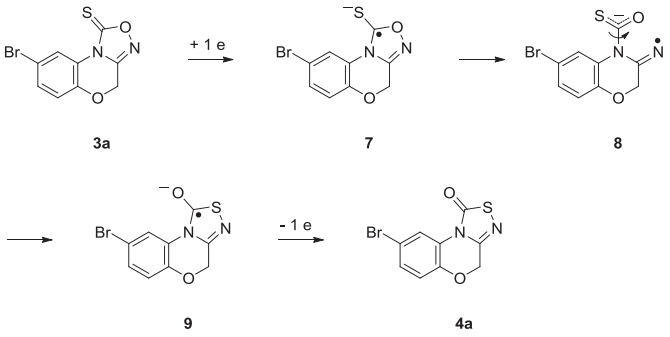
R	Catalyst (mol %)	Solvent (mL)	Temp (°C)	Time (h)	Yield[a] (%)
Br	Cu (10)	PhMe (0.5)	110	1	**4a** (88)
Br	$Pd_2(OAc)_2$ (10)	PhMe (0.5)	110	2	**4a** (93)
Br	$Pd_2(dba)_2$ (10)	PhMe (0.5)	110	0.3	**4a** (90)
Br	Pd/C (20)	PhMe (0.5)	110	3	**4a** (81)
Br	In (100)	Dioxane (0.5)	100	1	**4a** (93)
Br	In (10)	Dioxane (0.5)	100	24	[b]
Br	In (100)	PhMe (0.5)	110	24	[b]
4-$MeOC_6H_4$	Cu (10)	PhMe (0.5)	110	1	**4b** (86)
4-ClC_6H_4	Cu (10)	PhMe (0.5)	110	1	**4c** (88)
3-$O_2NC_6H_4$	Cu (20)	PhMe (0.5)	110	1	**4d** (80)

[a] Recrystallized yields.
[b] Incomplete reaction.

All three 8-aryl substituted carbamothioates **3b**–**d** isomerized in the presence of Cu(0) in good yields (80–88%), however, we found that the 3-nitrophenyl analogue isomerized more slowly using only 10 mol % of copper and for the reaction to reach completion in 1 h 20 mol % of copper powder was needed. Furthermore, treating a pure sample of the thiocarbamate **4a** with indium, copper or palladium led only to recovery of unreacted thiocarbamate. Despite this stability, when the Suzuki–Miyaura coupling chemistry was attempted with the 8-bromo derivative **4a** to prepare independently the thiocarbamates **4b**–**d** we failed to get any reaction. This is now under investigation.

2.3. Mechanistic rational for isomerization of carbamothioates 3 into thiocarbamates 4

To the best of our knowledge the isomerization of 1,2,5-thiadiazole-5(*H*)-thiones into 1,2,5-thiadiazol-5(*H*)-ones using either indium or palladium reagents has not been reported. The mechanism for the indium and palladium metal promoted isomerization, however, could be similar to that proposed by Pelter and Sümengen,[8a] i.e., single electron transfer to give the radical anion **7**, which then undergoes a ring open-ring closure sequence via intermediates **8** and **9** to give the more stable thioester **4a** (Scheme 4).



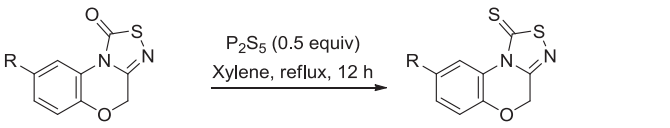
3a **7** **8** **9** **4a**

Scheme 4.

Tentatively, the $Pd(OAc)_2$ promoted isomerization may be catalyzed by the presence of Pd(0) species generated in the reaction mixture. This was supported by the successful isomerization in the presence of heterogeneous and homogenous sources of Pd(0), Pd/C and the $Pd_2(dba)_2$, respectively. Interestingly, the latter homogeneous catalyst gave a very rapid reaction (20 min) (Table 1). Furthermore, it was of interest that indium powder (1 equiv) gave the cleanest reactions but that these were also dependent on the solvent used, working well with dioxane but not with toluene, which could be of mechanistic interest since a purely radical mechanism should not be affected so significantly by solvent polarity.

2.4. Preparation of carbamodithioates 5 via thionation of thiocarbamates 4

Finally, treatment of the thiocarbamates **4a**–**d** with diphosphorus pentasulfide (0.5 equiv) in xylene at ca. 150 °C for 12 h gave the carbamodithioates **5a**–**d** in good yields (72–89%) (Scheme 5).



4a (R = Br)
4b (R = 4-$MeOC_6H_4$)
4c (R = 4-ClC_6H_4)
4d (R = 3-$O_2NC_6H_4$)

5a (R = Br), 89%
5b (R = 4-$MeOC_6H_4$), 78%
5c (R = 4-ClC_6H_4), 75%
5d (R = 3-$O_2NC_6H_4$), 72%

Scheme 5.

Similar to the carbamothioates **3a**–**d** the carbamodithioates **5a**–**d** gave a down field signal for H-9 in the ^{1}H NMR spectra $\delta_{H\text{-}9}$ 9.71–9.86 ppm owing to the deshielding effect of the thione, while the thiocarbonyl group gave the most down field signals in the ^{13}C NMR spectra, $\delta_{C=S}$ 194.6–195.2 ppm. As with the thiocarbamate **4a** attempted Suzuki–Miyaura coupling reactions with the carbamodithioate **5a** only gave back unreacted starting material. With these final compounds prepared we now had a small library of NS2028 analogues with a systematic variation of substituent at C-8 combined with a variation of the oxadiazolone moiety. Biological studies on these new analogues of the NS2028 sGC inhibitor are now underway.

