Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

Formation of reagent-selective products from 2-(4,5-dihydrothi-azol-2-ylthio)-1-arylethanone with different nucleophiles

S. Saravanan [a] , P. Mohan [a] & S. Muthusubramanian [a]
[a] School of Chemistry , Madurai Kamaraj University , Madurai , 625 021 , India
Published online: 29 Nov 2010.

To cite this article: S. Saravanan , P. Mohan & S. Muthusubramanian (2011) Formation of reagent-selective products from 2-(4,5-dihydrothi- azol-2-ylthio)-1-arylethanone with different nucleophiles, Journal of Sulfur Chemistry, 32:1, 71-84, DOI: 10.1080/17415993.2010.533772

To link to this article: http://dx.doi.org/10.1080/17415993.2010.533772

Journal of Sulfur Chemistry
Vol. 32, No. 1, February 2011, 71–84

Taylor & Francis
Taylor & Francis Group

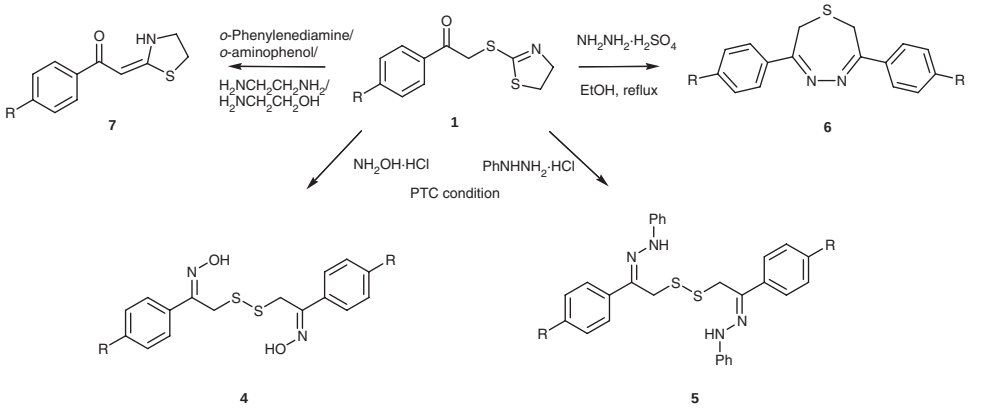
Formation of reagent-selective products from 2-(4,5-dihydrothiazol-2-ylthio)-1-arylethanone with different nucleophiles

S. Saravanan†, P. Mohan and S. Muthusubramanian*

School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India

(*Received 25 August 2010; final version received 16 October 2010*)

The reactions of 2-(4,5-dihydrothiazol-2-ylthio)-1-arylethanone with different nucleophiles including semicarbazide hydrochloride, hydroxylamine hydrochloride, hydrazine, ethylenediamine and aminoethanol have been investigated, and the formation of a variety of products with different reagents is highlighted.



Keywords: thiazolidinethiol; nucleophiles; selenium dioxide; thionyl chloride; phase transfer catalyst

1. Introduction

The synthesis of heterocyclic compounds containing selenium/sulfur is of interest not only because of their synthetic utility for the preparation of alkynes (*1*), but also because of their pharmacological properties such as antifungal (*2*) and antibacterial (*3*) activities. Some of the 1,2,3-selenadiazole derivatives exhibit antimicrobial, anti-haemostatic and insecticidal activities (*4*). 4,5-Bis(*p*-methoxyphenyl)-1,2,3-thiadiazole possesses platelet aggregation inhibitory activity in humans (*5*). Recently, *N*-substituted hydrazones are found to yield selenadiazole

*Corresponding author. Email: muthumanian2001@yahoo.com
†Present address: Department of Chemistry, A.N.J.A. College, Sivakasi 626 124, India.

ISSN 1741-5993 print/ISSN 1741-6000 online

DOI: 10.1080/17415993.2010.533772
http://www.informaworld.com

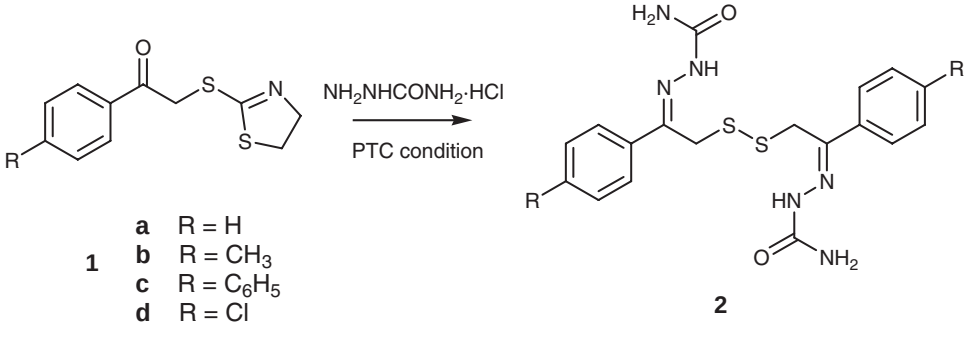
on selenium dioxide treatment (*6*), though conventionally semicarbazones are used as the precursors (*7*).

In our continued interest on the synthesis of selenium/sulfur-containing heterocycles (*8*), we planned to prepare 1,2,3-selena/thiadiazole linked to thiazolidine ring by a sulfur atom. During this attempt, we found that 2-(4,5-dihydrothiazol-2-ylthio)-1-arylethanones react differently with different nucleophiles giving a variety of products. This article summarizes some interesting results of the related investigations.

