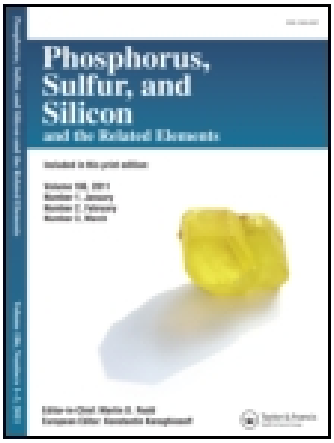

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Cyclodesulfurization of Substituted Thiosemicarbazides into 1,3,4-Oxadiazoles via Hydrazonoyl Chlorides

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CYCLODESULFURIZATION OF SUBSTITUTED THIOSEMICARBAZIDES INTO 1,3,4-OXADIAZOLES VIA HYDRAZONOYL CHLORIDES

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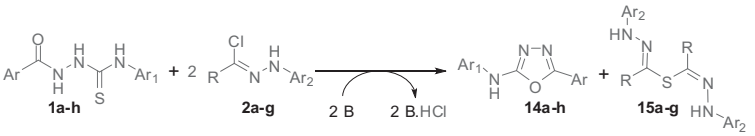
GRAPHICAL ABSTRACT



Abstract *The reaction of thiosemicarbazides **1a–h** with hydrazonoyl chlorides **2a–g** at ambient temperature, in the presence of triethylamine yielded, in each case, two products. The structure of these compounds was confirmed as 1,3,4-oxadiazoles **14a–h** and hydrazonothioates **15a–g**. The structure of **15b** was confirmed through single crystal X-ray diffraction. A mechanism was proposed for this cyclodesulfurization reaction.*

Keywords Cyclodesulfurization; thiosemicarbazides; 1,3,4-oxadiazoles; hydrazonoyl chlorides

INTRODUCTION

Thiosemicarbazides **1** (Figure 1) are useful intermediates in the synthesis of several heterocycles such as 1,3-thiazoles,[1] 1,3,4-oxadiazoles,[2] 1,2,4-triazoles,[3] and 1,3,4-thiadiazoles.[4] A number of these heterocycles are important in pharmaceutical and medicinal applications, for example, the 1,3,4-oxadiazole moiety is the main scaffold in several drugs like Isentress, Nesapidil, and Furamizole.[5]

Hydrazonoyl halides **2** (Figure 1) have been received much attention owing to their synthetic potential in the construction of a huge series of products, and the varied biological activity exhibited by a number of these products. As main contributors to this field, Shawali

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/gpss.

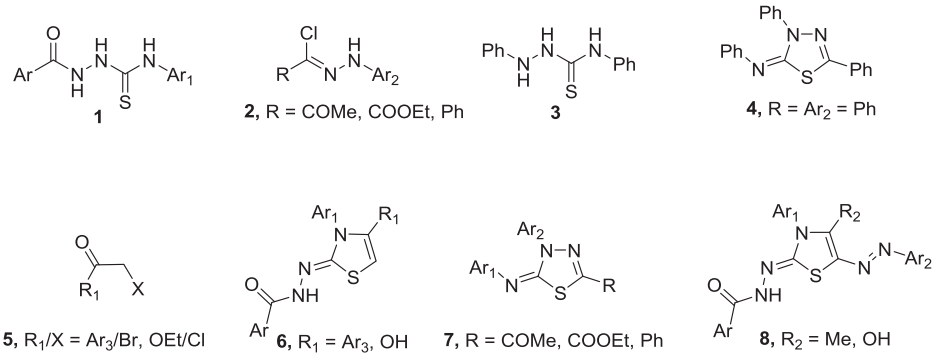
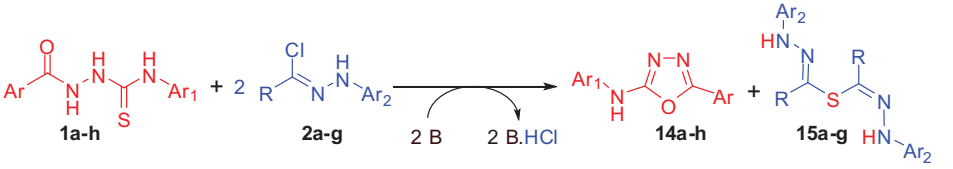


