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Reactions of α-mercaptocarboxylic acid hydrazides with triethyl *ortho*esters: synthesis of 1,3,4-thiadiazin-5(6*H*)-ones and 1,3,4-oxadiazoles

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2-(1-Mercaptomethyl)-1,3,4-oxadiazoles
Reduction

ABSTRACT

Reactions of α-mercapto-β-phenylpropionic and α-mercaptophenylacetic acid hydrazides with triethyl *ortho*esters were conducted under N_2 in glacial acetic acid and resulted in the formation of two groups of products, derivatives of 1,3,4-thiadiazin-5(6*H*)-ones and 2-(1-mercaptomethyl)-1,3,4-oxadiazoles. When conducting the same transformations on α-mercaptophenylacetic acid hydrazide in the presence of air, two different products from the 1,3,4-oxadiazole family, the appropriate bis(1,3,4-oxadiazol-2-yl-phenylmethyl) disulfides and 2-benzyl-1,3,4-oxadiazoles, were formed with the liberation of free sulfur. The oxygenated bis(1,3,4-oxadiazol-2-yl-phenylmethyl) disulfides were reduced to the corresponding 2-(1-mercaptomethyl)-1,3,4-oxadiazoles with the use of zinc powder under mild conditions.

1. Introduction

1,3,4-Thiadiazines are an important class of six-membered heterocycles with a broad spectrum of biological activities.[1] Many compounds containing such a scaffold demonstrate excellent cardiotonic, spasmolytic and hypertensive activities.[2] Additionally, compounds of this class are used in the treatment of anaemia, asthma and allergies.[3] Some 1,3,4-thiadiazines are also applied in agriculture as herbicides, fungicides, insecticides or plant-growth regulators.[4] The most commonly reported methodologies for the synthesis of this group of compounds use thiohydrazides and α-halocarbonyl compounds such as α-haloketones, α-haloaldehydes or alkyl-bromoacetates.[5] Other methodologies include the reaction of hydrazonyl chlorides with α-mercaptocarboxylic acid derivatives or the transformations of tetrazines under the influence of thioformate.[6]

1,3,4-Oxadiazoles constitute another interesting class of heterocyclic compounds.[7] They display antibacterial, anticonvulsant, antidepressant, anticancer and antifungal activities, which makes them potentially useful agents for medicine and agriculture.[8] Conjugated macrocyclic arrangements possessing a 1,3,4-oxadiazole backbone exhibit interesting electron-transfer or luminescent properties and are used in organic light-emitting diodes (OLEDs), optical brighteners, and laser dyes.[9] Generally, the most popular methods for preparing 1,3,4-oxadiazole scaffold use acid hydrazides or *N*,*N*′-diacylhydrazines, or they involve transformations of another ring, such as 1,2,4-oxadiazole.[10]

In our previous work on the application of α-substituted acid hydrazides as effective reagents for synthesizing some heterocyclic rings, we obtained different heterocyclic scaffolds, including 1,2,4-triazoles, 1,3,4-oxadiazoles, 1,3,4-oxadiazin-5(6*H*)-ones, 1,2,4-triazin-6(5*H*)-ones and 5(1*H*)-imidazolones.[10c–d,11] The acid hydrazides that were investigated included structures with α-hydroxy, free α-amino, protected α-amino and α-sulfur-containing substituents. The present study was undertaken to investigate another interesting group of acid hydrazides possessing the mercapto functional group. The work reported here describes a convenient and practical methodology for synthesizing of 1,3,4-thiadiazin-5(6*H*)-ones and 2-(1-mercaptomethyl)-1,3,4-oxadiazoles from α-mercaptocarboxylic acid hydrazides and commercially available triethyl *ortho*esters. To the best of our knowledge, the synthesis of six-membered 1,3,4-thiadiazin-5(6*H*)-one derivatives from the above-mentioned reagents has not been previously reported.

2. Results and discussion

The subjects of this study were α-mercapto-β-phenylpropionic acid hydrazide (**5a**) and α-mercaptophenylacetic acid hydrazide (**5b**), which are two acid hydrazides that both possess the reactive mercapto group at the α position. These compounds were prepared according to a few-step procedure from commercially available racemic mixtures of DL-α-phenylalanine (**1a**) and DL-mandelic acid (**1b**).

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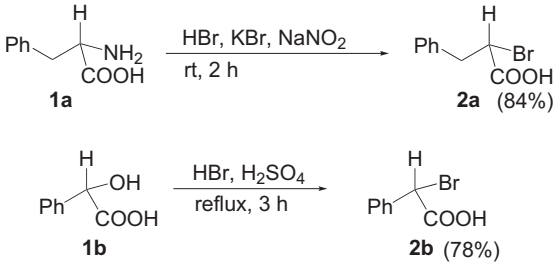
To replace the hydroxyl and amino groups in the starting acids (**1a**–**b**), it was necessary to transform the acidic substrates into the more reactive α-bromo derivatives (**2a**–**b**).[12] The reaction was performed with concentrated HBr, and in the case of DL-α-phenylalanine (**1a**), diazotization was required prior to substitution (Scheme 1).[13]

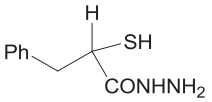
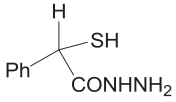


Scheme 1. Synthesis of α-bromocarboxylic acids (**2a**–**b**).

The resulting α-bromocarboxylic acids (**2a**–**b**) were treated with an aqueous solution of NaSH, esterified with methanol and finally treated with hydrazine hydrate to form the desired hydrazides **5a**–**b** in satisfactory yields (Scheme 2). It should be noted that the hydrazide of α-mercaptophenylacetic acid (**5b**) has been briefly mentioned in the literature.[14] However, the only evidence presented by the authors to prove its structure was a melting point (mp 203–204 °C), that differed considerably from the melting point of the product obtained according to our procedure (**5b**, mp 155–157 °C). Because the structure of **5b** was confirmed by elemental analysis and typical spectroscopic methods, the high melting point of the product described in the literature suggests that the previously obtained compound was 1,1′-diphenylthiodiacetic acid dihydrazide (mp 209–210 °C).[11d]

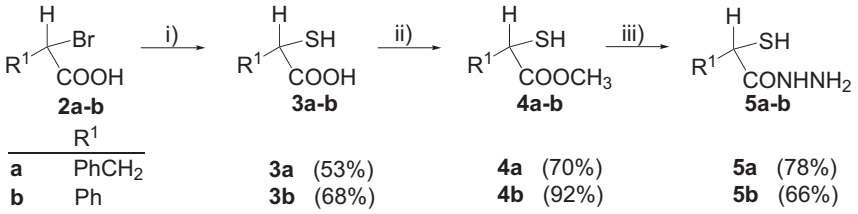
triethyl *ortho*acetate (Table 1, 72–86%). In contrast, the yields of the five-membered 1,3,4-oxadiazoles increased for molecules with larger *ortho*ester substituents R^2 and varied from 15% to 58%. Additionally, the reaction with triethyl *ortho*formate did not result in the formation of the corresponding 1,3,4-oxadiazole but gave only 6-benzyl-1,3,4-thiadiazin-5(6*H*)-one (**6a**), which testifies to the distinct nucleophilic nature of the mercapto group.

Table 1
Products of the reaction of α-mercaptocarboxylic acid (**5a**–**b**) hydrazide with triethyl *ortho*esters

Entry	Hydrazide	R^2	Synthesis A[a]		
			Time [h]	Product **6** yield [%]	Product **7** yield [%]
a	 **5a**	H	8	86	—
b		CH_3	5	72	15
c		C_2H_5	3	52	25
d		Ph	1	24	58
e	 **5b**	H	7	53	20
f		CH_3	5	48	35
g		C_2H_5	5	46	40
h		Ph	3	—	74

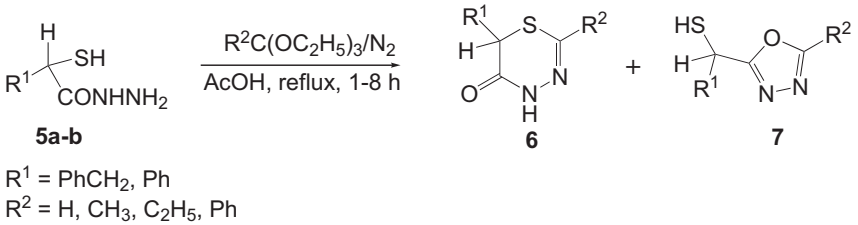
[a] The reaction was conducted in excess of *ortho*ester under N_2 and in AcOH (reflux).

The series of reactions with α-mercaptophenylacetic acid hydrazide (**5b**) produced mixtures of the analogous heterocyclic products, 6-phenyl-1,3,4-thiadiazin-5(6*H*)-ones (**6e**–**g**) and 2-(1-mercapto-1-phenylmethyl)-1,3,4-oxadiazoles (**7e**–**h**). However, the yields of the six-membered derivatives **6e**–**g** were relatively



Scheme 2. Synthesis of α-mercaptocarboxylic acid hydrazides (**5a**–**b**): (i) $NaSH \cdot H_2O$, H_2O, rt, 24 h; (ii) CH_3OH, H_2SO_4, reflux, 6 h; (iii) $N_2H_4 \cdot H_2O$, CH_3OH, 0 °C, 3 h.