2. Results and discussion

2-(4,5-Dihydrothiazol-2-ylthio)-1-arylethanones have been identified as the precursors for the generation of a new set of selena/thiodiazoles, which are easily prepared from substituted phenacyl bromide and thiazolidinethiol. Thus, the β-ketosulfides (**1**) were obtained in good yield by treating thiazolidinethiol with respective phenacyl bromide in DMF–ethanol medium in the presence of triethylamine. The popular method of preparing 1,2,3-thiadiazole and 1,2,3-selenadiazole is the treatment of the semicarbazones having α-methylene hydrogens with thionyl chloride and selenium dioxide, respectively (*7*). Accordingly, the thioketone (**1**) was treated with semicarbazide hydrochloride and anhydrous sodium acetate in ethanol to prepare the corresponding semicarbazones. When this reaction was carried out under the conventional condition, a pasty mass was obtained, which was found to be an inseparable mixture of geometrical isomers of the semicarbazone. However, if the reaction was effected under phase transfer condition in water:dioxane medium in the presence of tetrabutylammonium bromide, only one of the geometrical isomer of the semicarbazone (**2**) was obtained in good yield with no trace of the other geometrical forms. Thus, the reaction under phase transfer catalyst seems to be selective.

The inspection of the ^{1}H NMR spectrum of the products **2** reveals the absence of the pair of triplets showing that the thiazolidine part is not present in the semicarbazone derivative. The aliphatic region of the proton NMR spectrum consists of only a singlet at around 4.2 ppm. The ^{13}C NMR spectrum of **2d** has signals at 157.3, 140.0, 133.3, 132.8, 126.9, 126.5 and 29.4 ppm. The presence of the semicarbazone unit, an aryl group and a methylene carbon is very much evident, and the product obtained was found to be not the semicarbazone of 2-(4,5-dihydrothiazol-2-ylthio)-1-arylethanone, but the bis-semicarbazone of 2,2′-disulfanedilylbis(1-phenylethanone) (Scheme 1).



Scheme 1. Reaction of **1** with semicarbazide hydrochloride.

The structure of bis-semicarbazone **2** has been unambiguously confirmed by single-crystal X-ray analysis and the crystal data for **2a** (CCDC number 753001) are presented in the Table 1.

Table 1. Crystal data and structural refinement for **2a**, **3c** and **7a**.

Parameters	**2a**	**3c**	**7a**
Empirical formula	$C_{18}H_{20}N_6O_2S_2$	$C_{14}H_{10}N_2S$	$C_{11}H_{11}NOS$
Formula weight	416.52	238.30	205.27
Temperature	293(2) K	293(2) K	293(2) K
Wavelength	0.71069 Å	0.71069 Å	0.71073 Å
Crystal system, space group	Triclinic, *P*-1	Orthorhombic, *Pbc*21	Monoclinic, *P* 21/*n*
Unit cell dimensions	$a = 14.9782(8)$ Å, $\alpha = 97.804(11)°$, $b = 15.8713(9)$ Å, $\beta = 96.863(9)°$, $c = 17.9615$ Å, $\gamma = 116.856(12)°$	$a = 5.6512(6)$ Å, $\alpha = 90.00°$, $b = 7.6661(7)$ Å, $\beta = 90.00°$, $c = 26.3483(11)$ Å, $\gamma = 90.00°$	$a = 7.3007(7)$ Å, $\alpha = 90°$, $b = 6.0446(6)$ Å, $\beta = 96.2170(10)°$, $c = 22.268(2)$ Å, $\gamma = 90°$
Z, Volume	6, 3694.2(4) Å^3	4, 1141.48(17) Å^3	4, 976.90(16) Å^3
Density (calculated)	1.123 mg/m^3	1.387 mg/m^3	1.396 mg/m^3
Absorption coefficient	0.238 mm^{-1}	0.259 mm^{-1}	0.294 mm^{-1}
$F(000)$	1308	496	432
Crystal size	0.18 × 0.17 × 0.16 mm	0.21 × 0.19 × 0.15 mm	0.37 × 0.36 × 0.16 mm
Theta range for data collection	1.47–25.96°	3.09–24.97°	1.84–25.96°
Index ranges	$-18 \le h \le 18$, $-19 \le k \le 19$, $-22 \le l \le 21$	$0 \le h \le 6$, $0 \le k \le 94$, $-1 \le l \le 31$	$-8 \le h \le 8$, $\times 7 \le k \le 7$, $-27 \le l \le 27$
Reflections collected	38,397	1076	9595
Independent reflections	14,342 [R(int) = 0.0482]	1076 [R(int) = 0.0000]	1912 [R(int) = 0.0245]
Absorption correction	None	Psi-scans	Semi-empirical
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	14,342/0/757	1076/1/154 Flack value = 0.02(13)	1912/0/128
Goodness-of-fit on F^2	0.946	1.145	1.055
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0696$, w$R_2 = 0.1816$	$R_1 = 0.0288$, w$R_2 = 0.0716$	$R_1 = 0.0374$, w$R_2 = 0.0957$
R indices (all data)	$R_1 = 0.1252$, w$R_2 = 0.2029$	$R_1 = 0.0421$, w$R_2 = 0.0780$	$R_1 = 0.0419$, w$R_2 = 0.0987$
Largest diff. peak and hole	0.552 and −0.260e Å^{-3}	0.137 and −0.182e Å^{-3}	0.239 and −0.270e Å^{-3}

There are three independent molecules in the asymmetric unit and only one of them is shown in the ORTEP diagram of **2a** (Figure 1) with the atomic-numbering scheme. The other two residues are having the same atomic-numbering scheme with the last alphabets as C/D and E/F. During the structure analysis, it was observed that the unit cell contains large accessible voids in the crystal structure, the number of electrons in the voids being ca. 34 with the volume of 843 Å^3. This tends to host disordered solvent water molecules. This affects the diffraction pattern, mostly at low scattering angles; this was corrected with the SQUEEZE program.