Figure 1 Structure of compounds **1–8**.

has reported 11 reviews on the reactivity and reactions of hydrazonoyl halides including their reactions with thiol/thione compounds.[6,7]

The reaction of *N'*-phenylbenzohydrazonoyl chloride (**2**) (R = Ar_2 = Ph) with 1,4-diphenylthiosemicarbazide (**3**) in the presence of triethylamine resulted in the formation of *N*-(3,5-diphenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)aniline (**4**) (Figure 1) and phenylhydrazine, which acted as the eliminated deprotonating agent.[8] On the other hand, the straightforward preparation of thiosemicarbazides **1** was reported by the reaction of acid hydrazides with isothiocyanates and their reaction with halo derivatives **5** has been published to produce 1,3-thiazoles **6** (Figure 1).[1,9,10]

In continuation of our interest in the chemistry of hydrazonoyl chlorides,[11–16] we aimed to study the reaction of thiosemicarbazides **1** with hydrazonoyl chlorides **2**. This reaction did not afford the possible 1,3,4-thiadizoles **7** or 5-arylazo-1,3-thiazoles **8** (Figure 1) where hydrazonoyl chlorides **2** act as cyclodesulfurization agent for **1** to produce the corresponding 1,3,4-oxadiazoles **14** (Scheme 1). However, the reported cyclization protocols for thiosemicarbazides **1** into 1,3,4-oxadiazole **14** were extensively investigated using several desulfurization reagents that include mercuric salts, lead oxide, I_2/NaOH, TsCl (*p*-toluenesulfonyl chloride), DCC (*N*,*N'*-dicyclohexylcarbodiimide), EDC (ethylene dichloride), polymer-supported DCC, PS-carbodiimides, TBTU (O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate), and hypervalent iodine (V).[5,17] In the light of above data, we investigated, in this work, the behavior of hydrazonoyl chlorides **2** toward thiosemicarbazides **1**.



Scheme 1 The reaction of thiosemicarbazides **1a–h** with hydrazonoyl chlorides **2a–g**.

RESULTS AND DISCUSSION

The role of base in reactions of **2** is to generate nitrilimines **10** via 1,3-elimination reaction during dehydrohalogenation process (Figure 2).[6] The reactions of nitrilimines **10**

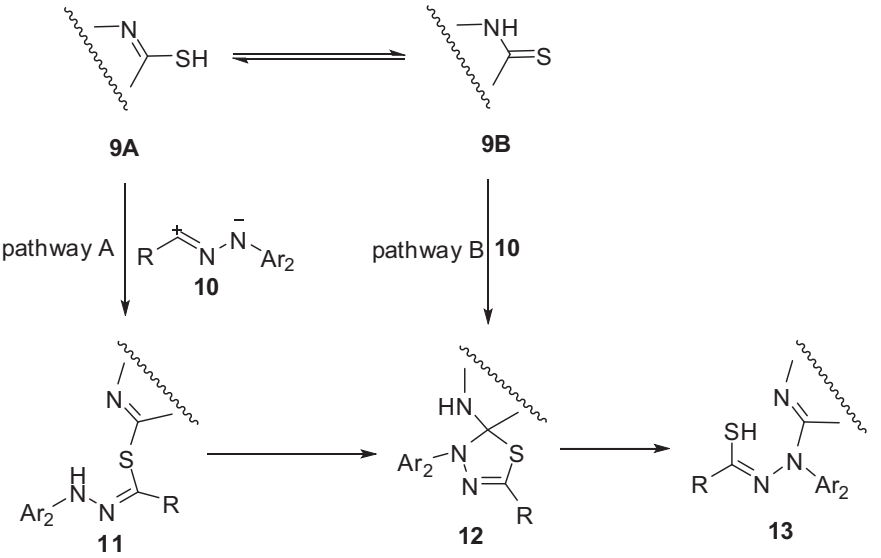


Figure 2 The reaction of nitrilimines **10** with tautomeric thiol/thione compounds **9A/9B**.