3. Conclusion

NS2028 thione **3a** has been prepared via thionation of NS2028 **1a** using P_2S_5 and via the reaction of 6-bromo-2*H*-benzo[*b*][1,4]

oxazin-3(4*H*)-one oxime (**6**) with TCDI in 80 and 83% yields, respectively. Several 8-aryl analogues of NS2028 **1b**–**d** were also readily thionated to give the corresponding thiones **3b**–**d** in high yields. Treating the carbamothioate **3a** with either In, Cu or Pd led to isomerization and provided the thiocarbamate **4a** in good yields. Cu and Pd could be used catalytically; however, the reactions were accompanied by minor side products. On the other hand the reactions with 1 equiv of indium powder gave only pure product. Treatment of the thiocarbamates **4a**–**d** with P_2S_5 gave the corresponding carbamodithioates **5a**–**d** in good yields. The scope of using these reagents for similar isomerizations is now being investigated. Finally, the biological properties of these new NS2028 analogues are currently under investigation.

4. Experimental

4.1. General methods and materials

Toluene and xylene (mixture of isomers) were freshly distilled from sodium under argon. Reactions were protected from atmospheric moisture by $CaCl_2$ drying tubes. All volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used throughout for all non-TLC scale chromatographic separations using Merck Silica Gel 60 (less than 0.063 mm).[9] Melting and decomposition points were determined using a TA Instruments DSC Q1000 with samples hermetically sealed in aluminium pans under an argon atmosphere; using heating rates of 5 °C/min. Solvents used for recrystallization are indicated after the melting point. UV spectra were obtained using a Perkin–Elmer Lambda-25 UV/vis spectrophotometer and inflections are identified by the abbreviation 'inf'. IR spectra were recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer with a Pike Miracle Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w, respectively. ^{1}H NMR spectra were recorded on a BrukerAvance 300 machine at 300 MHz. ^{13}C NMR spectra were recorded on a BrukerAvance 300 or BrukerAvance 500 machines (at 75 and 125 MHz, respectively). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GC/MS with direct inlet probe. 8-Bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one (NS2028) **1a**,[7b] 8-(4-methoxyphenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazine-1-one **1b**,[7b] 8-(4-chlorophenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazine-1-one **1c**[7b] and 8-(3-nitrophenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazine-1-one **1d**[7b] were prepared using literature procedures. Copper fine powder GR particle size <63 μm was purchased from Merck; phosphorus pentasulfide (P_4S_{10}) 99% from Aldrich.

4.2. Thionation of 8-substituted 4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-ones

*4.2.1. 8-Bromo-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazine-1-thione (**3a**), method A (Scheme 1).* To the solution of 6-bromo-2*H*-1,4-benzo[*b*][1,4]oxazin-3(4*H*)-one oxime (**6**) (1.00 g, 4.11 mmol) in dry THF (10 mL) was added thiocarbonyl diimidazole (TCDI) (0.807 g, 4.53 mmol). The reaction mixture was then allowed to stir at ca. 66 °C for 0.5 h and then cooled to ca. 20 °C. The solvent was removed in vacuo and the residue dissolved in DCM (25 mL) and washed with water (2×25 mL). The organic layer was dried (Na_2SO_4), filtered and the filtrate was evaporated under reduced pressure. The resulting solid material was recrystallized to give the *title compound* **3a** (0.97 g, 83%) as colourless prisms, mp (DSC) onset: 184 °C, peak max: 190 °C (from chloroform), R_f (DCM) 0.72; found: C, 37.9; H, 1.7; N, 9.8. $C_9H_5BrN_2O_2S$ requires C, 37.9; H, 1.8; N, 9.8%; λ_{max} (DCM)/nm 230 (log ε 2.93), 232 inf (2.91), 240 inf (2.83), 273 inf (3.02), 279 (3.15), 298 inf (3.10), 303 (3.11); ν_{max}/cm^{-1} 3102w, 3075w and 3015w (Ar CH), 2913w, 1771w, 1626m, 1595w, 1487s, 1449m, 1387m, 1360s, 1296m, 1260m, 1242m, 1219w, 1136w, 1115m, 1074w, 1042w, 1030m, 993w, 949w, 941w, 918w, 887w, 870m, 854w, 831m, 816m, 785m; δ_H (300 MHz, $CDCl_3$) 9.32 (1H, d, *J* 2.1, *H*-9), 7.45 (1H, dd, *J* 8.7, 2.3, *H*-7), 7.06 (1H, d, *J* 8.7, *H*-6), 5.19 (2H, s, C*H*$_2$O); δ_C (75 MHz, DMSO-d_6) 179.2 (*C*=S), 152.5 (C_q), 144.8 (C_q), 131.5 (Ar *C*H), 132.4 (C_q), 119.9 (Ar *C*H), 118.7 (Ar *C*H), 113.4 (C_q), 59.5 (*C*H$_2$O); *m*/*z* (EI) 286 (M$^+$+2, 100%), 284 (M$^+$, 97), 258 (6), 256 (6), 226 (24), 224 (22), 212 (10), 199 (38), 197 (37), 186 (7), 184 (8), 172 (52), 170 (66), 158 (15), 156 (18), 144 (6), 129 (5), 117 (12), 109 (8), 103 (6), 90 (18), 76 (77), 63 (95), 50 (44).