It is surprising that the treatment of thioketone with semicarbazide hydrochloride has led to the formation of a bis-semicarbazone with a disulfide linkage. The thiazolidine ring has been removed probably by a homolytic cleavage of the bond connecting sulfur and thiazolidine resulting in the thiyl radical, which would have dimerized to give the disulfide. This disulfide ultimately undergoes semicarbazone formation. This dissociation seems to be facile as the other radical formed can itself be stabilized by a tandem process of 1,3-hydrogen migration and hydrogen loss to give a stable aromatized species – thiazole, as shown in Scheme 2. Unfortunately, there is no evidence for the formation of thiazole. The NMR spectrum of the crude reaction mixture is very complex in the aromatic region to locate the signals due to thiazole. Attempts to isolate any byproducts from the reaction mixture were also not successful. An alternate route for the formation of **2** from **1** is the attack of the nucleophile on electron-deficient carbon of the imino carbon of the heterocyclic ring displacing thio group and the corrresponding thiol may undergo dimerization.

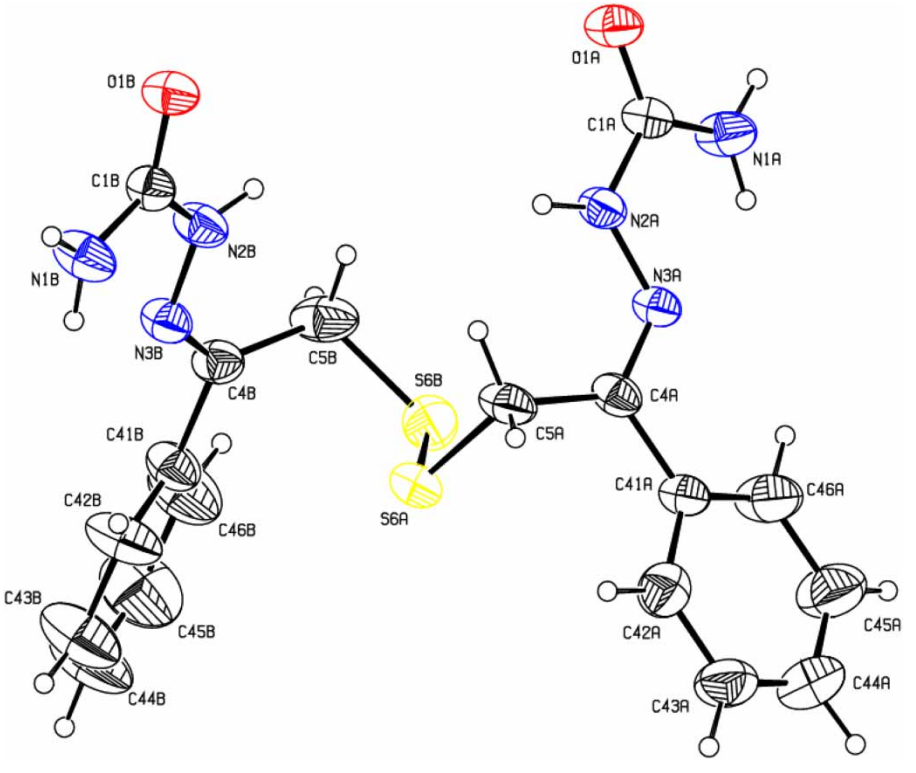
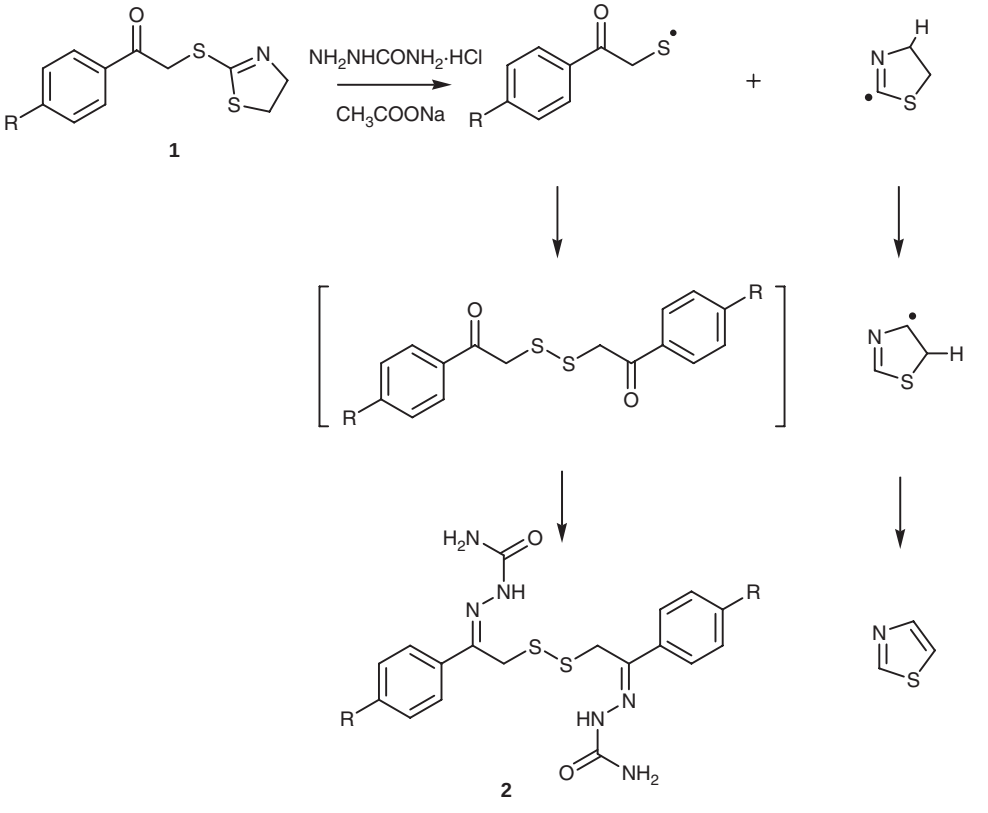