with tautomeric thiol/thione compounds **9A/9B** may proceed via two pathways: pathway A, 1,3-addition reaction where C-SH tautomer **9A** acts as a protic nucleophile to form thiohydrazonate **11**, or pathway B, 1,3-dipolar cycloaddition reaction where C=S tautomer **9B** acts as dipolarophile to give the spirocyclo adduct **12** (Figure 2). Both **11** and **12** usually undergo further in situ reactions according to their structures such as compound **13** (Figure 2). Some of the latter intermediates were isolated as final products in certain reactions.[18] In this work, we aimed to react the tautomeric thiol/thione thiosemicarbazides **1A/1B** with base-generated nitrilimines **10** (Scheme 1).

Therefore, the reaction of thiosemicarbazide **1a** (Ar = Ar_1 = Ph) with 2-oxo-*N*-arylpropanehydrazonoyl chlorides **2a**–**e** in ethanol at ambient temperature, in the presence of triethylamine yielded, in each case, two products as examined by thin layer chromatography (TLC; *n*-hexane/AcOEt, 4:1, v:v) (Scheme 1, Table 1). The solvent was evaporated and the residue treated with water. The fractional crystallization of the latter residue from *n*-hexane separated these products as soluble/insoluble compounds. Alternatively, the latter crude material has been separated by column chromatography (*n*-hexane/AcOEt, 4:1, v:v).

In each case, the *n*-hexane insoluble products exhibited identical physical properties and spectroscopic data (IR, ^{1}H, and ^{13}C NMR). The elemental analysis and mass spectra of these products are compatible with the same molecular formula $C_{14}H_{11}N_3O$, which proved the structure as *N*,5-diphenyl-1,3,4-oxadiazol-2-amine **14a** for these compounds. Next, we extended our investigations to react thiosemicarbazides **1b**–**h** with 2-oxo-*N*-phenylpropanehydrazonoyl chloride **2a** (R = COMe, Ar_2 = Ph) under the same conditions (Scheme 1, Table 1) and two reaction products were isolated, in each case, following the same work up. The *n*-hexane insoluble products were identified as 1,3,4-oxadiazoles **14b**–**h**, respectively.

On the other hand, *n*-hexane soluble products for the latter reaction showed dissimilar physical properties and spectroscopic data (IR, ^{1}H, and ^{13}C NMR). ^{1}H NMR of these products appeared a singlet signal integer to six protons in the region δ 2.29–2.35 in addition to D_2O exchangeable in the region δ 11.01–11.23 due to two protons. However, X-ray

Table 1 The structure and yields of 1,3,4-oxadiazoles **14a–h** and hydrazonothioates **15a–g**

14	Ar	Ar_1	Yield (%)	15	*R*	Ar_2	Yield (%)
14a	Ph	Ph	74	15a	COMe	Ph	49
			75	15b	COMe	2-MeC_6H_4	40
			66	15c	COMe	4-BrC_6H_4	47
			68	15d	COMe	4-ClC_6H_4	45
			67	15e	COMe	4-$NH_2SO_2C_6H_4$	39
			62	15f	COOEt	Ph	43
			60	15g	Ph	Ph	40
14b	Ph	4-ClC_6H_4	75	15a	COMe	Ph	48
14c	Ph	4-$MeOC_6H_4$	74	15a	COMe	Ph	41
14d	4-$MeOC_6H_4$	Ph	66	15a	COMe	Ph	45
14e	Thiophen-2-yl	Ph	70	15a	COMe	Ph	47
14f	Pyridin-4-yl	Ph	65	15a	COMe	Ph	39
14g	Pyridin-4-yl	4-ClC_6H_4	76	15a	COMe	Ph	43
14h	Pyridin-4-yl	4-FC_6H_4	67	15a	COMe	Ph	38

analysis for single crystal of **15b** (Figure 3, Tables 2 and 3)[19] showed the structure (1*Z*)-1-[2-(aryl)hydrazinylidene]-2-oxopropyl (1*Z*)-*N*-(aryl)-2-oxopropanehydrazonothioates **15a–e** for these products and proved that the reaction proceeded in 2:1 molar ratio for **1a**:**2a–e**.