*4.2.2. 8-Bromo-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazine-1-thione (**3a**), method B (typical procedure, see Scheme 2).* To a solution of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one (**1a**) (100 mg, 0.372 mmol) in xylene (5 mL) was added P_2S_5 (41.3 mg, 0.186 mmol). The reaction mixture was then allowed to stir at ca. 140 °C for 48 h and then cooled to ca. 20 °C. The solvent was removed in vacuo and the residue dissolved in DCM (5 mL), adsorbed onto silica and chromatographed (DCM) to give the *title compound* **3a** (86 mg, 80%) as colourless prisms, mp (DSC) onset: 184 °C, peak max: 190 °C (from chloroform), R_f (DCM) 0.72; identical to that described above.

*4.2.3. 8-(4-Methoxyphenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazine-1-thione (**3b**), method B.* Similar treatment of 8-(4-methoxyphenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **1b** (100 mg, 0.338 mmol) with P_2S_5 (41.3 mg, 0.186 mmol) in xylene (5 mL) at ca. 140 °C for 48 h gave the *title compound* **3b** (90 mg, 86%) as colourless cotton needles, mp (DSC) onset: 201.6 °C, peak max: 201.8 °C (from 1,2-dichloroethane), R_f (DCM) 0.56; found: C, 61.4; H, 3.8; N, 8.9. $C_{16}H_{12}N_2O_3S$ requires C, 61.5; H, 3.9; N, 9.0%; λ_{max} (DCM)/nm 228 (log ε 3.08), 277 (3.50); ν_{max}/cm^{-1} 3015w (Ar CH), 2963w, 2945w, 2918w, 2841w, 1630w, 1609m, 1528w, 1499s, 1487w, 1470w, 1458w, 1437w, 1418w, 1389w, 1354s, 1319m, 1294m, 1277m, 1254m, 1238s, 1219m, 1186m, 1105s, 1051w, 1040m, 1032m, 1020m, 878w, 841m, 833m, 818m, 810m, 802m, 779w; δ_H (300 MHz, $CDCl_3$) 9.37 (1H, d, *J* 2.3, *H*-9), 7.55 (2H, d, *J* 8.9, Ar *H*), 7.50 (1H, dd, *J* 8.5, 2.3, *H*-7), 7.20 (1H, d, *J* 8.5, *H*-6), 7.01 (2H, d, *J* 8.9, Ar *H*), 5.20 (2H, s, C*H*$_2$O), 3.86 (3H, s, C*H*$_3$O); δ_C (75 MHz, $CDCl_3$) 179.8 (*C*=S), 159.6 (C_q), 151.8 (C_q), 144.1 (C_q), 136.7 (C_q), 131.6 (C_q), 128.0 (Ar *C*H), 126.9 (Ar *C*H), 122.6 (C_q), 118.2 (Ar *C*H), 115.3 (Ar *C*H), 114.5 (Ar *C*H), 59.8 (*C*H$_2$O), 55.4 (*C*H$_3$O); *m*/*z* (EI) 312 (M$^+$, 100%), 284 (9), 272 (7), 251 (9), 244 (7), 237 (23), 225 (17), 209 (20), 201 (4), 195 (4), 182 (5), 169 (7), 155 (5), 140 (13), 127 (19), 114 (8), 101 (5), 89 (6), 77 (10), 63 (11), 51 (6).

*4.2.4. 8-(4-Chlorophenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazine-1-thione (**3c**), method B.* Similar treatment of 8-(4-chlorophenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **1c** (100 mg, 0.333 mmol) with P_2S_5 (41.3 mg, 0.186 mmol) in xylene (5 mL) at ca. 140 °C for 48 h gave the *title compound* **3c** (95 mg, 91%) as pink prisms, mp (DSC) onset: 218 °C, peak max: 221 °C (from 1,2-dichloroethane), R_f (DCM) 0.71; found: C, 56.9; H, 2.8; N, 8.9. $C_{15}H_9ClN_2O_2S$ requires C, 56.9; H, 2.9; N, 8.8%; λ_{max} (DCM)/nm 228 (log ε 3.26), 272 (3.52), 301 inf (3.09); ν_{max}/cm^{-1} 3080w, 3003w (Ar CH), 2913w, 2866w, 1628w, 1609w, 1516w, 1485s, 1454m, 1410m, 1387w, 1358s, 1319w, 1273m, 1246w, 1223w, 1190w, 1146w, 1099s, 1049w, 1038m, 1020w, 1013m, 959w, 885w, 849w, 833m, 820s, 797w; δ_H (300 MHz, acetone-d_6) 9.49 (1H, d, *J* 2.3, *H*-9), 7.71 (1H, dd, *J* 8.5, 2.3, *H*-7), 7.70 (2H, d, *J* 8.7, Ar *H*), 7.54 (2H, d, *J* 8.7, Ar *H*), 7.33 (1H, d, *J* 8.5, *H*-6), 5.53 (2H, s, C*H*$_2$O); δ_C (75 MHz, acetone-d_6)

181.0 (*C*=S), 153.6 (C_q), 146.4 (C_q), 138.9 (C_q), 135.3 (C_q), 134.2 (C_q), 130.0 (Ar *C*H), 129.1 (Ar *C*H), 127.9 (Ar *C*H), 124.1 (C_q), 119.3 (Ar *C*H), 115.9 (Ar *C*H), 60.7 (CH_2O); *m*/*z* (EI) 318 (M^++2, 35%), 316 (M^+, 100), 290 (5), 288 (14), 258 (15), 256 (32), 242 (13), 229 (13), 216 (6), 202 (18), 200 (10), 177 (6), 164 (8), 153 (17), 139 (48), 126 (14), 113 (7), 101 (9), 87 (7), 75 (15), 69 (8), 63 (13), 51 (8).