Figure 1. An ORTEP diagram of **2a**, with the atom-numbering scheme and 30% probability displacement ellipsoids.

Though the expected semicarbazone with the thioazolidine ring has not been obtained, the product formed during the reaction is again a suitable precursor for the generation of sulfur/selenium heterocycles with two additional nitrogen atoms. A quantitative conversion would probably lead to two 1,2,3-thia/selenadiazole units linked by the disulfide group. The resultant heterocyclic systems may assume importance as compounds with disulfide linkage are biologically important. For example, the disulfide functionality is known to be responsible for the biological activity of the potassium channel blocking dendrotoxins (*9*). Several diaryl disulfides have been analyzed for their second-order nonlinear optical properties, illustrating the applications of this class of compounds (*10*). Hence, it has been planned to effect the oxidative cyclization using thionyl chloride and selenium dioxide on the bis-semicarbazones **2**.

The semicarbazones **2** upon treatment with thionyl chloride at a low temperature (−5 °C) followed by the removal of excess thionyl chloride gave a single product **3** in 30–40% yield. The identity of the isolated compound has been arrived at as follows. The proton NMR spectrum of **3d** shows a singlet at 8.65 ppm for one hydrogen and a pair of doublets at 8.0 and 7.5 ppm each accounting for two hydrogens. The ^{13}C NMR spectrum exhibits six signals at 161.7, 135.3, 130.2, 129.4, 129.2 and 128.6 ppm. The presence of *p*-chlorophenyl ring, two additional olefinic carbons, the chemical shift positions of the left out olefinic carbons and the presence of a singlet at 8.65 ppm in the ^{1}H NMR spectrum all suggest the compound to be 4-(4-chlorophenyl)-1,2,3-thiadiazole. The melting point of the compound agrees with the reported one (*11*). Similarly, compounds **3a**–**c** have been found to be the respective 4-aryl-1,2,3-thiadiazoles (*5*, *12*, *13*). The single-crystal X-ray analysis of the 4-(4-phenylphenyl)thiadiazole (**3c**) has been carried out and the results are presented in Table 1, and the ORTEP diagram of **3c** is shown in Figure 2 (CCDC number 753359).



Scheme 2. Mechanism for the formation of **2**.

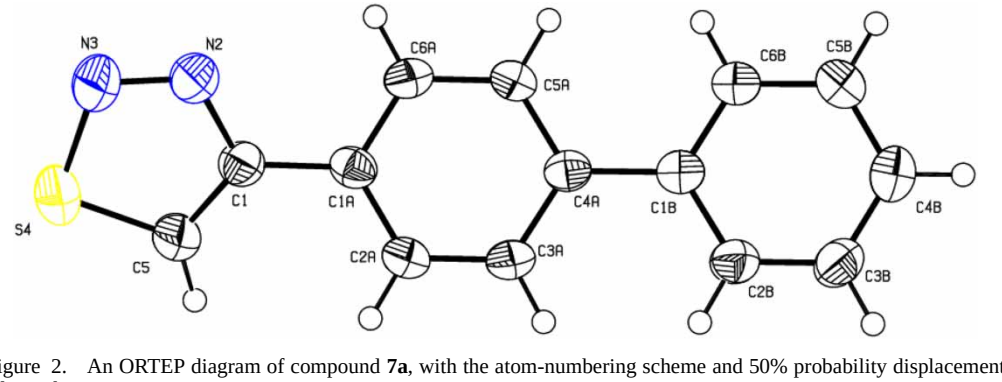
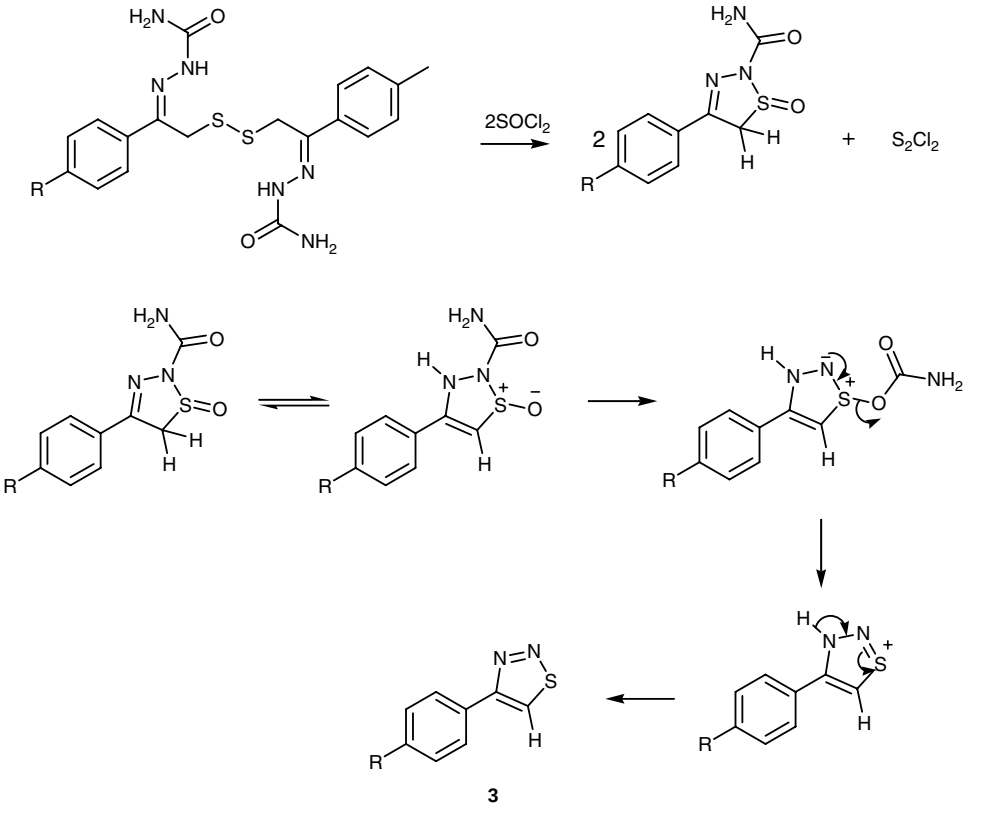