Similarly, the above reaction was conducted for **1a** with ethyl 2-chloro-2-(2-phenylhydrazono)acetate **2f** (R = COOEt, Ar_2 = Ph) and *N'*-phenylbenzohydrazonoyl chloride **2g** (R = Ar_2 = Ph), respectively, and the products were found to be hydrazonothioates **15f** and **15g**, respectively, in addition to 1,3,4-oxadiazole **14a**, in each case. The reaction of **1b–h** with **2a** gave, in each case, (1*Z*)-1-[2-(phenyl)hydrazinylidene]-2-oxopropyl (1*Z*)-*N*-(phenyl)-2-oxopropanehydrazonothioate **15a** in addition to the corresponding 1,3,4-oxadiazoles **14b–h** (Scheme 1, Table 1).

The possible mechanism for the cyclodesulfurization reaction of thiosemicarbazide **1** by **2** is shown in Figure 4. This reaction is proposed to proceed following pathway A via a preliminary formation of intermediate thiohydrazonate **16**. This conversion involves the initial reaction of -SH tautomer **1A** with nitrilimine **10** to form this desired intermediate, which activates cyclization process to form 1,3,4-oxadiazole thiohydrazonate **17**. The latter

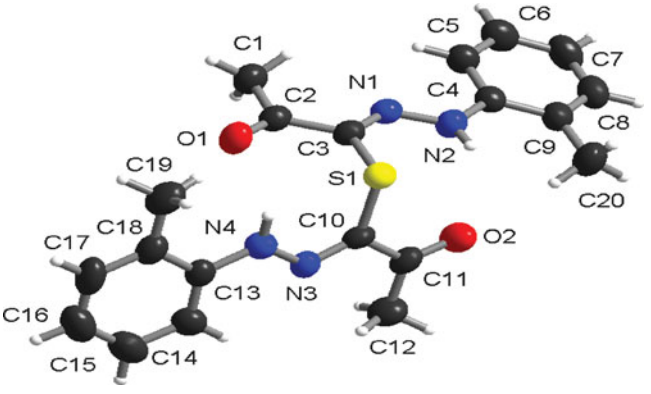


Figure 3 ORTEP diagram of **15b**, 50% probability ellipsoid.

Table 2 The crystallographic data and refinement information for **15b**

Compound	**15b**
Empirical formula	$C_{20}H_{22}N_4O_2S$
Formula weight	382.48
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	11.785 (1) Å
b/Å	8.0747 (7) Å
c/Å	21.3142 (19) Å
α/°	90°
β/°	103.818 (3)°
γ/°	90°
V/Å^3	1969.6 (3) Å^3
Z	4
μ (mm^{-1})	0.19 mm^{-1}
Color/shape	Yellow/crystal
Temp (K)	294 K
R_{int}	0.102
θ_{max}	27.5°
Goodness of fit on F^2	1.04
Measured reflections	41731
Independent reflections	4525
$R[F^2 > 2\sigma(F^2)]$	0.087
$wR(F^2)$	0.239
$\Delta\rho_{max}$	0.37 eÅ^{-3}
$\Delta\rho_{min}$	−0.35 eÅ^{-3}

intermediate undergoes in situ Smiles rearrangement[20] as soon as they are formed to yield the thiohydrazides **20**. Then the consequent cyclization of intermediate **20** combined with the elimination of thiol **22**, which reacts with another molecule of **10**, leads to the formation of **14** and **15** as final products. The second possible pathway B involves 1,3-dipolar cycloaddition reaction of **10** into C═S tautomer **1B** to give the spirointermediate **18** that undergoes in situ Smiles rearrangement to form thiohydrazides **19** and then the cyclized intermediate **20**. On the other side, the formation of carbodiimide **21** as nonisolable