*4.2.5. 8-(3-Nitrophenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazine-1-thione (**3d**), method B.* Similar treatment of 8-(3-nitrophenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one (**1d**) (150 mg, 0.482 mmol) with P_2S_5 (41.3 mg, 0.186 mmol) in xylene (5 mL) at ca. 140 °C for 48 h gave the *title compound* **3d** (67 mg, 64%) as yellow prisms, mp (DSC) onset: 223 °C, peak max: 226 °C (from 1,2-dichloroethane), R_f (DCM) 0.70; found: C, 54.9; H, 2.7; N, 12.7. $C_{15}H_9N_3O_4S$ requires C, 55.0; H, 2.8; N, 12.8%; λ_{max} (DCM)/nm 230 (log ε 3.39), 258 (3.58), 272 inf (3.55), 295 inf (3.21); ν_{max}/cm^{-1} 3067w (Ar CH), 1624w, 1607w, 1558w, 1531s, 1510m, 1474m, 1460m, 1441w, 1427w, 1391m, 1371s, 1348s, 1321m, 1310w, 1273m, 1263m, 1238w, 1213w, 1144w, 1111m, 1084w, 1053w, 1042m, 1020m, 982w, 962w, 934w, 914w, 889m, 881m, 839m, 827m, 806s, 760w; δ_H (300 MHz, $CDCl_3$) 9.51 (1H, d, *J* 2.3, *H*-9), 8.46 (1H, dd, *J* 1.9, 1.9, *H*-2′), 8.25 (1H, ddd, *J* 8.2, 2.2, 1.0, Ar *H*), 7.95 (1H, ddd, *J* 7.8, 1.8, 1.0, Ar *H*), 7.67 (1H, dd, *J* 8.0, 8.0, *H*-5′), 7.61 (1H, dd, *J* 8.6, 2.2, *H*-7), 7.31 (1H, d, *J* 8.5, *H*-6), 5.27 (2H, s, CH_2O); δ_C (125 MHz, $CDCl_3$) 179.7 (*C*=S), 151.5 (C_q), 148.9 (C_q), 145.5 (C_q), 140.8 (C_q), 134.4 (C_q), 132.9 (Ar *C*H), 130.2 (Ar *C*H), 127.6 (Ar *C*H), 123.0 (C_q), 122.7 (Ar *C*H), 121.7 (Ar *C*H), 118.8 (Ar *C*H), 116.0 (Ar *C*H), 59.8 (CH_2); *m*/*z* (EI): 327 (M^+, 100%), 299 (25), 267 (32), 253 (13), 241 (15), 221 (9), 213 (5), 209 (9), 207 (7), 193 (28), 179 (5), 167 (43), 153 (18), 139 (75), 126 (21), 113 (9), 100 (5), 89 (9), 76 (12), 70 (7), 63 (19), 60 (8), 50 (9).

4.3. Isomerization of 8-substituted 4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-thiones

*4.3.1. 8-Bromo-4H-[1,2,4]thiadiazolo[3,4-c][1,4]benzoxazine-1-one (**4a**) (typical procedure, see Table 1).* To a solution of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-thione (**3a**) (49.9 mg, 0.175 mmol) in toluene (0.5 mL) was added copper powder (1.14 mg, 0.018 mmol). The reaction mixture was then allowed to stir at ca. 110 °C for 1 h and then cooled to ca. 20 °C. The solvent was removed in vacuo and the residue dissolved in DCM (5 mL). This solution was passed through a thin layer of silica gel and then rinsed with additional DCM. The filtrate was evaporated in vacuo to give the crude product with quantitative yield. Recrystallization of the crude product gave the *title compound* **4a** (44 mg, 88%) as pale yellow needles, mp (DSC) onset: 157 °C, peak max: 158 °C (from acetone), R_f (DCM) 0.56; found: C, 38.1; H, 1.9; N, 9.8. $C_9H_5BrN_2O_2S$ requires C, 38.0; H, 1.8; N, 9.8%; λ_{max} (DCM)/nm 232 (log ε 3.28), 255 inf (3.10), 261 inf (3.04), 288 (2.95), 295 inf (2.92); ν_{max}/cm^{-1} 3113w, 3076w (Ar CH), 3005w, 2909w, 1879w, 1753w, 1674s (C=O), 1649m, 1612m, 1595m, 1578w, 1555w, 1528w, 1483s, 1447w, 1429m, 1366s, 1290m, 1258m, 1246w, 1215m, 1140m, 1080w, 1057s, 1020s, 997w, 941w, 878m, 826m, 812m, 785m, 777m; δ_H (300 MHz, acetone-d_6) 8.53 (1H, d, *J* 2.5, *H*-9), 7.46 (1H, dd, *J* 8.7, 2.3, *H*-7), 7.16 (1H, d, *J* 8.7, *H*-6), 5.12 (2H, s, CH_2O); δ_C (125 MHz, acetone-d_6) 174.9 (*C*=O), 149.7 (C_q), 146.2 (C_q), 131.1 (Ar *C*H), 126.7 (C_q), 121.1 (Ar *C*H), 120.2 (Ar *C*H), 115.2 (C_q), 66.4 (CH_2O); *m*/*z* (EI): 286 (M^++2, 100%), 284 (M^+, 98), 258 (59), 256 (61), 231 (6), 229 (6), 225 (15), 223 (15), 212 (27), 210 (25), 200 (17), 198 (18), 184 (10), 182 (9), 177 (9), 170 (7), 156 (7), 149 (9), 129 (7), 119 (4), 109 (5), 103 (28), 76 (42), 72 (13), 63 (38), 50 (25).