Figure 2. An ORTEP diagram of compound **7a**, with the atom-numbering scheme and 50% probability displacement ellipsoids.

The formation of this simple 1,2,3-thiadiazole rather than the expected 4,5-disubsituted thiadiazole is surprising and a possible mechanism is postulated in Scheme 3. It is proposed that in the first step, thionyl chloride reacts with the bis-semicarbazone to give disulfur dichloride and the heterocyclic sulfoxide ring, probably *via* a radical mechanism. Disulfur dichloride is a popular reagent to effect the sulfuration of aromatic rings (*14*). This reagent has also been used with aluminum chloride for the chlorination of the aromatic ring (*15*). The formation of thiadiazoles from sulfoxides, as shown in Scheme 3, is well established and has been corroborated with kinetics



Scheme 3. Mechanism for the formation of **3** from **2** by the reaction of thionyl chloride.

studies (*12*). This conversion of sulfoxide system to thiadiazole has been shown to be catalyzed either by acid or by base and acceptable mechanisms for both routes have been suggested. A mechanism involving the initial formation of an intermediate (**X**) (Figure 3) is ruled out as the presence of the two active methylene hydrogens is essential for further reaction.

The bis-semicarbazone is then subjected to selenium dioxide treatment in THF in the hope of getting 4,5-disubsituted 1,2,3-selenadiazole. However, the expected oxidative cyclization has not occurred and the product obtained in 30–40% as a single entity was found to be 5-subsituted-1,2,3-thiadiazole, very much identical to the product obtained in the earlier case. It is unexpected

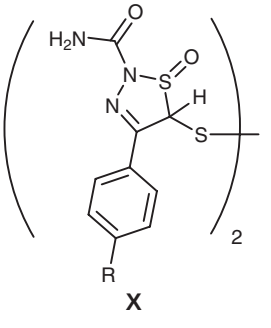
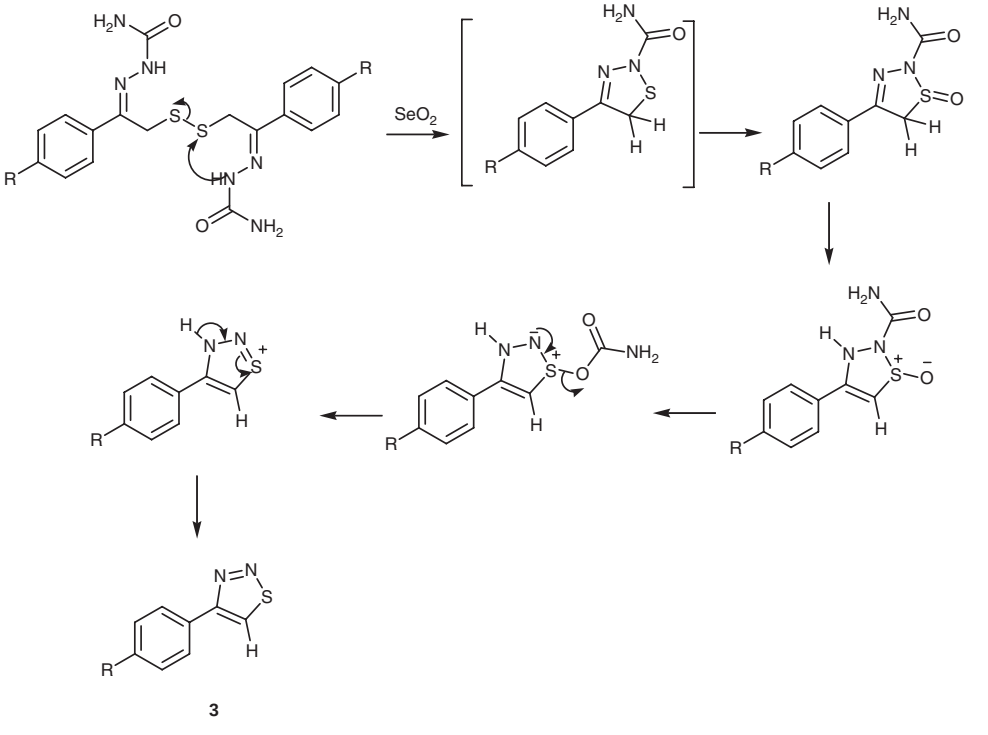