The initial experiments involved the reactions of α-mercapto-β-phenylpropionic acid hydrazide (**5a**). Because compounds possessing a free mercapto group are susceptible to oxidation, the trials were conducted under a nitrogen atmosphere.[15] Heating hydrazide **5a** for a few hours with an excess of various triethyl *ortho*esters (R=H, Me, Et, Ph, Scheme 3) in the presence of glacial acetic acid afforded a mixture of six-membered 1,3,4-thiadiazin-5(6*H*)-ones (**6a**–**d**) and five-membered 2-(1-mercaptoethyl)-1,3,4-oxadiazoles (**7a**–**c**). The highest yields for the six-membered derivatives were obtained in the reactions conducted with triethyl *ortho*formate and low compared to the previous reactions conducted with α-mercapto-β-phenylpropionic acid hydrazide (**5a**) and varied from 46 to 53%. This low yield is a result of the proximity of the bulky and electron-withdrawing phenyl group, which decreased the nucleophilicity of the mercapto group and caused steric hindrance. Deactivation was particularly notable in the reaction with triethyl *ortho*benzoate, where no 1,3,4-thiadiazin-5(6*H*)-one was obtained, and the only product, 5-phenyl-2-(1-mercapto-1-phenylmethyl)-1,3,4-oxadiazole (**7h**), was isolated in 74% yield. It is worth mentioning that similar trends were observed previously while studying



Scheme 3. The reaction of hydrazides (**5a**–**b**) with triethyl *ortho*esters under N_2 and in the presence of AcOH (synthesis A).

the reactions of α-hydroxycarboxylic acid hydrazides with triethyl *ortho*esters, where both 1,3,4-oxadiazin-5(6*H*)-ones and 1,3,4-oxadiazoles were formed.[10c] The yields of the six-membered oxygen-containing derivatives were lower than their sulfur-containing counterparts, which reflect the stronger nucleophilicity of the mercapto group relative to the hydroxyl group.

The identities of products were confirmed with elemental analyses and typical spectroscopic methods (^{1}H and ^{13}C NMR, UV, IR). In the ^{1}H NMR spectra of 1,3,4-thiadiazin-5(6*H*)-ones **6**, the diagnostic signal is the singlet corresponding to the proton associated with the ring nitrogen atom at position 4, which is observed between 9.32 and 9.63 ppm. Another characteristic proton adjacent to carbon C6 is seen in the range between 3.70 and 4.70 ppm. The diagnostic signals in the ^{13}C NMR spectra of the six-membered heterocycles **6** belong to carbon C5 from the carbonyl group and the neighbouring carbon C6; these signals are observed in the range of 160–162 ppm for C5 and 40–43 ppm for C6. The structure of one of the 1,3,4-thiadiazin-5(6*H*)-ones was confirmed by X-ray analysis. The displacement ellipsoid drawing of 6-benzyl-2-methyl-1,3,4-thiadiazin-5(6*H*)-one **6b** with the atomic numbering scheme is shown in Fig. 1.

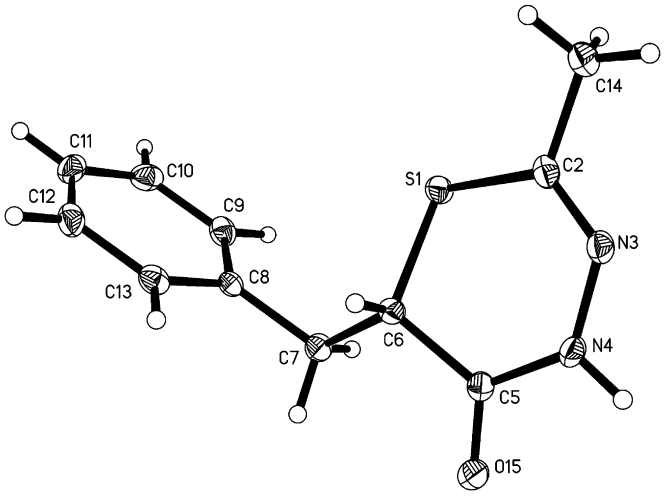
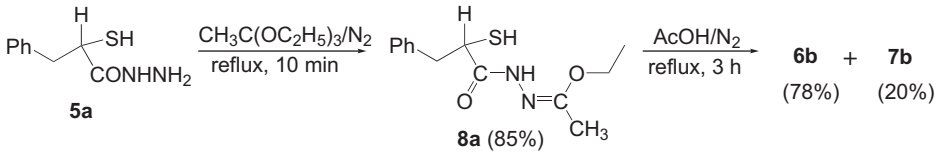


Fig. 1. The molecular structure of 6-benzyl-2-methyl-1,3,4-thiadiazin-5(6*H*)-one (**6b**), showing 50% displacement ellipsoids (arbitrary spheres for the H atoms).

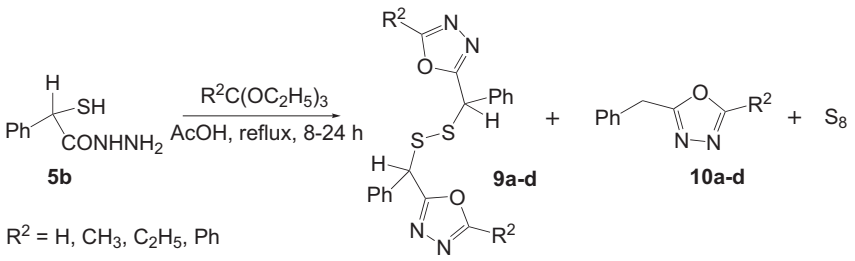
Previous studies on the synthesis of *N*-protected 2-aminom ethyl-1,3,4-oxadiazole derivatives via the reaction of *N*-protected phenylglycine hydrazides and triethyl *ortho*esters showed that the reactions proceeded through derivatives of N^2-ethoxymethylene-α-*N*-BOC-amino acid hydrazide. These stable acyclic intermediates underwent further cyclization to the corresponding 1,3,4-oxadiazoles in an acidic medium at elevated temperatures.[11b] In contrast to the protected scaffold, the hydrazides of free α-amino-carboxylic acids converted directly to heterocyclic compounds without forming any stable acyclic intermediates.[11c] To determine if α-mercapto substituted compounds could also form stable acyclic intermediates, hydrazide **5a** was heated for a short time in triethyl *ortho*acetate, which led to the appropriate acyclic product, N^2-(1-ethoxyethylene)-2-mercapto-3-phenylpropionic acid hydrazide (**8a**). This product then underwent subsequent cyclization in glacial acetic acid to form 1,3,4-thiadiazin-5(6*H*)-one (**6b**) and 2-(1-mercaptoethyl)-1,3,4-oxadiazole (**7b**) (Scheme 4).

Different results were obtained when the reactions between α-mercaptophenylacetic acid hydrazide (**5b**) and triethyl *ortho*esters were conducted under air. Heating for a few hours in glacial acetic acid resulted in the formation of the five-membered heterocyclic products, bis(1,3,4-oxadiazol-2-yl-phenylmethyl) disulfides (**9a**–**d**) and 2-benzyl-1,3,4-oxadiazoles (**10a**–**d**) (Scheme 5, Table 2) with the liberation of free sulfur. The presence of the latter was confirmed by the reaction with Ph_3P.[16] Althought the production of disulfides **9** might be generally explained by oxidation processes,[15a,b] the formation of 2-benzyl-1,3,4-oxadiazoles was quite unexpected. Additionally, no traces of the six-membered heterocyclic products were found in the post-reaction mixture, which provided evidence for the fast deactivation of the nucleophilic mercapto group under these reaction conditions. Thus, it was concluded that the simultaneous formation of both disulfide derivatives **9a**–**d** and 2-benzyl-1,3,4-oxadiazoles **10a**–**g** is the result of disproportionation, which might occur with starting hydrazide **5b**, acyclic intermediate **8** or the oxidized form of **8**. Similar observations were made during studies on the reactions of 1,1′-diphenylthiodiacetic acid dihydrazide with triethyl *ortho*esters, where the appropriate 2-benzyl-1,3,4-oxadiazoles were also produced.[11d]

To establish the structures of derivatives **9**, X-ray analysis was performed. The molecular structure of bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenylmethyl) disulfide **9c** with the atomic numbering scheme is shown in Fig. 2. The absolute configurations of the two stereogenic

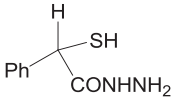


Scheme 4. The reaction of hydrazide **5a** with triethyl *ortho*acetate under N_2 and the following cyclization in AcOH.



Scheme 5. The reaction of hydrazide (**5b**) with triethyl *ortho*esters under air and in the presence of AcOH (synthesis B).

Table 2
Products of the reaction of α-mercaptocarboxylic acid hydrazide (**5b**) with triethyl *ortho*esters

Entry	Hydrazide	R^2	Synthesis B[a]		
			Time [h]	Product **9** yield [%]	Product **10** yield [%]
a	 **5b**	H	24	30	28
b		CH_3	15	33	24
c		C_2H_5	15	35	27
d		Ph	8	42	35

[a] The reaction was conducted with the use of **5b** in excess of *ortho*ester under air and in AcOH (reflux).

a symmetrical structure. The most characteristic peak is associated with the proton adjacent to the carbon atom, that is, directly attached to the bridging sulfur atoms –S–S–, which appears as a singlet in the range of 5.12–5.36 ppm. The carbon atom mentioned above is observed in the ^{13}C NMR spectra at approximately 50 ppm.

We then investigated which of the previously mentioned compounds underwent carbon–sulfur fission upon formation of a benzyl derivative. Initial trials with hydrazide **5b** revealed that it is quite stable and does not undergo fission. It reacted readily with refluxing glacial AcOH, yielding N^2-acetyl-α-mercaptophenylacetic acid hydrazide (**11**), and heating for a short time with triethyl *ortho*acetate gave N^2-(1-ethoxyethylene)-α-mercaptophenylacetic acid hydrazide (**8b**) in satisfactory yield (Scheme 6). ^1H NMR spectroscopic analysis of **8b** showed twice the number of expected peaks due to the presence of *syn* and *anti* forms.