*4.3.2. 8-(4-Methoxyphenyl)-4H-[1,2,4]thiadiazolo[3,4-c][1,4]benzoxazine-1-one (**4b**).* Similar treatment of 8-(4-methoxyphenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-thione (**3b**) (50.0 mg, 0.160 mmol) with copper powder (1.02 mg, 0.016 mmol) in toluene (0.5 mL) at ca. 110 °C for 1 h gave the *title compound* **4b** (43 mg, 86%) as colourless cotton needles, mp (DSC) onset: 107 °C, peak max: 108 °C (from acetone/pentane), R_f (DCM) 0.47; found: C, 61.5; H, 3.8; N, 8.8. $C_{16}H_{12}N_2O_3S$ requires C, 61.5; H, 3.9; N, 9.0%; λ_{max} (DCM)/nm 230 inf (log ε 3.26), 263 (3.48); ν_{max}/cm^{-1} 3011w (Ar CH), 2970w, 2941w, 2835w, 1713s (C=O), 1703m, 1686m, 1665w, 1612m, 1595m, 1587m, 1555w, 1526w, 1497s, 1447m, 1412m, 1369s, 1314m, 1292m, 1277m, 1260m, 1238s, 1225m, 1188m, 1180m, 1146m, 1065m, 1045s, 1018s, 885w, 878w, 833m, 814s, 804s, 779m, 768w; δ_H (300 MHz, acetone-d_6) 8.62 (1H, d, *J* 2.1, *H*-9), 7.58 (2H, d, *J* 8.9, Ar *H*), 7.52 (1H, dd, *J* 8.5, 2.1, *H*-7), 7.23 (1H, d, *J* 8.5, *H*-6), 7.04 (2H, d, *J* 8.9, Ar *H*), 5.11 (2H, s, CH_2O), 3.85 (3H, s, CH_3O); δ_C (75 MHz, acetone-d_6) 174.9 (*C*=O), 160.4 (C_q), 150.3 (C_q), 145.7 (C_q), 136.6 (C_q), 132.8 (C_q), 128.6 (Ar *C*H), 126.2 (Ar *C*H), 125.8 (C_q), 118.6 (Ar *C*H), 116.2 (Ar *C*H), 115.2 (Ar *C*H), 66.3 (CH_2O), 55.6 (OCH_3); *m*/*z* (EI): 312 (M^+, 100%), 284 (21), 269 (4), 251 (10), 238 (19), 225 (21), 210 (9), 195 (6), 167 (3), 153 (3), 140 (7), 127 (7), 119 (3), 115 (4), 105 (3), 89 (3), 77 (4), 63 (5), 51 (3).

*4.3.3. 8-(4-Chlorophenyl)-4H-[1,2,4]thiadiazolo[3,4-c][1,4]benzoxazine-1-one (**4c**).* Similar treatment of 8-(4-chlorophenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-thione (**3c**) (50.0 mg, 0.158 mmol) with copper powder (1.02 mg, 0.016 mmol) in toluene (0.5 mL) at ca. 110 °C for 1 h gave the *title compound* **4c** (44 mg, 88%) as colourless cotton needles, mp (DSC) onset: 195 °C, peak max: 196 °C (from chloroform), R_f (DCM) 0.47; found: C, 56.9; H, 2.8; N, 8.9. $C_{15}H_9ClN_2O_2S$ requires C, 56.9; H, 2.9; N, 8.8%; λ_{max} (DCM)/nm 230 inf (log ε 3.33), 256 (3.53); ν_{max}/cm^{-1} 3103w, 1695s (C=O), 1670m, 1616w, 1597m, 1551w, 1528w, 1516w, 1485s, 1443m, 1402m, 1366m, 1315w, 1287m, 1267w, 1250m, 1229m, 1194w, 1144m, 1097m, 1069w, 1061m, 1036m, 1013m, 991w, 891w, 885w, 843w, 827w, 814s, 793w, 760m; δ_H (300 MHz, acetone-d_6) 8.67 (1H, d, *J* 1.9, *H*-9), 7.66 (2H, d, *J* 8.5, Ar *H*), 7.59 (1H, dd, *J* 8.5, 2.1, *H*-7), 7.51 (2H, d, *J* 8.5, Ar *H*), 7.27 (1H, d, *J* 8.5, *H*-6), 5.13 (2H, s, CH_2O); δ_C (75 MHz, $CDCl_3$) 174.3 (*C*=O), 148.3 (C_q), 145.2 (C_q), 138.1 (C_q), 135.6 (C_q), 133.8 (C_q), 129.1 (Ar *C*H), 128.2 (Ar *C*H), 126.1 (Ar *C*H), 124.8 (C_q), 118.0 (Ar *C*H), 116.4 (Ar *C*H), 65.7 (CH_2O); *m*/*z* (EI): 318 (M^++2, 36%), 316 (M^+, 100), 290 (16), 288 (41), 261 (6), 255 (16) 242 (25), 230 (15), 214 (9), 200 (4), 177 (15), 164 (5), 152 (22), 144 (7), 139 (33), 126 (14), 113 (6), 99 (6), 89 (6), 75 (14), 69 (5), 63 (10), 51 (7).