Figure 3. Possible intermediate for the formation of **3**.

to get a sulfur heterocycle by selenium dioxide treatment and it is very clear that one of the sulfur of the disulfide linkage has entered into the ring and not the selenium as in the conventional reaction. The formation of the product can be explained by postulating a tentative mechanism as shown in Scheme 4.

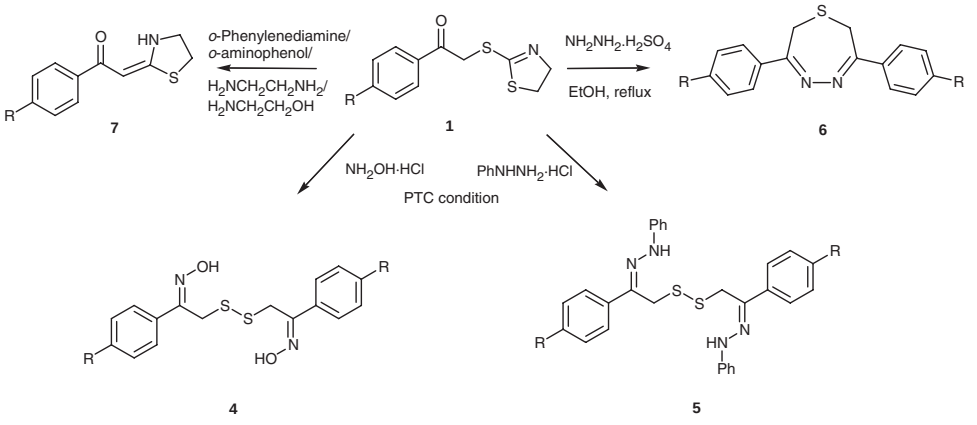


Scheme 4. Mechanism for the formation of **3** from **2** by the reaction of selenium dioxide.

The elimination of the alkyl thiol-type compound – by radical or ionic mechanism – can be proposed in the first step leading to the ring sulfide formation. This can be easily oxidized to sulfoxide by selenium dioxide. The formation of the thiadiazole from this sulfoxide can be explained by proposing the established mechanism shown in the previous transformation involving thionyl chloride.

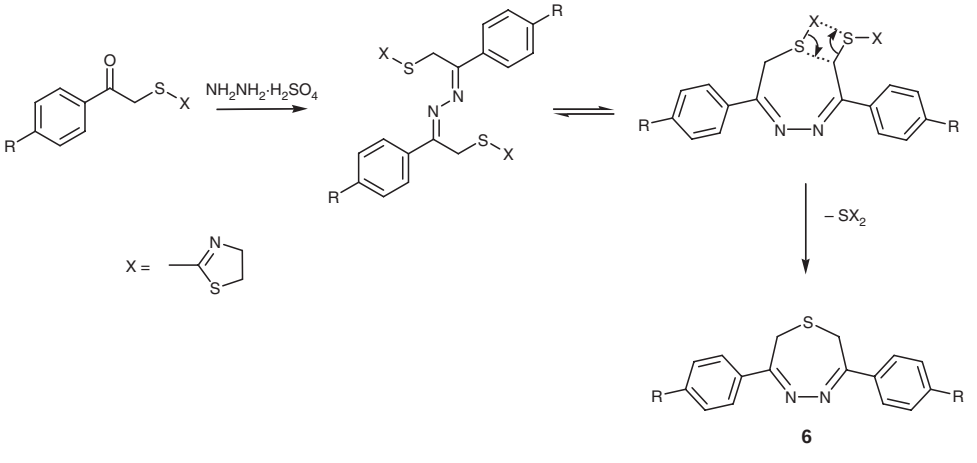
Having realized that the reaction of semicarbazide hydrochloride had not yielded the expected semicarbazone, we tried to prepare the corresponding oximes and hydrazones. The reaction of hydroxylamine hydrochloride with the thioketone **1** in the presence of phase transfer catalyst has been found to lead to the formation of the 2((2-(hydroxyimino)-2-phenylethyl)disulfanyl)-1-arylethanone oximes (**4**), the bis oximes of the 2,2′-difulfanedilylbis(1-arylethanone). An attempted generation of phenylhydrazone from the ketone **1** has also ended with the formation of the phenylhydrazone of difulfanedilylbis(1-arylethanone) (**5**) and not that of the ketone **1** (Scheme 5). In both the cases, only one product is obtained quantitatively. The mechanism for the formation of **4** and **5** is similar to that of **2** as described in Scheme 2.

The reaction of ketone **1** with hydrazine is found to be very interesting. When 1 mol of hydrazine sulfate is treated with ketone **1a**, the reaction gives only one product predominantly under the reflux condition. The product formed has the molecular ion peak at m/e 266 and intense fragment ions at m/e 232 and 163. The ^{1}H NMR spectrum has signals at 7.9 and 7.4 ppm in the ratio 2:3 with two doublets at 3.35 and 3.65 ppm ($J = 12.6$ Hz), The ^{13}C NMR spectrum has signals at 26.4, 127,



Scheme 5. Reaction of **1** with different nucleophiles.