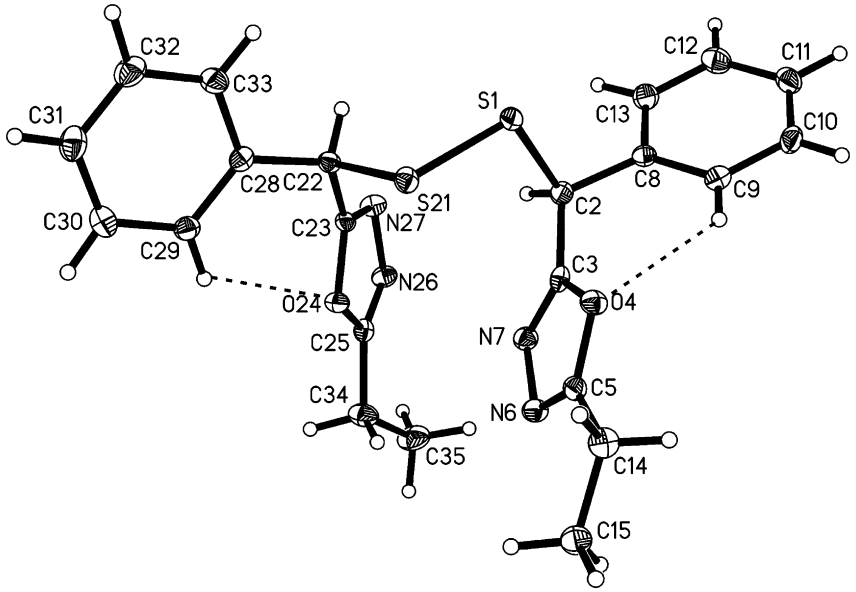
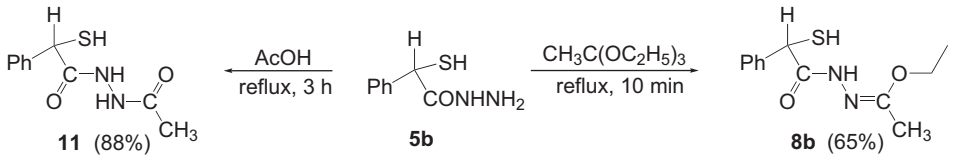


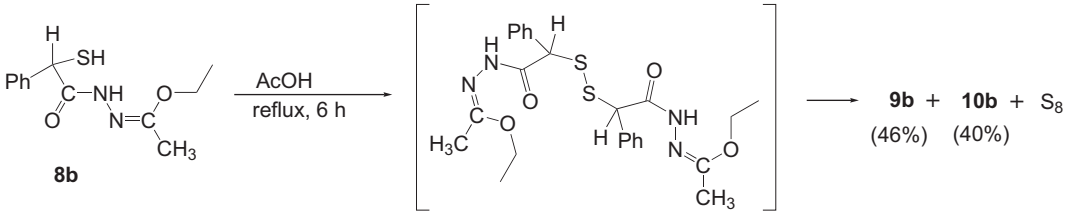
Fig. 2. The molecular structure of bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenylmethyl) disulfide **9c**, showing 50% displacement ellipsoids (arbitrary spheres for the H atoms). Dashed lines indicate intramolecular hydrogen bonds.



Scheme 6. The transformations of hydrazide **5b** in different media.

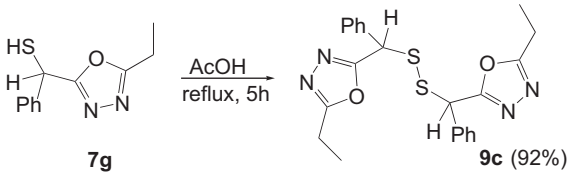
centres C2 and C22 were determined to be (*S*,*R*), which means that the analyzed crystal is the *meso* form.[19] The ^1H NMR spectra of bis(1,3,4-oxadiazol-2-yl-phenylmethyl) disulfides **9** show a reduced number of proton signals because these compounds possess

Further experiments on N^2-(1-ethoxyethylene)-α-mercaptophenylacetic acid hydrazide (**8b**) showed that considerable amounts of fission occurred upon heating this intermediate in glacial AcOH for a few hours (Scheme 7).



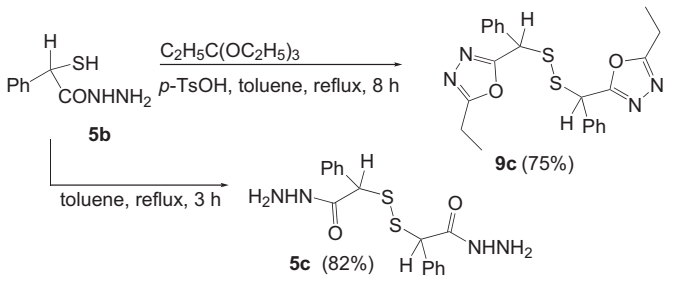
Scheme 7. The transformation of N^2-(1-ethoxyethylene)-2-mercapto-2-phenylacetic acid hydrazide (**8b**) in the presence of AcOH.

Finally, it was necessary to determine if 2-mercaptomethyl-1,3,4-oxadiazoles (**7**), the title cyclocondensation products that were obtained in the reactions conducted under nitrogen, undergo carbon–sulfur fission. Heating 2-mercaptomethyl-1,3,4-oxadiazole **7g** in glacial AcOH at reflux led exclusively to the oxygenated product, disulfide **9c** (Scheme 8). This led to the conclusion that only the extended arrangements possessing an electron-withdrawing phenyl group and a hydrogen at the α-carbon atom can easily undergo fission, yielding 2-benzyl-1,3,4-oxadiazoles (**10**) and the appropriate 1,3,4-oxadiazole-containing disulfides (**9**) with the liberation of free elemental sulfur. Similar observations were made earlier for (α-benzoylmethylthio)acetic acid derivatives and other related compounds.[17]



Scheme 8. The transformation of **7g** in the presence of AcOH.

An additional experiment was run using a different solvent and catalyst to investigate whether this would influence the transformation. Glacial acetic acid, which plays the dual role of both polar solvent and catalyst, was replaced with toluene and *p*-toluenesulfonic acid, producing symmetrically substituted disulfide **9c** (Scheme 9) as the main reaction product. Under these conditions, no traces of 2-benzyl-1,3,4-oxadiazole (**10c**) were found in the post-reaction mixture.

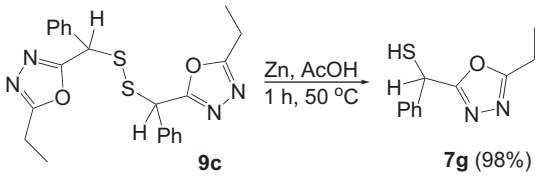


Scheme 9. The reaction of hydrazide (**5b**) in different media.

In summary, acyclic N^2-(1-ethoxyethylene)-α-mercaptocarboxylic acid hydrazides (**8**), which possess an electron-withdrawing phenyl group and a hydrogen α to the carbonyl group, undergo simultaneous cyclization and disproportionation when heated with triethyl *ortho*esters in a polar solvent (glacial AcOH) in the presence of air. Carbon–sulfur fission resulted in the formation of elemental sulfur and two products from the 1,3,4-oxadiazole family, the appropriate oxygenated form of bis(1,3,4-oxadiazol-2-yl-phenylmethyl) disulfide (**9**) and the reduced 2-benzyl-1,3,4-oxadiazole (**10**). A similar transformation was not observed for reactions conducted with hydrazide **5a**, in which the reactive benzyl group is separated from the carbonyl by an additional methylene group.

The last stage of the study involved the cleavage of symmetrical disulfides **9**. According to the literature, the reduction of this group can be accomplished with a range of reducing agents, including zinc or tin in acetic acid, hydrogen sodium telluride in ethanol, diethylphosphinoethane in tetrahydrofuran, sodium in liquid ammonia or $NaBH_4$.[18]

Zinc powder in glacial acetic acid, a versatile and common reducing agent, was reacted with bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenylmethyl) disulfide (**9c**). Heating of the reaction mixture for 1 h under mild conditions resulted in the formation of 5-ethyl-2-(1-mercapto-1-phenylmethyl)-1,3,4-oxadiazole (**7g**) in excellent yield (98%, Scheme 10).



Scheme 10. The reduction of disulfide **9c** with zinc powder in AcOH.

3. Conclusions

The reported procedure, which makes use of α-mercaptocarboxylic acid hydrazides and triethyl *ortho*esters, offers a novel, facile and effective way to synthesize both six-membered 1,3,4-thiadiazin-5(6*H*)-ones and 2-(1-mercaptomethyl)-1,3,4-oxadiazoles. The acyclic products, N^2-(1-ethoxyethylene)-2-mercapto-2-phenylacetic acid hydrazides, when heated in glacial acetic acid and in the presence of air, undergo disproportionation with carbon–sulfur fission to produce the corresponding bis(1,3,4-oxadiazol-2-yl-phenylmethyl)disulfides, 2-benzyl-1,3,4-oxadiazoles and free sulfur. Bis(1,3,4-oxadiazol-2-yl-phenylmethyl) disulfides may be easily reduced to the corresponding 2-(1-mercaptomethyl)-1,3,4-oxadiazoles with the use of zinc powder under mild conditions.

4. Experimental

4.1. General

Melting points were measured using a Stuart SMP3 melting point apparatus. UV spectra were recorded on a Shimadzu UV-2102 spectrophotometer. Elemental analyses were performed with a VarioEL analyser in PAN Zabrze. The ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 300 and Varian 600 spectrometers in DMSO or $CDCl_3$ solutions using TMS as an internal standard. FTIR spectra were recorded between 4000 and 650 cm^{-1} on an FTIR Nicolet 6700 apparatus with a Smart iTR accessory. Thin layer chromatography was performed on silica gel 60 F_{254} (Merck) thin layer chromatography plates.