*4.3.4. 8-(3-Nitrophenyl)-4H-[1,2,4]thiadiazolo[3,4-c][1,4]benzoxazine-1-one (**4d**).* Similar treatment of 8-(3-nitrophenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-thione (**3d**) (50.1 mg, 0.153 mmol) with copper powder (1.91 mg, 0.030 mmol) in toluene (0.5 mL) at ca. 110 °C for 1 h gave the *title compound* **4d** (40 mg, 80%) as pale yellow needles, mp (DSC) onset: 198 °C, peak max: 198 °C (from chloroform), R_f (DCM) 0.33; found: C, 55.2; H, 2.7; N, 12.9. $C_{15}H_9N_3O_4S$ requires C, 55.1; H, 2.8; N, 12.8%; λ_{max} (DCM)/nm 232 inf (log ε 3.49), 255 (3.63), 320 (2.37); ν_{max}/cm^{-1} 3094w, 3073w (Ar CH), 2995w, 1711s (C=O), 1692m, 1647w, 1614w, 1585m, 1535s, 1510s, 1477m, 1449m, 1425m, 1369m, 1344s, 1302w, 1285m, 1275m, 1246m, 1225m, 1177w, 1152m, 1103w, 1090w, 1067m, 1057m, 1049m, 1030s, 999w, 951w, 935w, 922w, 903w, 876m, 860m, 826m, 800m, 791m, 772m; δ_H (300 MHz, $CDCl_3$) 8.73 (1H, d, *J* 2.1, *H*-9), 8.43 (1H, dd, *J* 2.0, 2.0, *H*-2′), 8.22 (1H, ddd, *J* 8.2, 2.2, 1.0, Ar *H*), 7.91 (1H, ddd, *J* 7.8, 1.8, 1.0, Ar *H*), 7.63 (1H, dd, *J* 7.9, 7.9, *H*-5′), 7.50 (1H, dd, *J* 8.5, 2.3, *H*-7), 7.26 (1H, d, *J* 8.5, *H*-6), 5.00 (2H, s, CH_2O); δ_C (75 MHz, $CDCl_3$) 174.3 (*C*=O), 148.8 (C_q), 148.0 (C_q), 145.9 (C_q), 141.3 (C_q), 134.2 (C_q), 132.9 (Ar *C*H), 129.9 (Ar *C*H), 126.4 (Ar *C*H), 125.0 (C_q), 122.3 (Ar *C*H), 121.8 (Ar *C*H), 118.3 (Ar *C*H), 116.6 (Ar *C*H), 65.7 (CH_2O); *m*/*z* (EI): 327 (M^+, 100%), 299 (50), 272 (4), 266 (15), 253 (24), 241 (23), 225 (4), 220 (3), 213 (3), 207 (13), 195 (8), 179 (8), 167 (18), 152 (13), 139 (51), 126 (17), 113 (7), 101 (4), 89 (8), 76 (11), 63 (15), 50 (8).

4.4. Thionation of 8-substituted 4*H*-[1,2,4]thiadiazolo[3,4-*c*][1,4]benzoxazin-1-ones

*4.4.1. 8-Bromo-4H-[1,2,4]thiadiazolo[3,4-c][1,4]benzoxazine-1-thione (**5a**) (typical procedure, see Scheme 5).* To a solution of 8-bromo-4*H*-[1,2,4]thiadiazolo[3,4-*c*][1,4]benzoxazin-1-one (**4a**) (100 mg, 0.351 mmol) in xylene (2 mL) was added P_2S_5 (38.9 mg, 0.175 mmol). The reaction mixture was then allowed to stir at ca. 140 °C for 12 h and then cooled to ca. 20 °C. The solvent was removed in vacuo and the residue dissolved in DCM (5 mL), adsorbed onto silica and chromatographed (DCM) to give the *title compound* **5a** (94 mg, 89%) as pale yellow needles, mp (DSC) onset: 203 °C, peak max: 205 °C (from chloroform), R_f (DCM) 0.67; found: C, 36.0; H, 1.6; N, 9.2. $C_9H_5BrN_2OS_2$ requires C, 35.9; H, 1.7; N, 9.3%; λ_{max} (DCM)/nm 237 (log ε 3.38), 251 inf (3.25), 288 (2.97), 298 (2.97), 332 (3.26); ν_{max}/cm^{-1} 3105w, 3080w (Ar CH), 2903w, 1638w, 1607w, 1593w, 1553w, 1477s, 1441w, 1420m, 1354w, 1327m, 1294s, 1265m, 1238m, 1223s, 1192s, 1171m, 1121w, 1076m, 1049m, 1022s, 1011m, 968w, 943w, 872m, 866m, 816s, 783m, 777m; δ_H (300 MHz, $CDCl_3$) 9.71 (1H, d, *J* 1.9, *H*-9), 7.44 (1H, dd, *J* 8.7, 1.9, *H*-7), 7.07 (1H, d, *J* 8.7, *H*-6), 5.03 (2H, s, CH_2O); δ_C (125 MHz, $CDCl_3$) 195.0 (C=S), 153.0 (C_q), 145.9 (C_q), 132.0 (Ar CH), 126.9 (C_q), 122.1 (Ar CH), 119.4 (Ar CH), 115.0 (C_q), 65.4 (CH_2O); *m*/*z* (EI): 302 (M^++2, 100%), 300 (M^+, 96), 262 (16), 260 (15), 238 (10), 236 (10), 230 (22), 228 (20), 202 (11), 200 (11), 196 (7), 172 (10), 170 (19), 168 (10), 153 (3), 121 (5), 117 (5), 110 (20), 94 (5), 88 (6), 76 (25), 63 (23), 50 (13).