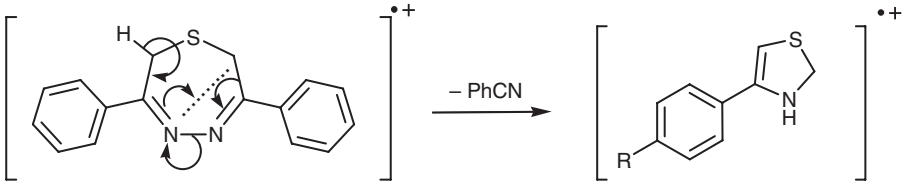
128, 130, 135 and 151 ppm. All the data suggest that the compound is 3,6-diphenyl-2,7-dihydro-1,4,5-thiadizepine **6**. The spectral data are very much matching with the reported one (*16*). The formation of thiadizepine can be formulated as indicated in Scheme 6. There is no evidence for the formation of SX_2, although the mechanism requires the formation of a quantitative amount of this product. No positive support from the crude product's NMR spectrum, though the ^{1}H NMR clearly indicated that some other byproduct has been formed. The compound may not be stable and would have undergone decomposition and hence could not be isolated during purification.



Scheme 6. Mechanism for the formation of **6**.

The peak at *m*/*e* 232 in the mass spectrum of **6** is due to M-H_2S ion, while the peak at *m*/*e* 163 can be accounted for M-C_7H_5N ion peak, whose formation can be explained as shown in Scheme 7.

As the reaction of ketone **1a** with nucleophiles of the type H_2N-X yielded different products with different H_2N-X, it was planned to investigate the reaction of **1a** with compounds having two vicinal nucleophilic centers such as ethylene diamine, *o*-phenylenediamine, ethanolamine and *o*-aminophenol. Here again, the reaction took a different route giving only one product irrespective of the dinucleophilic reagents employed. The product formed in all the cases was found to be



Scheme 7. Fragmentation pattern of **6**.

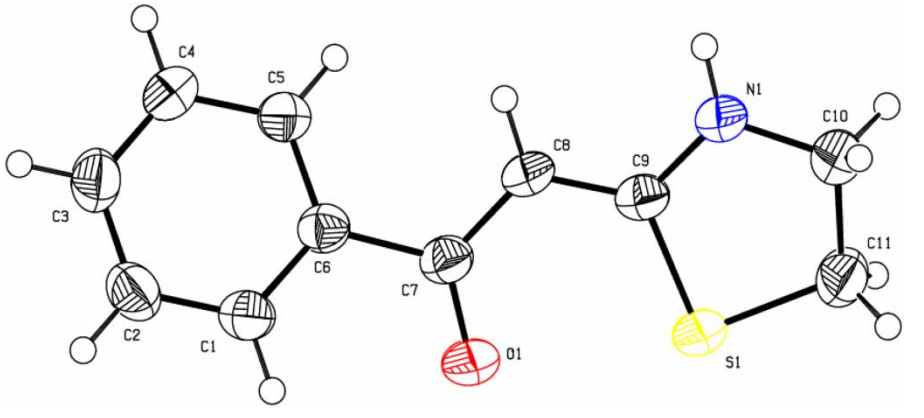
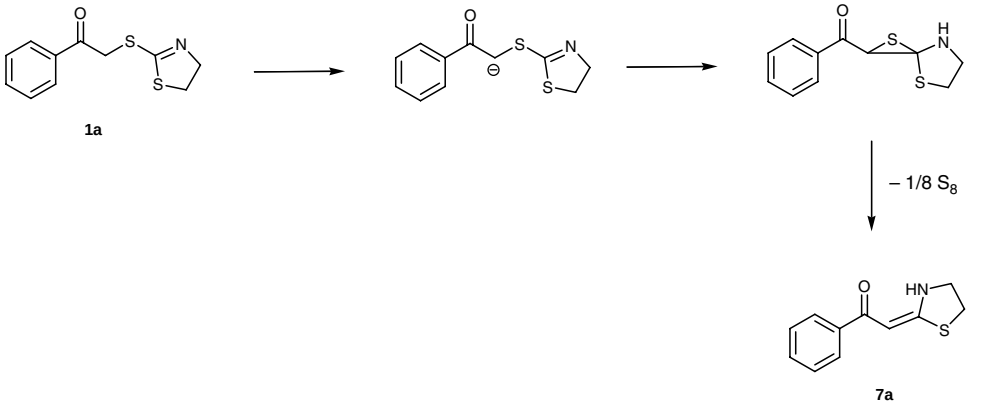


Figure 4. An ORTEP diagram of **7a**, with the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level.

1-phenyl-2-(thiazolidin-2-ylidene)ethanone (**7a**) (*17*). The compound has its ^{1}H NMR signals at 3.2, 3.9 (7.2 Hz) 10.6, 5.99, 7.8 and 7.4 ppm and ^{13}C NMR signals at 49, 29, 87,169, 186, 127, 128, 130 and 139 ppm. The single-crystal X-ray analysis (CCDC number 784001; Figure 4, Table 1) also proves the structure of the product unambiguously. The formation of **7a** can presumably be explained as presented in Scheme 8. Thus, the basic character of the ethylene diamine, *o*-phenylenediamine, ethanolamine and *o*-aminophenol seems to dominate over their nucleophilic character.