4.2. Synthesis of α-bromo-β-phenylpropionic acid 2a

DL-Phenylalanine **1a** (29.7 g; 0.18 mol) was gradually introduced into a mixture of 40% HBr (130 mL), KBr (90.0 g, 0.75 mol), and water (300 mL), which was then cooled to 0 °C. Next, a solution of $NaNO_2$ (23.7 g, 0.375 mol) in 60 mL of water was added dropwise over a period of 30 min. The reaction mixture was stirred at room temperature for 2 h, extracted twice with diethyl ether (2×200 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator. The crude product was distilled under reduced pressure, yielding pure α-bromo-β-phenylacetic acid **2a** as a yellow oil. The product was then crystallised from a hexane/benzene mixture yielding light-yellow crystals (34.2 g, 83% yield), mp 46–48 °C (lit.:[20] mp 50 °C), R_f (benzene/ethyl acetate/AcOH 5:1:1 v/v/v) 0.50.

4.3. Synthesis of α-bromophenylacetic acid 2b

DL-Mandelic acid **1b** (30.4 g; 0.20 mol) was gradually introduced into a solution of 40% HBr (56 mL) and concentrated

H_2SO_4 (22 mL). The mixture was refluxed for 3 h, cooled and poured onto ice (150 g). The solution was then extracted twice with diethyl ether (2×75 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator. The remaining brown solution was distilled under reduced pressure. The crude product was crystallised from hexane, yielding pure α-bromophenylacetic acid **2b** as light-yellow crystals (33.5 g, 78% yield), mp 83–84 °C (lit.:[12] mp 68–69 °C), R_f (benzene/ethyl acetate/AcOH, 1:3:1 v/v/v) 0.70.

4.4. General procedure for the preparation of α-mercaptocarboxylic acids 3a–b

A solution of 23.2 g (315 mmol) of $NaSH \cdot H_2O$ in 300 mL of water was cooled to −5 °C, α-bromocarboxylic acid **2a**–**2b** (150 mmol) was slowly added and the reaction mixture was stirred for 12 h. The reaction was then heated for 2 h on a steam bath, cooled and treated with 10 mL of 30% H_2SO_4. The cold mixture was washed with diethyl ether (3×50 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator. The crude product was distilled under reduced pressure to yield pure acid **3a**–**b** as a thin, vile-smelling oil.

*4.4.1. α-Mercapto-β-phenylpropionic acid (**3a**).* Colourless oil (14.5 g, 53% yield); bp 200–204 °C/25 Torr; mp 46–48 °C (lit.:[21] mp 48–49 °C); R_f (benzene/ethyl acetate/AcOH, 5:1:1 v/v/v) 0.44; δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.15 (1H, d, *J* 8.7 Hz, SH), 3.00 (1H, dd, *J* 8.1 Hz and 13.8 Hz, Ph–CH_2–), 3.24 (1H, dd, *J* 8.1 Hz and 13.8 Hz, Ph–CH_2–), 3.61 (1H, q, *J* 8.1 Hz, CH), 7.18–7.31 (5H, m, Ph), 11.10 (1H, br s, COOH); δ_C ($CDCl_3$) 41.0, 42.1, 127.0, 128.4, 128.9, 137.2, 178.9.

*4.4.2. α-Mercaptophenylacetic acid (**3b**).* Yellow oil (17.2 g, 68% yield); bp 174–178 °C/10 Torr (lit.:[22] bp 148 °C/3 Torr); R_f (benzene/ethyl acetate/AcOH, 1:3:1 v/v/v) 0.56; δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.69 (1H, d, *J* 7.8 Hz, SH), 4.78 (1H, d, *J* 7.8 Hz, CH), 7.35–7.55 (5H, m, Ph), 11.50 (1H, br s, COOH); δ_C ($CDCl_3$) 45.7, 127.7, 128.9, 129.2, 134.2, 178.0.

4.5. General procedure for the preparation of methyl α-mercaptocarboxylate 4a–b

α-Mercaptocarboxylic acid **3a**–**b** (100 mmol), 100 mL of methanol and concentrated H_2SO_4 (2 mL) were heated under reflux for 6 h. The methanol was then removed on a rotary evaporator. The residue was dissolved in 150 mL of diethyl ether, washed with a saturated aqueous Na_2CO_3 solution (50 mL) and then washed with water (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated on the rotary evaporator, yielding crude methyl α-mercaptocarboxylate **4a**–**b** as colourless oil. The crude product was distilled under reduced pressure to yield pure ester **4a**–**b**.

*4.5.1. Methyl α-mercapto-β-phenylpropionate (**4a**).* Colourless oil (13.7 g, 70% yield); bp 106–110 °C/4 Torr (lit.:[23] bp 100–105 °C/2 Torr); R_f (benzene/ethyl acetate, 1:3 v/v) 0.66; δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.12 (1H, d, *J* 9.0 Hz, SH), 3.01 (1H, dd, *J* 7.5 Hz and 13.8 Hz, Ph–CH_2–), 3.24 (1H, dd, *J* 7.5 Hz and 13.8 Hz, Ph–CH_2–), 3.58 (1H, m, CH), 3.66 (3H, s, OCH_3), 7.17–7.32 (5H, m, Ph); δ_C ($CDCl_3$) 41.7, 42.2, 52.4, 126.9, 128.4, 128.9, 137.6, 173.1.

*4.5.2. Methyl α-mercaptophenylacetate (**4b**).* Colourless oil (16.7 g, 92% yield); bp 118–120 °C/4 Torr (lit.:[24] bp 134–142 °C/0.4 Torr); R_f (benzene/ethyl acetate, 1:3 v/v) 0.75; δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.59 (1H, d, *J* 7.8 Hz, SH), 3.73 (3H, s, OCH_3), 4.69 (1H, d, *J* 7.8 Hz, CH), 7.29–7.45 (5H, m, Ph); δ_C ($CDCl_3$) 45.4, 52.8, 127.6, 128.0, 128.6, 138.1, 171.7.

4.6. General procedure for the preparation of α-mercaptocarboxylic acid hydrazide 5

Methyl α-mercaptocarboxylate **4a**–**b** (90 mmol) was dissolved in 15 mL of methanol, cooled to −5 °C and treated with 18 mL (360 mmol) of hydrazine hydrate. The mixture was agitated at 0 °C for 24 h, diluted with 120 mL of methanol and saturated with CO_2 until the precipitation of gummy hydrazine carbonate was completed. The supernatant solution was concentrated on a rotary evaporator to yield the crude hydrazide **5**, which was crystallised from water–methanol solution.

*4.6.1. α–Mercapto-β-phenylpropionic acid hydrazide (**5a**).* White solid (13.7 g, 78% yield); mp 129–131 °C, R_f (benzene/ethyl acetate, 1:3 v/v) 0.25; [Found: C, 54.99; H, 6.11; N, 14.29. $C_9H_{12}N_2OS$ requires C, 55.07; H, 6.17; N, 14.26%]; λ_{max} (MeOH): 205 nm ($\varepsilon \times 10^{-3}$ 15.17 $cm^{-1}M^{-1}$); δ_H (300 MHz, DMSO-d_6, Me_4Si) 2.82 (1H, dd, *J* 7.8 Hz and 13.8 Hz, Ph–CH_2–), 3.10 (1H, dd, *J* 7.8 Hz and 13.8 Hz, Ph–CH_2–), 3.32 (1H, br s, SH), 3.46 (1H, m, CH), 4.19 (2H, br s, NH_2), 7.15–7.28 (5H, m, Ph), 9.12 (1H, br s, NH); δ_C (DMSO-d_6) 41.0, 41.6, 126.4, 128.1, 129.0, 138.6, 170.9; ν_{max} (ATR) 3300, 3146, 3024, 2921, 2711, 2549, 2024, 1650, 1628, 1603, 1526, 1491, 1454, 1373, 1317, 1292, 1184, 1126, 1077, 1028, 984, 894, 844, 791, 750, 729, 679 cm^{-1}.

*4.6.2. α-Mercaptophenylacetic acid hydrazide (**5b**).* White solid (10.8 g, 66% yield); mp 155–157 °C (lit.:[14] mp 203–204 °C); R_f (MeOH/$CHCl_3$, 1:1 v/v) 0.74; [Found: C, 53.75; H, 5.50; N, 15.31. $C_8H_{10}N_2OS$ requires C, 53.81; H, 5.54; N, 15.36%]; λ_{max} (MeOH): 206 nm ($\varepsilon \times 10^{-3}$ 18.90 $cm^{-1}M^{-1}$); δ_H (300 MHz, DMSO-d_6, Me_4Si) 3.33 (1H, d, *J* 7.5 Hz, SH), 4.40 (2H, br s, NH_2), 4.61 (1H, d, *J* 7.5 Hz, CH), 7.26–7.44 (5H, m, Ph), 9.47 (1H, br s, NH); δ_C (DMSO-d_6) 57.2, 128.8, 129.0, 129.3, 137.2, 168.8; ν_{max} (ATR) 3274, 3028, 2547, 1651, 1603, 1522, 1492, 1453, 1359, 1317, 1239, 1185, 1135, 1076, 1030, 1013, 1001, 960, 852, 803, 772, 726, 690 cm^{-1}.

4.7. General procedure for the reactions of α-mercaptocarboxylic acid hydrazides with triethyl *ortho*esters

Synthesis A- The starting hydrazide **5a**–**b** (11 mmol) was added to a mixture of the appropriate triethyl *ortho*ester (22 mmol) and 4 mL (4.00 g, 70 mmol) of glacial AcOH. The mixture was flushed with N_2 and then refluxed under N_2 until the starting hydrazide was fully consumed (monitored by TLC, 1–8 h). After cooling and filtering, the excess *ortho*ester and AcOH were evaporated under reduced pressure. The crude products were purified by column chromatography using silica gel and an eluent of benzene/AcOEt (1:3).