*4.4.2. 8-(4-Methoxyphenyl)-4H-[1,2,4]thiadiazolo[3,4-c][1,4]benzoxazine-1-thione (**5b**).* Similar treatment of 8-(4-methoxyphenyl)-4*H*-[1,2,4]thiadiazolo[3,4-*c*][1,4]benzoxazin-1-one (**4b**) (100 mg, 0.320 mmol) with P_2S_5 (35.6 mg, 0.160 mmol) in xylene (2 mL) at ca. 140 °C for 12 h gave the *title compound* **5b** (82 mg, 78%) as colourless cotton needles, mp (DSC) onset: 142 °C, peak max: 143 °C (from 1,2-dichloroethane), R_f (DCM) 0.69; found: C, 58.6; H, 3.6; N, 8.4. $C_{16}H_{12}N_2O_2S_2$ requires C, 58.5; H, 3.7; N, 8.5%; λ_{max} (DCM)/nm 256 (log ε 3.59), 273 inf (3.48), 333 (3.14); ν_{max}/cm^{-1} 3005w (Ar CH), 2945w, 2828w, 1607w, 1597w, 1585w, 1572w, 1524w, 1493s, 1468w, 1439m, 1408w, 1364w, 1333m, 1308m, 1292m, 1277m, 1254m, 1242m, 1229s, 1202m, 1180s, 1136w, 1117w, 1049m, 1020m, 966w, 955w, 930w, 881m, 854w, 831m, 816s, 806m, 783m, 752m; δ_H (300 MHz, $CDCl_3$) 9.73 (1H, d, *J* 2.1, *H*-9), 7.54 (2H, d, *J* 8.9, Ar *H*), 7.49 (1H, dd, *J* 8.5, 2.3, *H*-7), 7.21 (1H, d, *J* 8.5, *H*-6), 6.99 (2H, d, *J* 8.9, Ar *H*), 5.04 (2H, s, CH_2O), 3.85 (3H, s, CH_3O); δ_C (75 MHz, $CDCl_3$) 195.0 (C=S), 159.3 (C_q), 153.6 (C_q), 145.4 (C_q), 135.6 (C_q), 131.7 (C_q), 127.8 (Ar CH), 126.8 (Ar CH), 126.2 (C_q), 118.0 (Ar CH), 117.2 (Ar CH), 114.3 (Ar CH), 65.3 (CH_2O), 55.3 (CH_3O); *m*/*z* (EI): 328 (M^+, 100%), 313 (7), 282 (3), 264 (10), 256 (20), 237 (8), 228 (5), 224 (18), 209 (7), 196 (4), 185 (3), 164 (5), 157 (4), 153 (6), 140 (3), 127 (9), 114 (2), 101 (2), 89 (2), 77 (3), 63 (3), 51 (2).

*4.4.3. 8-(4-Chlorophenyl)-4H-[1,2,4]thiadiazolo[3,4-c][1,4]benzoxazine-1-thione (**5c**).* Similar treatment of 8-(4-chlorophenyl)-4*H*-[1,2,4]thiadiazolo[3,4-*c*][1,4]benzoxazin-1-one (**4c**) (100 mg, 0.316 mmol) with P_2S_5 (35.1 mg, 0.158 mmol) in xylene (2 mL) at ca. 140 °C for 12 h gave the *title compound* **5c** (79 mg, 75%) as violet prisms, mp (DSC) onset: 193 °C, peak max: 194 °C (from 1,2-dichloroethane), R_f (DCM) 0.80; found: C, 54.2; H, 2.7; N, 8.4. $C_{15}H_9ClN_2OS_2$ requires C, 54.1; H, 2.7; N, 8.4%; λ_{max} (DCM)/nm 253 (log ε 3.64), 332 (3.19); ν_{max}/cm^{-1} 3084w, 3017w (Ar CH), 1618w, 1597m, 1570w, 1547w, 1510w, 1483s, 1449w, 1435w, 1393w, 1369w, 1333m, 1298s, 1248s, 1240s, 1209s, 1182w, 1144w, 1123w, 1094m, 1051m, 1028m, 1009m, 964w, 939w, 893w, 878m, 839w, 826s, 814s, 795m, 787m, 760m; δ_H (300 MHz, $CDCl_3$) 9.78 (1H, d, *J* 2.3, *H*-9), 7.54 (2H, d, *J* 8.7, Ar *H*), 7.51 (1H, dd, *J* 8.5, 2.3, *H*-7), 7.43 (2H, d, *J* 8.7, Ar *H*), 7.25 (1H, d, *J* 8.5, *H*-6), 5.06 (2H, s, CH_2O); δ_C (125 MHz, $CDCl_3$) 195.2 (C=S), 153.5 (C_q), 146.2 (C_q), 137.8 (C_q), 134.8 (C_q), 133.8 (C_q), 129.1 (Ar CH), 128.1 (Ar CH), 127.2 (Ar CH), 126.4 (C_q), 118.3 (Ar CH), 117.7 (Ar CH), 65.4 (CH_2O); *m*/*z* (EI): 334 (M^++2, 41%), 332 (M^+, 100), 286 (3), 268 (7), 260 (31), 256 (7), 232 (11), 228 (11), 200 (9), 174 (4), 164 (6), 152 (5), 148 (6), 139 (25), 126 (5), 114 (9), 99 (3), 87 (3), 75 (6), 69 (4), 63 (6), 51 (2).