Table 3 Characteristic bond lengths [Å] and angles [°] of **15b**

Bond lengths [Å]		Bond angles [°]	
S1–C3	1.781 (4)	C3–S1–C10	102.03 (16)
S1–C10	1.789 (3)	N2–N1–C3	120.5 (3)
O1–C2	1.222 (5)	N1–N2–C4	118.4 (3)
O2–C11	1.227 (5)	N4–N3–C10	120.0 (3)
N1–N2	1.323 (4)	N3–N4–C13	119.9 (3)
N1–C3	1.295 (5)	O1–C2–C1	121.2 (3)
N2–C4	1.414 (5)	O1–C2–C3	120.2 (3)
N3–N4	1.313 (4)	S1–C3–C2	118.7 (3)
N3–C10	1.301 (4)	N1–C3–C2	116.2 (3)
N4–C13	1.412 (5)	S1–C3–N1	125.1 (3)

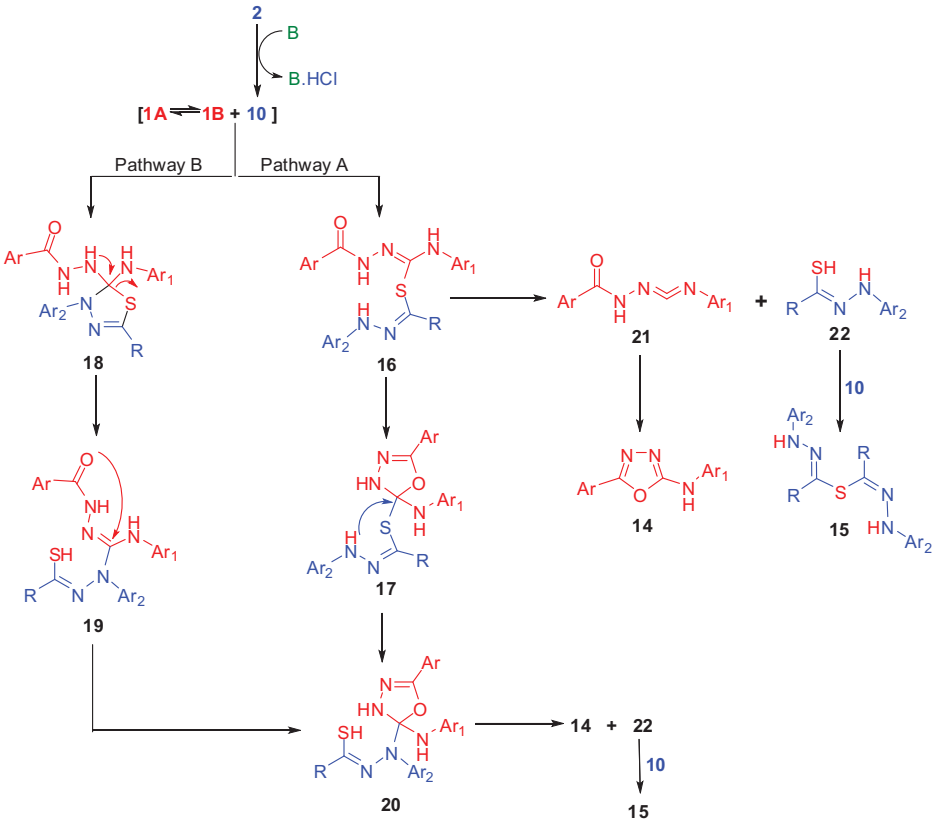


Figure 4 Mechanism for the reaction of thiosemicarbazides **1a–h** with hydrazonoyl chlorides **2a–g**.

intermediate and its subsequent cyclization resulting in 1,3,4-oxadiazoles **14** is possible third pathway.[17]

CONCLUSION

In conclusion, isolation of unexpected cyclodesulfurization products, 1,3,4-oxadiazoles **14a–h**, with moderate yields, from the reaction of **1a–h** with **2a–g**, showed the significant behavior of hydrazonoyl chlorides **2a–g** toward **1a–h** rather than their ordinary behaviors with possible products.