*4.7.1. 6-Benzyl-1,3,4-thiadiazin-5(6H)-one (**6a**).* Colourless solid (1.95 g, 86% yield); mp 98–100 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.62; [Found: C, 58.17; H, 4.85; N, 13.54. $C_{10}H_{10}N_2OS$ requires C, 58.22; H, 4.89; N, 13.57%]; λ_{max} (MeOH): 205 nm ($\varepsilon \times 10^{-3}$ 17.46 $cm^{-1}M^{-1}$), 256 (2.11), 291 (3.00); δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.84 (1H, dd, *J* 5.1 Hz and 14.1 Hz, C6–CH_2), 3.33 (1H, dd, *J* 5.1 Hz and 14.1 Hz, C6–CH_2), 3.70 (1H, m, C6–H), 7.19–7.30 (5H, m, Ph), 7.47 (1H, s, C2–H), 9.55 (1H, s, NH); δ_C ($CDCl_3$) 37.0, 40.5, 127.3, 128.6, 129.3, 134.3, 135.8, 161.2; ν_{max} (ATR) 3200, 3086, 3032, 2929, 2163, 1639, 1581, 1496, 1474, 1454, 1371, 1339, 1261, 1223, 1149, 1078, 1045, 1031, 955, 933, 872, 848, 784, 734, 694 cm^{-1}.

*4.7.2. 6-Benzyl-2-methyl-1,3,4-thiadiazin-5(6H)-one (**6b**).* Colourless solid (1.74 g, 72% yield); mp 110–112 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.60; [Found: C, 59.95; H, 5.45; N, 12.67. $C_{11}H_{12}N_2OS$ requires C, 59.97; H, 5.50; N, 12.71%]; λ_{max} (MeOH): 207 nm ($\varepsilon \times 10^{-3}$ 16.85 $cm^{-1}M^{-1}$), 287 (3.95); δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.17 (3H, s, C2–CH_3), 2.85 (1H, dd, *J* 4.5 Hz and 14.1 Hz,

C6–CH_2), 3.32 (1H, dd, *J* 4.5 Hz and 14.1 Hz, C6–CH_2), 3.67 (1H, m, C6–H), 7.18–7.36 (5H, m, Ph), 9.32 (1H, s, NH); δ_C ($CDCl_3$) 23.9, 37.0, 41.0, 127.2, 128.5, 129.3, 136.1, 144.5, 161.3; ν_{max} (ATR) 3187, 3110, 3032, 2911, 2162, 1949, 1734, 1660, 1602, 1495, 1479, 1451, 1373, 1354, 1332, 1306, 1259, 1223, 1148, 1079, 1039, 1024, 944, 912, 808, 776, 745, 733, 695 cm^{-1}.

*4.7.3. 2-1-Mercapto-2-phenylethyl-5-methyl-1,3,4-oxadiazole (**7b**).* Colourless oil (0.36 g, 15% yield); R_f (benzene/ethyl acetate, 1:3 v/v) 0.44; [Found: C, 59.88; H, 5.42; N, 12.65. $C_{11}H_{12}N_2OS$ requires C, 59.97; H, 5.50; N, 12.71%]; λ_{max} (MeOH): 207 nm ($\varepsilon\times10^{-3}$ 17.31 $cm^{-1}M^{-1}$); δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.24 (1H, d, *J* 7.8 Hz, SH), 2.51 (1H, s, CH_3), 3.24 (1H, dd, *J* 7.8 Hz and 14.1 Hz, Ph–CH_2), 3.46 (1H, dd, *J* 7.8 Hz and 14.1 Hz, Ph–CH_2), 4.38 (1H, q, *J* 7.8 Hz, C2–CH), 7.17–7.29 (5H, m, Ph); δ_C ($CDCl_3$) 10.9, 42.2, 47.5, 127.2, 128.6, 129.0, 136.8, 164.0, 167.5; ν_{max} (ATR) 3028, 2927, 2569, 1671, 1588, 1561, 1494, 1454, 1437, 1390, 1347, 1222, 1078, 1030, 973, 954, 749, 732, 698, 666 cm^{-1}.

*4.7.4. 6-Benzyl-2-ethyl-1,3,4-thiadiazin-5(6H)-one (**6c**).* Colourless solid (1.34 g, 52% yield); mp 65–67 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.66; [Found: C, 61.46; H, 5.99; N, 11.91. $C_{12}H_{14}N_2OS$ requires C, 61.50; H, 6.03; N, 11.95%]; λ_{max} (MeOH): 207 nm ($\varepsilon\times10^{-3}$ 17.19 $cm^{-1}M^{-1}$), 286 (3.64); δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.18 (3H, t, *J* 7.2 Hz, C2–CH_2CH_3), 2.45 (2H, q, *J* 7.2 Hz, C2–CH_2CH_3), 2.83 (1H, dd, *J* 4.8 Hz and 14.1 Hz, C6–CH_2), 3.30 (1H, dd, *J* 4.8 Hz and 14.1 Hz, C6–CH_2), 3.68 (1H, m, C6–H), 7.19–7.36 (5H, m, Ph), 9.37 (1H, s, NH); δ_C ($CDCl_3$) 11.5, 31.2, 37.1, 40.9, 127.2, 128.5, 129.3, 136.1, 149.6, 161.5; ν_{max} (ATR) 3192, 3105, 3065, 2974, 2899, 2162, 1950, 1655, 1604, 1495, 1452, 1377, 1351, 1332, 1316, 1259, 1228, 1179, 1133, 1079, 1063, 1038, 1024, 961, 916, 810, 770, 732, 695 cm^{-1}.

*4.7.5. 5-Ethyl-2-(1-mercapto-2-phenylethyl)-1,3,4-oxadiazole (**7c**).* Colourless oil (0.64 g, 25% yield); R_f (benzene/ethyl acetate, 1:3 v/v) 0.58; [Found: C, 61.43; H, 5.95; N, 11.89. $C_{12}H_{14}N_2OS$ requires C, 61.50; H, 6.03; N, 11.95%]; λ_{max} (MeOH): 206 nm ($\varepsilon\times10^{-3}$ 17.28 $cm^{-1}M^{-1}$); δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.24 (3H, t, *J* 7.2 Hz, C5–CH_2CH_3), 2.14 (1H, d, *J* 7.2 Hz, SH), 2.75 (2H, q, *J* 7.2 Hz, C5–CH_2CH_3), 3.17 (1H, dd, *J* 7.2 Hz and 13.8 Hz, Ph–CH_2), 3.36 (1H, dd, *J* 7.2 Hz, 13.8 Hz, Ph–CH_2), 4.30 (1H, q, *J* 7.2 Hz, C2–CH), 7.10–7.25 (5H, m, Ph); δ_C ($CDCl_3$) 10.6, 19.1, 42.3, 47.6, 127.3, 128.6, 129.1, 136.8, 164.7, 167.3; ν_{max} (ATR) 3028, 2981, 2939, 2569, 1670, 1581, 1559, 1494, 1454, 1380, 1259, 1184, 1064, 1029, 981, 958, 799, 746, 698 cm^{-1}.

*4.7.6. 6-Benzyl-2-phenyl-1,3,4-thiadiazin-5(6H)-one (**6d**).* Colourless solid (0.74 g, 24% yield); mp 85–87 °C; R_f (benzene/ethyl acetate, 5:1 v/v) 0.46; [Found: C, 68.01; H, 4.96; N, 9.86. $C_{16}H_{14}N_2OS$ requires C, 68.05; H, 5.00; N, 9.91%]; λ_{max} (MeOH): 204 nm ($\varepsilon\times10^{-3}$ 31.35 $cm^{-1}M^{-1}$), 251 (14.16), 275 (11.56), 312 (8.38); δ_H (600 MHz, $CDCl_3$, Me_4Si) 2.84 (1H, dd, *J* 5.4 Hz and 13.8 Hz, C6–CH_2), 3.36 (1H, dd, *J* 5.4 Hz and 13.8 Hz, C6–CH_2), 3.77 (1H, dd, *J* 5.4 Hz and 13.8 Hz, C6–H), 7.21 (2H, d, *J* 8.4 Hz, C6–Ph: H2″, H6″), 7.28–7.35 (3H, m, C6–Ph: H3″, H4″, H5″), 7.39–7.44 (3H, m, C2–Ph: H3′, H4′, H5′), 7.21 (2H, d, *J* 8.4 Hz, C6–Ph: H2″, H6″), 7.81 (2H, d, *J* 7.8 Hz, C2–Ph: H2′, H6′), 9.63 (1H, s, NH); δ_C ($CDCl_3$) 36.4, 41.4, 127.3, 127.4, 128.3, 128.6, 128.7, 129.5, 130.9, 134.7, 136.1, 145.5, 162.2; ν_{max} (ATR) 3193, 3096, 2922, 2164, 1948, 1647, 1585, 1568, 1492, 1481, 1454, 1446, 1359, 1336, 1312, 1260, 1149, 1117, 1075, 1039, 1001, 961, 923, 809, 761, 745, 690 cm^{-1}.

*4.7.7. 2-(1-Mercapto-2-phenylethyl)-5-phenyl-1,3,4-oxadiazole (**7d**).* Colourless oil (1.80 g, 58% yield); R_f (benzene/ethyl acetate, 5:1 v/v) 0.59; [Found: C, 67.92; H, 4.95; N, 9.84. $C_{16}H_{14}N_2OS$ requires C, 68.05; H, 5.00; N, 9.91%]; λ_{max} (MeOH): 205 nm ($\varepsilon\times10^{-3}$ 41.69 $cm^{-1}M^{-1}$), 254 (29.72); δ_H (600 MHz, $CDCl_3$, Me_4Si) 2.24 (1H, d, *J* 7.8 Hz, SH), 3.24 (1H, dd, *J* 7.8 Hz and 14.4 Hz, Ph–CH_2), 3.45 (1H, dd, *J* 7.8 Hz and 14.4 Hz, Ph–CH_2), 4.40 (1H, q, *J* 7.8 Hz, C2–CH), 7.12–7.25 (5H, m, Ph), 7.32–7.44 (3H, m, C5–Ph: H3′, H4′, H5′), 7.93 (2H, d, *J* 7.8 Hz, C5–Ph: H2′, H6′); δ_C ($CDCl_3$) 35.3, 42.4, 47.5, 123.6, 127.0, 127.3, 128.3, 128.7, 129.0, 131.9, 136.8, 164.9, 167.3; ν_{max} (ATR) 3063, 3028, 2915, 2569, 1714, 1608, 1559, 1541, 1490, 1449, 1372, 1273, 1228, 1175, 1157, 1092, 1070, 964, 946, 925, 843, 777, 748, 727, 698, 685 cm^{-1}.