*4.4.4. 8-(3-Nitrophenyl)-4H-[1,2,4]thiadiazolo[3,4-c][1,4]benzoxazine-1-thione (**5d**).* Similar treatment of 8-(3-nitrophenyl)-4*H*-[1,2,4]thiadiazolo[3,4-*c*][1,4]benzoxazin-1-one (**4d**) (100 mg, 0.306 mmol) with P_2S_5 (34.0 mg, 0.153 mmol) in xylene (2 mL) at ca. 140 °C for 12 h gave the *title compound* **5d** (76 mg, 72%) as pale yellow needles, mp (DSC) onset: 238.6 °C, peak max: 239.4 °C (from 1,2-dichloroethane), R_f (DCM) 0.69; found: C, 52.6; H, 2.6; N, 12.2. $C_{15}H_9N_3O_3S_2$ requires C, 52.5; H, 2.6; N, 12.2%; λ_{max} (DCM)/nm 252 (log ε 3.70), 330 (3.23); ν_{max}/cm^{-1} 3094w, 3084w, 3073w, 3015w (Ar CH), 1614w, 1597w, 1558w, 1526m, 1504s, 1477w, 1449w, 1406w, 1352s, 1335s, 1317m, 1308m, 1296s, 1273w, 1242s, 1229s, 1204s, 1179w, 1171w, 1105w, 1088w, 1055m, 1032s, 966w, 928w, 905w, 878m, 856m, 829m, 804m, 785s, 766w; δ_H (300 MHz, DMSO-d_6) 9.86 (1H, d, *J* 2.3, *H*-9), 8.41 (1H, dd, *J* 2.1, *H*-2′), 8.23 (1H, ddd, *J* 8.3, 2.3, 0.9, Ar *H*), 8.09 (1H, ddd, *J* 7.7, 1.7, 0.9, Ar *H*), 7.85 (1H, dd, *J* 8.5, 2.3, *H*-7), 7.80 (1H, dd, *J* 8.3, 8.3, *H*-5′), 7.43 (1H, d, *J* 8.5, *H*-6), 5.32 (2H, s, CH_2O); δ_C (125 MHz, DMSO-d_6) 194.6 (C=S), 154.6 (C_q), 148.4 (C_q), 146.9 (C_q), 140.2 (C_q), 132.5 (Ar CH), 131.7 (C_q), 130.6 (Ar CH), 127.6 (Ar CH), 126.3 (C_q), 122.1 (Ar CH), 120.5 (Ar CH), 118.5 (Ar CH), 116.8 (Ar CH), 65.0 (CH_2O); *m*/*z* (EI): 343 (M^+, 100%), 303 (6), 279 (7), 271 (25), 243 (12), 239 (13), 225 (2), 211 (4), 197 (6), 193 (9), 171 (3), 164 (15), 153 (6), 139 (39), 126 (8), 114 (5), 101 (2), 89 (4), 76 (7), 63 (9), 51 (4).

4.5. X-ray crystallographic studies

Data were collected on an Oxford-Diffraction Supernova diffractometer, equipped with a CCD area detector utilizing Mo Kα radiation (λ=0.71073 Å). Suitable crystals were attached to glass fibres using paratone-N oil and transferred to a goniostat where they were cooled for data collection. Unit cell dimensions were determined and refined by using 14,618 ($3.19 \le \theta \le 28.65°$) and 1944 ($3.00 \le \theta \le 28.60°$) reflections for compounds **3a** and **4a**, respectively. Empirical absorption corrections (multi-scan based on symmetry-related measurements) were applied using CrysAlis RED software.[10] The structures were solved by direct methods using SIR92[11] and refined on F^2 using full-matrix least squares using SHELXL97.[12] Software packages used: CrysAlis CCD[10] for data collection, CrysAlis RED[10] for cell refinement and data reduction, WINGX for geometric calculations[13] and DIAMOND[14] for molecular graphics. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were placed in calculated, ideal positions and refined as riding on their respective carbon atoms.

*4.5.1. Crystal refinement data for compound **3a**.* $C_9H_5BrN_2O_2S$, *M*=285.12, monoclinic, space group $P2_1/n$, *a*=10.4815(2), *b*=7.3094(2), c=12.7848(2) Å, β=93.450(2)°, *V*=977.71(3) Å^3, *Z*=4, *T*=100(2) K, ρ_{calcd}=1.937 g cm^{-3}, $2\theta_{max}$=54. Refinement of 136 parameters on 2246 independent reflections out of 19,667 measured reflections (R_{int}=0.0341) led to R_1=0.0175 [$I>2\sigma(I)$], wR_2=0.0449 (all data), and *S*=1.092 with the largest difference peak and hole of 0.345 and −0.244 e^{-3}, respectively.

*4.5.2. Crystal refinement data for compound **4a**.* $C_9H_5BrN_2O_2S$, *M*=285.12, orthorhombic, space group $P2_12_12_1$, *a*=4.5350(2), *b*=8.0134(3), c=25.4590(7) Å, *V*=925.20(6) Å^3, *Z*=4, *T*=100(2) K, ρ_{calcd}=2.047 g cm^{-3}, $2\theta_{max}$=54. Refinement of 136 parameters on 1852 independent reflections out of 2821 measured reflections (R_{int}=0.0278) led to R_1=0.0358 [$I>2\sigma(I)$], wR_2=0.0860 (all data),

and S=1.048 with the largest difference peak and hole of 0.544 and −0.532 e^{-3}, respectively.

Crystallographic data for compounds **3a** and **4a** have been deposited with the Cambridge Crystallographic Data Centre with deposit numbers CCDC-817083 and CCDC-817084, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

The authors wish to thank the Cyprus Research Promotion Foundation [grant no. ΥΓΕΙΑ/ΒΙΟΣ/0308(ΒΕ)/16] and the following organizations in Cyprus for generous donations of chemicals and glassware: the State General Laboratory, the Agricultural Research Institute, the Ministry of Agriculture and Biotronics Ltd. Furthermore, we thank the A.G. Leventis Foundation for helping to establish the NMR facility in the University of Cyprus.

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