EXPERIMENTAL

General

Infrared (IR) spectra were recorded as KBr disks using a Perkin Elmer FT-IR Spectrum BX apparatus. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were scanned in DMSO-d_6 on a Bruker NMR spectrometer operating at 500 MHz for ^{1}H and 125.76 MHz for ^{13}C at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia. Chemical shifts are expressed

in δ values (ppm) relative to tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are expressed in Hz and D_2O was added to confirm the exchangeable protons. Mass spectra were measured on an Agilent Triple Quadrupole 6410 QQQ LC/MS equipped with an ESI (electrospray ionization) source. The elemental analyses were performed at the Microanalytical Center of Cairo University. The homogeneity of the compounds was checked by TLC performed on Silica gel G coated plates (Merck). An iodine chamber was used for the visualization of TLC spots.

N-(4-Aryl)-2-aryl$_1$-carbonyl)hydrazinecarbothioamides **1a**–**h**[5,17,21] and hydrazonoyl chlorides **2a**–**g**[22–24] were prepared according to the reported method.

The Reaction of Thiosemicarbazides 1 with Hydrazonoyl Chlorides 2

To a solution of compounds **1a**–**h** (10 mmol) in absolute ethanol (50 mL), the appropriate hydrazonoyl chloride **2a–g** (20 mmol) and triethylamine (40 mmol) were added. The reaction mixture was stirred overnight. The solvent was evaporated, and then the remained residue was treated with water (20 mL). The solid formed was collected by filtration and washed with water. The fractional recrystallization of the solid formed from *n*-hexane afforded the insoluble compounds **14a**–**h** and the soluble hydrazonothioates **15a**–**g**.

The physical properties and spectroscopic data of 1,3,4-oxadiazoles **14a–f**,[5,17] hydrazonothioates **15f**,[25] and **15g**[8] were found to be identical with those described in the literature.

N-(4-Chlorophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (14g)

Colorless powder; mp: 310–312 °C (ethanol (EtOH)/dimethylformamide (DMF)) (Lit. mp = 238–240 °C).[26]

N-(4-Fluorophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (14h)

Colorless crystals; mp: 250–252 °C (EtOH/DMF); IR (KBr) ν 3279 (NH) cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.61–8.80 (m, 8H, Ar-H), 10.85 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 117.2, 118.4, 119.8, 120.8, 134.0, 144.3, 150.7, 153.3, 156.0 (C=N), 164.2 (C=N), 166.3 (C=N); MS (ESI) m/z: 257.1 $[M+1]^+$. Anal. Calcd. for $C_{13}H_9FN_4O$ (256.24): C, 60.94; H, 3.54; N, 21.87%. Found: C, 59.82; H, 3.65; N, 22.02%.

(1Z)-2-Oxo-1-(2-phenylhydrazinylidene)propyl-(1Z)-2-oxo-N-phenylpropanehydrazonothioate (15a)

Pale yellow fibers; mp: 215–217 °C (EtOH/DMF); IR (KBr) ν 3178 (NH), 1648 (C=O), 1531 (C=N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.29 (s, 6H, 2CH_3), 7.10–7.42 (m, 6 H, Ar-H), 7.47–7.91 (m, 4 H, Ar-H), 11.01 (s, D_2O exch., 2H, 2NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 24.9 (CH_3), 116.1, 120.1, 126.0, 127.4, 128.4, 129.0, 133.8, 141.3, 146.9 (C=N), 194.1 (C=O); MS (ESI) m/z: 355.2 $[M+1]^+$; Anal. Calcd. for $C_{18}H_{18}N_4O_2S$ (354.43): C, 61.00; H, 5.12; N, 15.81; S, 9.05%. Found: C, 61.23; H, 5.04; N, 15.96; S, 9.07%.