*4.7.8. 6-Phenyl-1,3,4-thiadiazin-5(6H)-one (**6e**).* Colourless solid (1.12 g, 53% yield); mp 166–168 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.56; [Found: C, 56.18; H, 4.17; N, 14.50. $C_9H_8N_2OS$ requires C, 56.22; H, 4.20; N, 14.56%]; λ_{max} (MeOH): 204 nm ($\varepsilon\times10^{-3}$ 19.06 $cm^{-1}M^{-1}$), 294 (2.25); δ_H (300 MHz, DMSO-d_6, Me_4Si) 4.99 (1H, s, C6–H), 7.24–7.40 (5H, m, Ph), 7.86 (1H, s, C2–H), 10.12 (1H, s, NH); δ_C (DMSO-d_6) 42.3, 127.6, 128.8, 129.1, 135.3, 153.8, 159.2; ν_{max} (ATR) 3194, 2962, 2163, 1959, 1652, 1581, 1494, 1454, 1366, 1259, 1148, 1074, 1017, 928, 797, 730, 694 cm^{-1}.

*4.7.9. 2-(1-Mercapto-1-phenylmethyl)-1,3,4-oxadiazole (**7e**).* Colourless oil (0.42 g, 20% yield); R_f (benzene/ethyl acetate, 1:3 v/v) 0.63; [Found: C, 56.14; H, 4.15; N, 14.48. $C_9H_8N_2OS$ requires C, 56.22; H, 4.20; N, 14.56%]; δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.04 (1H, br s, SH), 5.21 (1H, br s, CH), 7.26–7.39 (5H, m, Ph), 8.42 (1H, s, H–C5); δ_C ($CDCl_3$) 50.1, 128.7, 128.9, 129.1, 133.6, 154.8, 167.5; λ_{max} (MeOH): 204 nm ($\varepsilon\times10^{-3}$ 22.83 $cm^{-1}M^{-1}$); ν_{max} (ATR) 3138, 3119, 2954, 2569, 2162, 1978, 1563, 1510, 1495, 1455, 1326, 1302, 1231, 1092, 1077, 1028, 1003, 972, 958, 899, 849, 730, 712, 695 cm^{-1}.

*4.7.10. 2-Methyl-6-phenyl-1,3,4-thiadiazin-5(6H)-one (**6f**).* Colourless solid (1.09 g, 48% yield); mp 158–160 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.58; [Found: C, 58.19; H, 4.83; N, 13.60. $C_{10}H_{10}N_2OS$ requires C, 58.22; H, 4.89; N, 13.57%]; λ_{max} (MeOH): 205 nm ($\varepsilon\times10^{-3}$ 17.15 $cm^{-1}M^{-1}$), 288 (2.85); δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.20 (3H, s, C2–CH_3), 4.64 (1H, s, C6–H), 7.29–7.38 (5H, m, Ph), 9.40 (1H, s, NH); δ_C ($CDCl_3$) 23.8, 42.9, 127.5, 128.6, 129.0, 135.4, 144.9, 160.0; ν_{max} (ATR) 3193, 3070, 2943, 2161, 1980, 1655, 1598, 1498, 1459, 1430, 1378, 1367, 1330, 1301, 1249, 1177, 1157, 1126, 1080, 1029, 1004, 977, 928, 899, 866, 853, 801, 747, 699, 668 cm^{-1}.

*4.7.11. 2-(1-Mercapto-1-phenylmethyl)-5-methyl-1,3,4-oxadiazole (**7f**).* Colourless oil (0.79 g, 35% yield); R_f (benzene/ethyl acetate, 1:3 v/v) 0.43; [Found: C, 58.16; H, 4.81; N, 13.51. $C_{10}H_{10}N_2OS$ requires C, 58.22; H, 4.89; N, 13.57%]; δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.81 (3H, s, C2–CH_3), 2.49 (1H, d, *J* 7.2 Hz, SH), 5.61 (1H, d, *J* 7.2 Hz, CH), 7.21–7.41 (5H, m, Ph); δ_C (DMSO-d_6) 10.3, 48.2, 127.1, 128.6, 129.0, 134.5, 163.8, 165.2; ν_{max} (ATR) 2953, 2567, 2161, 1979, 1582, 1557, 1485, 1454, 1389, 1351, 1302, 1225, 1197, 1184, 1143, 1076, 1049, 1029, 988, 975, 953, 850, 774, 751, 732, 697, 665 cm^{-1}.

*4.7.12. 2-Ethyl-6-phenyl-1,3,4-thiadiazin-5(6H)-one (**6g**).* Yellow solid (1.11 g, 46% yield); mp 101–103 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.60; [Found: C, 59.90; H, 5.45; N, 12.69. $C_{11}H_{12}N_2OS$ requires C, 59.97; H, 5.50; N, 12.71%]; λ_{max} (MeOH): 205 nm ($\varepsilon\times10^{-3}$ 17.03 $cm^{-1}M^{-1}$), 290 (3.39); δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.25 (3H, t, *J* 7.5 Hz, C2–CH_2CH_3), 2.60 (2H, q, *J* 7.5 Hz, C2–CH_2CH_3), 4.76 (1H, s, C6–H), 7.38–7.42 (5H, m, Ph), 9.65 (1H, s, NH); δ_C ($CDCl_3$) 11.6, 31.3, 43.0, 127.8, 128.8, 129.2, 135.8, 150.4, 160.7; ν_{max} (ATR) 3201, 3068, 2937, 2161, 1980, 1655, 1599, 1497, 1455, 1420, 1369, 1329, 1249, 1168, 1112, 1077, 1023, 1002, 956, 929, 903, 863, 810, 778, 744, 695 cm^{-1}.

*4.7.13. 5-Ethyl-2-(1-mercapto-1-phenylmethyl)-1,3,4-oxadiazole (**7g**).* Colourless oil (0.97 g, 40% yield); R_f (benzene/ethyl acetate, 1:3 v/v) 0.53; [Found: C, 60.04; H, 5.45; N, 12.64. $C_{11}H_{12}N_2OS$ requires C, 59.97; H, 5.50; N, 12.71%]; λ_{max} (MeOH): 204 nm ($\varepsilon\times10^{-3}$

20.45 $cm^{-1}M^{-1}$); δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.40 (3H, t, *J* 7.8 Hz, CH_3), 2.05 (1H, br s, SH), 2.94 (2H, q, *J* 7.8 Hz, CH_2), 5.13 (1H, br s, CH), 7.36–7.48 (5H, m, Ph); δ_C ($CDCl_3$) 10.5, 19.2, 50.2, 128.8, 129.0, 129.1, 133.6, 164.3, 168.8; ν_{max} (ATR) 2983, 2567, 2162, 1980, 1575, 1552, 1485, 1463, 1451, 1385, 1301, 1197, 1180, 1163, 1074, 1025, 996, 965, 954, 853, 807, 733, 696 cm^{-1}.

*4.7.14. 2-(1-Mercapto-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazole (**7h**).* Colourless solid (2.18 g, 74% yield); mp 260–261 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.65; [Found: C, 67.04; H, 4.41; N, 10.39. $C_{15}H_{12}N_2OS$ requires C, 67.13; H, 4.52; N, 10.43%]; λ_{max} (MeOH): 204 nm ($\varepsilon\times10^{-3}$ 33.62 $cm^{-1}M^{-1}$), 252 (25.85); δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.80 (1H, br s, SH), 5.29 (1H, br s, C2–CH), 7.17–7.19 (5H, m, Ph); 7.40–7.48 (3H, m, C5: H3′, H4′, H5′), 7.96 (2H, d, *J* 7.8 Hz, C5: H2′, H6′); δ_C ($CDCl_3$) 47.4, 123.7, 126.9, 127.9, 128.6, 128.7, 128.8, 131.6, 135.3, 164.9, 166.7; ν_{max} (ATR) 3062, 2568, 2162, 1980, 1609, 1588, 1565, 1550, 1488, 1449, 1327, 1286, 1264, 1174, 1087, 1069, 1034, 1019, 957, 924, 851, 778, 734, 709, 695, 687 cm^{-1}.

4.8. General procedure for the preparation of N^2-(1-ethoxyethylene)-α-mercaptocarboxylic acid hydrazides 8a–b

The starting hydrazide **5a**–**b** (11 mmol) was dissolved in 20 mL of triethyl *ortho*acetate and kept under reflux until the starting hydrazide was fully consumed (monitored by TLC, 10 min). In the case of **5a**, the reaction was conducted under N_2. After cooling, the white precipitate was filtered off and crystallised from isopropanol.

*4.8.1. N^2-(1-Ethoxyethylene)-α-mercapto-β-phenylpropionic acid hydrazide (**8a**).* Colourless solid (2.49 g, 85% yield); mp 117–118 °C, R_f (benzene/ethyl acetate, 1:3 v/v) 0.50; [Found: C, 58.55; H, 6.76; N, 10. 44. $C_{13}H_{18}N_2O_2S$ requires C, 58.61; H, 6.82; N, 10.51%]; λ_{max} (MeOH): 203 nm ($\varepsilon\times10^{-3}$ 16.05 $cm^{-1}M^{-1}$), 235 (9.41); δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.19 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.62, (3H, s, CH_3), 2.84 (1H, dd, *J* 6.3 Hz and 12.9 Hz, Ph–CH_2), 2.92 (1H, m, SH), 3.12 (1H, dd, *J* 6.3 Hz and 12.9 Hz, Ph–CH_2), 3.64 (1H, m, CH), 4.00 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 7.18–7.26 (5H, m, Ph), 9.95 (1H, s, NH); δ_C (DMSO-d_6) 14.0, 15.0, 41.0, 41.6, 61.7, 126.4, 128.1, 129.0, 138.6, 165.5, 166.6; ν_{max} (ATR) 3215, 3034, 2979, 2548, 1665, 1640, 1618, 1563, 1497, 1476, 1449, 1419, 1365, 1299, 1256, 1223, 1190, 1151, 1131, 1049, 1029, 1016, 945, 911, 890, 838, 798, 739, 697 cm^{-1}.

*4.8.2. N^2-(1-Ethoxyethylene)-α-mercaptophenylacetic acid hydrazide (**8b**).* Colourless solid (1.25 g, 45% yield); mp 190–192 °C, R_f (benzene/ethyl acetate, 1:3 v/v) 0.53; [Found: C, 57.04; H, 6.37; N, 11. 13. $C_{12}H_{16}N_2O_2S$ requires C, 57.11; H, 6.40; N, 11.09%]; λ_{max} (MeOH): 205 nm ($\varepsilon\times10^{-3}$ 21.75 $cm^{-1}M^{-1}$), 232 (18.06); δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.20 (3H, m, OCH_2CH_3), 1.82, 1.84 (3H, s, CH_3), 3.31 (1H, br s, SH), 3.99–4.10 (2H, m, OCH_2CH_3), 4.77, 4.89 (1H, d, CH), 7.27–7.46 (5H, m, Ph), 10.17, 10.31 (1H, s, NH); δ_C (DMSO-d_6) 14.0, 15.4, 42.7, 61.9, 127.5, 128.3, 128.8, 135.6, 149.9, 163.9; ν_{max} (ATR) 3192, 3031, 2980, 2926, 2547, 2162, 1667, 1633, 1532, 1494, 1478, 1452, 1396, 1375, 1349, 1302, 1227, 1182, 1125, 1095, 1052, 1031, 1006, 991, 906, 853, 730, 692 cm^{-1}.

4.9. Reactions of α-mercaptophenylacetic acid hydrazide (5b) with triethyl *ortho*esters

Synthesis B- The starting hydrazide **5b** (2.00 g, 11 mmol) was added to a mixture of the appropriate triethyl *ortho*ester (22 mmol) and 4 mL (4.00 g, 70 mmol) of glacial AcOH. The mixture was refluxed until the starting hydrazide was fully consumed (monitored by TLC, 3–24 h). After cooling and filtering, the excess *ortho*ester and AcOH were evaporated under reduced pressure. The crude products (**9a**–**d**, **10a**–**d**) were purified by column chromatography using silica gel and an eluent of benzene/AcOEt (1:3). To detect the presence of sulfur, the remaining silica gel was washed with methanol and toluene, and the eluent was evaporated to dryness before diluting with 15 mL of dry toluene. The mixture was treated with Ph_3P and refluxed for 15 min. After cooling, yellow crystals of Ph_3PS precipitated, mp 162–163 °C (lit.:[16] mp 161–162 °C).

*4.9.1. Bis(1,3,4-oxadiazol-2-yl-phenylmethyl) disulfide (**9a**).* Colourless solid (0.31 g, 30% yield); mp 165–167 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.63; [Found: C, 56.46; H, 3.66; N, 14.69. $C_{18}H_{14}N_4O_2S_2$ requires C, 56.52; H, 3.70; N, 14.64%]; λ_{max} (MeOH): 204 nm ($\varepsilon\times10^{-3}$ 39.06 $cm^{-1}M^{-1}$); δ_H (300 MHz, $CDCl_3$, Me_4Si) 5.30 (1H, s, CH), 7.33–7.46 (5H, m, Ph), 8.48 (1H, s, H–C5); δ_C ($CDCl_3$) 49.9, 127.5, 128.7, 129.1, 134.4, 153.7, 164.8; ν_{max} (ATR) 3138, 3119, 2954, 2162, 1978, 1650, 1563, 1510, 1495, 1455, 1326, 1302, 1231, 1092, 1077, 1028, 1003, 972, 958, 899, 849, 730, 712, 695 cm^{-1}.

*4.9.2. 12-Benzyl-1,3,4-oxadiazole (**10a**).*[11d] Colourless liquid (0.25 g, 28% yield); R_f (benzene/ethyl acetate, 1:3 v/v) 0.66; δ_H (300 MHz, DMSO-d_6, Me_4Si) 4.28 (2H, s, CH_2), 7.23–7.36 (5H, m, Ph), 9.13 (1H, s, H–C5); δ_C (DMSO-d_6) 31.1, 127.9, 129.4, 129.5, 135.2, 155.4, 165.8.

*4.9.3. Bis(5-methyl-1,3,4-oxadiazol-2-yl-phenylmethyl) disulfide (**9b**).* Colourless solid (0.27 g, 33% yield); mp 165–167 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.50; [Found: C, 58.46; H, 4.47; N, 13.61. $C_{20}H_{18}N_4O_2S_2$ requires C, 58.51; H, 4.43; N, 13.64%]; λ_{max} (MeOH): 206 nm ($\varepsilon\times10^{-3}$ 42.75 $cm^{-1}M^{-1}$); δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.58 (3H, s, CH_3), 5.12 (1H, s, CH), 7.35–7.46 (5H, m, Ph); δ_C ($CDCl_3$) 11.5, 50.5, 129.0, 129.3, 129.4, 133.9, 164.9, 165.3; ν_{max} (ATR) 2954, 2162, 1980, 1684, 1585, 1557, 1486, 1455, 1391, 1351, 1302, 1256, 1226, 1197, 1183, 1146, 1076, 1049, 1028, 988, 974, 953, 849, 818, 774, 750, 732, 697, 664 cm^{-1}.

*4.9.4. 2-Benzyl-5-methyl-1,3,4-oxadiazole (**10b**).*[11d] Colourless liquid (0.23 g, 24% yield); R_f (benzene/ethyl acetate, 1:3 v/v) 0.44; δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.45 (3H, s, CH_3), 4.14 (2H, s, CH_2), 7.29–7.31 (5H, m, Ph); δ_C ($CDCl_3$) 10.9, 31.7, 127.5, 128.7, 128.8, 133.9, 164.1, 165.4.

*4.9.5. Bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenylmethyl) disulfide (**9c**).* Colourless solid (0.42 g, 35% yield); mp 145–147 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.62; [Found: C, 60.94; H, 5.03; N, 12.72. $C_{22}H_{22}N_4O_2S_2$ requires C, 60.24; H, 5.07; N, 12.77%]; λ_{max} (MeOH): 206 nm ($\varepsilon\times10^{-3}$ 49.06 $cm^{-1}M^{-1}$); δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.36 (3H, t, *J* 7.5 Hz, CH_2CH_3), 2.86 (2H, q, *J* 7.5 Hz, CH_2CH_3), 5.20 (1H, s, CH), 7.36–7.47 (5H, m, Ph); δ_C ($CDCl_3$) 10.8, 19.4, 49.9, 129.2, 129.3, 129.4, 134.4, 164.5, 169.0; ν_{max} (ATR) 2989, 2948, 2162, 1979, 1577, 1551, 1487, 1464, 1452, 1383, 1301, 1196, 1179, 1163, 1073, 1024, 997, 964, 954, 923, 852, 805, 735, 697 cm^{-1}.

*4.9.6. 2-Benzyl-5-ethyl-1,3,4-oxadiazole (**10c**).*[11d] Colourless liquid (0.28 g, 27% yield); R_f (benzene/ethyl acetate, 1:3 v/v) 0.56; δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.18 (3H, t, *J* 7.5 Hz, CH_2CH_3), 2.73 (2H, q, *J* 7.5 Hz, CH_2CH_3), 4.21 (2H, s, CH_2), 7.20–7.38 (5H, m, Ph); δ_C (DMSO-d_6) 10.9, 18.9, 31.1, 127.7, 129.3, 129.4, 135.3, 165.7, 168.4.

*4.9.7. Bis(5-phenyl-1,3,4-oxadiazol-2-yl-phenylmethyl) disulfide (**9d**).* Yellow solid (0.62 g, 42% yield); mp 200–201 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.67; [Found: C, 67.32; H, 4.11; N, 10.45. $C_{30}H_{22}N_4O_2S_2$ requires C, 67.39; H, 4.15; N, 10.47%]; λ_{max} (MeOH): 205 nm ($\varepsilon\times10^{-3}$ 77.88 $cm^{-1}M^{-1}$), 254 (52.13); δ_H (300 MHz, $CDCl_3$, Me_4Si) 5.36 (1H, s, CH), 7.31–7.60 (8H, m, Ph, C5: H3′, H4′, H5′), 8.04 (2H, d, *J* 6.3 Hz, C5: H2′, H6′); δ_C ($CDCl_3$) 49.8, 127.0, 127.1, 128.8, 129.0, 129.1, 129.2, 131.9, 134.0, 165.5, 168.7; ν_{max} (ATR) 3121, 2955,

2162, 1979, 1605, 1548, 1488, 1453, 1313, 1254, 1177, 1158, 1085, 1069, 1016, 975, 959, 922, 844, 777, 734, 708, 695, 683 cm^{-1}.

*4.9.8. 2-Benzyl-5-phenyl-1,3,4-oxadiazole (**10d**).* Colourless solid (0.45 g, 35% yield); mp 109–110 °C (lit.:[11d] mp 105–107 °C); R_f (benzene/ethyl acetate, 1:3 v/v) 0.54; δ_H (300 MHz, DMSO-d_6, Me_4Si) 4.34 (2H, s, CH_2), 7.34–7.36 (5H, m, Ph), 7.54–7.56 (3H, m, C5: H3′, H4′, H5′), 7.94 (2H, d, *J* 8.1 Hz, C5: H2′, H6′); δ_C (DMSO-d_6) 31.5, 124.0, 127.1, 127.9, 129.4, 129.6, 130.1, 132.6, 135.2, 164.9, 166.2.