(1Z)-1-[2-(2-Methylphenyl)hydrazinylidene]-2-oxopropyl-(1Z)-N-(2-methylphenyl)-2-oxopropanehydrazonothioate (15b)

Yellow crystals; mp: 220–222 °C (EtOH/DMF); IR (KBr) *v* 3165 (NH), 1658 (C=O), 1540 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 2.22 (s, 6H, $2CH_3$), 2.30 (s, 6H, $2CH_3$), 6.61–6.96 (m, 5H, Ar-H), 7.05–7.33 (m, 3H, Ar-H), 11.23 (s, D_2O exch., 2H, 2NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 16.7 (CH_3), 25.0 ($\underline{C}H_3$), 115.7, 124.1, 127.9, 128.4, 129.2, 140.3, 146.7 (C=N), 194.5 (C=O); MS (ESI) *m/z*: 382.7 $[M]^+$; Anal. Calcd. for $C_{20}H_{22}N_4O_2S$ (382.48): C, 62.80; H, 5.80; N, 14.65; S, 8.38%. Found: C, 62.55; H, 5.78; N, 14.77; S, 8.46%.

(1Z)-1-[2-(4-Bromophenyl)hydrazinylidene]-2-oxopropyl-(1Z)-N-(4-bromophenyl)-2-oxopropanehydrazonothioate (15c)

Yellow fibers; mp: 210–212 °C (EtOH/DMF); IR (KBr) *v* 3190 (NH), 1644 (C=O), 1527 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 2.35 (s, 6H, $2CH_3$), 7.11–7.25 (m, 4H, Ar-H), 7.31–7.65 (m, 4H, Ar-H), 11.10 (s, D_2O exch., 2H, 2NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.1 (CH_3), 114.8, 123.4, 128.8, 129.5, 144.8 (C=N), 194.0 (C=O); MS (ESI) *m/z*: 515.2 $[M+3]^+$; Anal. Calcd. for $C_{18}H_{16}N_4O_2SBr$ (512.22): C, 42.21; H, 3.15; N, 10.94; S, 6.26%. Found: C, 42.37; H, 3.14; N, 11.08; S, 6.14%.

(1Z)-1-[2-(4-Chlorophenyl)hydrazinylidene]-2-oxopropyl-(1Z)-N-(4-chlorophenyl)-2-oxopropanehydrazonothioate (15d)

Yellow needles; mp: 290–292 °C; IR (KBr) *v* 3208 (NH), 1653 (C=O), 1536 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 2.31 (s, 6H, $2CH_3$), 7.05–7.37 (m, 4H, Ar-H), 7.48–8.02 (m, 4H, Ar-H), 11.10 (s, D_2O exch., 2H, 2NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.3 (CH_3), 114.5, 125.4, 126.4, 127.3, 131.2, 137.8, 145.1 (C=N), 192.8 (C=O); MS (ESI) *m/z*: 424.3 $[M+1]^+$; Anal. Calcd. for $C_{18}H_{16}N_4O_2SCl$ (423.32): C, 51.07; H, 3.81; N, 13.24; S, 7.57%. Found: C, 50.94; H, 3.89; N, 13.20; S, 7.65%.

(1Z)-1-[2-(4-Sulphonamidophenyl)hydrazinylidene]-2-oxopropyl-(1Z)-N-(4-sulphoamidophenyl)-2-oxopropanehydrazonothioate (15e)

Yellow crystals; mp: 258–260 °C; IR (KBr) *v* 3400–3000 ($NH+NH_2$), 1651 (C=O), 1533 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 2.30 (s, 6H, $2CH_3$), 7.5 (d, 4H, $J = 8.5$ Hz, Ar-H), 7.35 (s, D_2O exch., 2H, SO_2NH_2), 7.70 (d, 4H, $J = 8.5$ Hz, Ar-H), 11.09 (s, D_2O exch., 2H, 2NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.0 (CH_3), 115.9, 128.7, 128.9, 130.8, 131.1, 144.9 (C=N), 194.3 (C=O); MS (ESI) *m/z*: 512.6 $[M]^+$; Anal. Calcd. for $C_{18}H_{20}N_4O_6S_3$ (512.58): C, 42.18; H, 3.93; N, 16.40; S, 18.77%. Found: C, 42.02; H, 3.99; N, 16.56; S, 18.92%.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website, www.tandfonline.com/gpss

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