4.10. Synthesis of N^2-acetyl-α-mercaptophenylacetic acid hydrazide (11)

The starting hydrazide **5b** (2.00 g, 11 mmol) was dissolved in 4 mL (4.00 g, 70 mmol) of glacial AcOH. The mixture was refluxed until the starting hydrazide was fully consumed (monitored by TLC, 3 h). After cooling, the solution was concentrated on a rotary evaporator to yield the crude product **11**, which was crystallised from ethanol.

*4.10.1. N^2-Acetyl-α-mercaptophenylacetic acid hydrazide (**11**).* Colourless solid (2.17 g, 88% yield); mp 265–266 °C, R_f (benzene/ethyl acetate, 1:3 v/v) 0.17; [Found: C, 53.49; H, 5.36; N, 12.49. $C_{10}H_{12}N_2O_2S$ requires C, 53.54; H, 5.40; N, 12.48%]; λ_{max} (MeOH): 205 nm ($\varepsilon\times10^{-3}$ 22.10 $cm^{-1}M^{-1}$); δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.88 (3H, s, CH_3), 3.63 (1H, s, SH), 4.85 (1H, s, CH), 7.28–7.47 (5H, m, Ph), 10.04 (1H, s, NH), 10.32 (1H, s, NH); δ_C (DMSO-d_6) 20.5, 56.2, 128.3, 128.5, 128.7, 135.9, 167.5, 168.1; ν_{max} (ATR) 3169, 3050, 2548, 1593, 1579, 1476, 1450, 1367, 1275, 1215, 1133, 1030, 1077, 1002, 940, 845, 795, 768, 724, 690, 675 cm^{-1}.

4.11. Reactions of N^2-(1-ethoxymethylene)-α-mercaptocarboxylic acid hydrazides (8a-b) in AcOH

The acyclic N^2-(1-ethoxymethylene)-α-mercaptocarboxylic acid hydrazide (**8a**–**b**) (4 mmol) was dissolved in 30 mL of glacial AcOH. The mixture was refluxed until the starting material was fully consumed (monitored by TLC, 3–6 h). After cooling, the solution was concentrated under reduced pressure. The oily residue was subjected to column chromatography using silica gel and an eluent of benzene/AcOEt (1:3). In the case of **8a** the reaction was conducted under nitrogen, producing **6b** and **7b** in 78% and 20% yield, respectively. The reaction starting from **8b** resulted in the formation of **9b** and **10b** in 46% and 40% yield, respectively. The presence of sulfur was confirmed by reaction with Ph_3P (see Experimental 1.9).

4.12. Reduction of bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenyl methyl) disulfide (9c)

Bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenylmethyl) disulfide (**9c**) (0.60 g, 1.37 mmol) was dissolved in 30.0 mL of glacial AcOH, and Zn powder (0.18 g, 2.74 mmol) was added to this solution. The mixture was stirred at a temperature of 50 °C until the starting material was fully consumed (1 h). The reaction mixture was concentrated on a rotary evaporator to yield the crude product **7g**, which was chromatographically pure (0.59 g, 98% yield).

4.13. Oxidation of 5-ethyl-2-(1-mercapto-1-phenylmethyl)-1,3,4-oxadiazole (7g)

The chromatographically pure 5-ethyl-2-(1-mercapto-1-phenylmethyl)-1,3,4-oxadiazole (**7g**) (0.50 g, 2.27 mmol) was dissolved in 30 mL of glacial AcOH. The mixture was refluxed for 5 h and then evaporated under reduced pressure to yield the crude **9c**, which was crystallised from methanol (0.46 g, 92% yield, mp 144–146 °C).

4.14. Synthesis of 1,1′-diphenyldithiodiacetic acid dihydrazide (5c)

Hydrazide **5b** (2.00 g, 11 mmol) was dissolved in 20 mL of toluene and refluxed until the starting hydrazide was fully consumed (monitored by TLC, 3 h). After cooling, the solution was concentrated on a rotary evaporator to yield the crude product **5c**, which was crystallised from methanol.

*4.14.1. 1,1′-diphenyldithiodiacetic acid dihydrazide (**5c**).* Colourless solid (1.63 g, 82% yield); mp 188–189 °C, R_f ($MeOH/CHCl_3$, 1:1 v/v) 0.61; [Found: C, 52.89; H, 4.96; N, 15.51. $C_{16}H_{18}N_4O_2S_2$ requires C, 53.01; H, 5.01; N, 15.45%]; λ_{max} (MeOH): 229 nm ($\varepsilon\times10^{-3}$ 16.60 $cm^{-1}M^{-1}$); δ_H (300 MHz, DMSO-d_6, Me_4Si) 4.42 (2H, s, NH_2), 4.62 (1H, s, CH), 7.28–7.37 (3H, m, Ph: H3′, H4′, H5′), 7.44 (2H, d, *J* 7.8 Hz, Ph: H2′, H6′), 9.51 (1H, s, NH); δ_C (DMSO-d_6) 56.5, 128.0, 128.3, 128.5, 136.5, 168.0; ν_{max} (ATR) 3278, 3028, 1686, 1651, 1603, 1518, 1492, 1454, 1359, 1316, 1239, 1186, 1135, 1077, 1031, 1013, 1001, 961, 918, 852, 803, 772, 725, 690 cm^{-1}.

4.15. Reaction of α-mercaptophenylacetic acid hydrazide (5b) with triethyl *ortho*propionate (toluene/*p*-TsOH)

The starting hydrazide **5b** (2.00 g, 11 mmol) was dissolved in a mixture of 4.5 mL (22 mmol) triethyl *ortho*propionate and 20 mL of toluene and refluxed for 8 h. After cooling, the solution was concentrated on a rotary evaporator to yield the crude product **9c**, which was crystallised from methanol (1.80 g, 75% yield, mp 143–145 °C).

4.16. X-ray structure determination for 6b

A single crystal (0.20×0.13×0.11 mm) of 6-benzyl-2-methyl-1,3,4-thiadiazin-5(6*H*)-one (**6b**) was used for data collection at 100.0 (2) K on a four-circle Oxford Diffraction Xcalibur diffractometer equipped with a two-dimensional area CCD detector using graphite monochromatised MoK_α radiation (λ=0.71073 Å) and the ω-scan technique. Integration of the intensities and correction for Lorenz and polarization effects were performed using CrysAlis RED software.[25] The crystal structures were solved by direct methods and refined by a full-matrix least-squares method on F^2 using the program SHELXL-97.[26] The H atoms were positioned geometrically and their positions and thermal parameters were not refined.

Empirical formula $C_{11}H_{12}N_2OS$, formula weight 220.29, crystal system monoclinic, space group C2, unit cell dimensions: a=19.6587(14), b=4.89300(10), c=14.524(2) Å, β=130.525(2), V=1061.92(18) $Å^3$, Z=4, calculated density 1.378 mg/m^3, absorption coefficient 0.278 mm^{-1}, $F(000)$=464, θ range for data collection: 3.69–26.00°, limiting indices: $-24\le h\le23$, $-4\le k\le6$, $-17\le l\le17$, reflections collected/unique: 3567/1488 [R_{int}=0.0129], data/restraints/parameters: 1488/1/136, goodness-of-fit on F^2 1.065, final R indices [$I>2\sigma(I)$]: R_1=0.0220, wR_2=0.0576, R indices (all data): R_1=0.0229, wR_2=0.0579, absolute structure parameter (Flack parameter)[27] 0.53(7), largest diff. peak and hole: 0.302 and −0.185 eA^{-3}.

Complete crystallographic details are available as a Supplementary data, and have been deposited at the Cambridge Crystallographic Data Centre (CCDC 855792) CCDC, 12 Union Road, Cambridge, CB21EZ, UK, e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk. Any request to the CCDC for this material should quote the full literature citation.

4.17. X-ray structure determination for 9c

A single crystal (0.21×0.16×0.14 mm) of bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenylmethyl)disulfide (**9c**) was used for data collection at 100.0 (2) K on a four-circle Oxford Diffraction Xcalibur

diffractometer equipped with a two-dimensional area CCD detector using graphite monochromatised MoK$_\alpha$ radiation (λ=0.71073 Å) and the ω-scan technique. Integration of the intensities and correction for Lorenz and polarization effects were performed using CrysAlis RED software.[25] The crystal structures were solved by direct methods and refined by a full-matrix least-squares method on F^2 using the program SHELXL-97.[26] The H atoms were positioned geometrically and their positions and thermal parameters were refined independently.

Empirical formula $C_{22}H_{22}N_4O_2S_2$, formula weight 438.58, crystal system triclinic, space group P-1, unit cell dimensions: a=10.1075(5), b=10.8476(6), c=10.8778(5) Å, α=95.600(4)°, β=116.092(5), γ=91.331(4), V=1063.08(9) Å^3, Z=2, calculated density 1.370 mg/m^3, absorption coefficient 0.277 mm^{-1}, F(000)=460, θ range for data collection: 2.99–25.00°, limiting indices: $-12\leq h\leq 12$, $-12\leq k\leq 12$, $-12\leq l\leq 9$, reflections collected/unique: 6681/3697 [R_{int}=0.0148], data/restraints/parameters: 3697/0/360, goodness-of-fit on F^2 1.151, final R indices [$I>2\sigma(I)$]: R_1=0.0295, wR_2=0.0712, R indices (all data): R_1=0.0389, wR_2=0.0728, largest diff. peak and hole: 0.283 and −0.185 eA^{-3}.

Complete crystallographic details are available as a Supplementary data, and have been deposited at the Cambridge Crystallographic Data Centre (CCDC 854303) CCDC, 12 Union Road, Cambridge, CB21EZ, UK, e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk. Any request to the CCDC for this material should quote the full literature citation.

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