Scheme 8. Mechanism for the formation of **7a**.

3. Experimental

Melting points are uncorrected. NMR spectra were recorded on a Bruker 300 MHz instrument in $CDCl_3$ using TMS as the internal standard. Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in hertz. The single-crystal X-ray data for **2a** and **3c** were collected on a CCD area detector diffractometer with MoK_α radiation ($\lambda = 0.71073$ Å) and Nonius MACH3 kappa diffractometer with MoK_α radiation ($\lambda = 0.71069$ Å), respectively. The structures were solved by direct methods from SHELXA97 and refined by full-matrix least squares on F^2 by SHELXTL97. Column chromatography was carried out in silica gel (60–120 mesh) using pet ether–ethyl acetate as an eluent. CCDC numbers 753001, 753359 and 784001 contain the supplementary crystallographic data for **2a**, **3c** and **7a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, Cambridge, UK, or deposit@ccdc.cam.ac.uk).

3.1. *General procedure for the preparation of 2-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-1-aryl-1-ethanone 1*

To a solution of 4,5-dihydro-1,3-thiazole-2-thiol (0.01 mol) in ethanol (10 ml) and *N*,*N*-dimethyl formamide (5 ml), 0.01 mol of 2-bromo-1-aryl-1-ethanone in ethanol (20 ml) and *N*,*N*-dimethyl formamide (5 ml) was added in portion. Then triethylamine (0.01 mol) was added to the reaction mixture dropwise, stirred for 2 h and poured onto crushed ice. The product obtained was filtered and then dried.

3.1.1. *2-(4,5-Dihydro-1,3-thiazol-2-ylsulfanyl)-1-phenyl-1-ethanone* ***(1a)***

Yield: 84%; mp = 56 °C (reported = 56-57.5 °C) (*18*). ^{1}H NMR ($CDCl_3$) δ: 3.42 (t, $J = 8.1$ Hz, 2H), 4.18 (t, $J = 8.1$ Hz, 2H), 4.69 (s, 2H), 7.48 (t, $J = 7.5$ Hz, 2H), 7.60 (t, $J = 7.5$ Hz, 1H), 8.00 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 36.1, 40.3, 63.9, 128.5, 128.7, 133.7, 135.4, 164.2, 193.0.

3.1.2. *2-(4,5-Dihydro-1,3-thiazol-2-ylsulfanyl)-1-(4-methylphenyl)-1-ethanone* ***(1b)***

Yield: 71%; mp = 71 °C. ^{1}H NMR ($CDCl_3$) δ: 2.46 (s, 3H), 3.46 (t, $J = 8.1$ Hz, 2H) 4.21 (t, $J = 8.1$ Hz, 2H), 4.71 (s, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 7.94 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.5, 35.9, 40.1, 63.8, 128.5, 129.2, 132.6, 144.5, 164.0, 192.4. Anal. Calcd. for $C_{12}H_{13}NOS_2$ (251.37): C 57.34, H 5.21, N 5.57; found: C 57.29, H 5.06, N 5.52.

3.1.3. *1-[1,1′-Biphenyl]-4-yl-2-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-1-ethanone* ***(1c)***

Yield: 87%; mp = 72 °C. ^{1}H NMR ($CDCl_3$) δ: 3.43 (t, $J = 7.8$ Hz, 2H), 4.19 (t, $J = 7.8$ Hz, 2H), 4.72 (s, 2H), 7.01–7.56 (m, 9H) ; ^{13}C NMR ($CDCl_3$) δ: 36.5, 40.7, 64.4, 127.7, 127.8, 128.8, 129.4, 129.6, 134.5, 140.0, 146.8, 164.8, 193.1. Anal. Calcd. for $C_{17}H_{15}NOS_2$ (313.44): C 65.14, H 4.82, N 4.47; found: C 65.11, H 4.94, N 4.44.

3.1.4. *1-(4-Chlorophenyl)-2-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-1-ethanone* ***(1d)***

Yield: 91%; mp = 67 °C. ^{1}H NMR ($CDCl_3$) δ: 4.70 (s, 2H), 3.52 (t, $J = 7.8$ Hz, 2H), 4.22 (t, $J = 7.8$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 2H), 8.01 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 36.1, 39.8, 63.7, 128.8, 129.8, 133.6, 139.9, 163.9, 191.9. Anal. Calcd. for $C_{11}H_{10}ClNOS_2$ (271.79): C 48.61, H 3.71, N 5.15; found: C 48.56, H 3.82, N 5.24.

3.2. *General procedure for the preparation of 2-[(Z)-2-(2-[(Z)-2-(aminocarbonyl) hydrazono]-2-arylethyldisulfanyl)-1-arylethylidene]-1-hydrazinecarboxamide (2)*

To a solution of appropriate ketone **1** (0.005 mol), semicarbazide hydrochloride (3.90 g, 0.035 mol) and sodium acetate (2.87 g, 0.035 mol) in a dioxane–water mixture (50 ml, 3:2 v/v), a catalytic amount of tetrabutylammonium bromide was added. The reaction mixture was stirred at room temperature for 3 days, poured onto crushed ice, extracted with chloroform and evaporated to dryness. The ethyl acetate insoluble portion was recrystallized from ethanol to give the respective semicarbazones.

3.2.1. *2-[(Z)-2-(2-[(Z)-2-(Aminocarbonyl)hydrazono]-2-phenylethyldisulfanyl)-1-phenylethylidene]-1-hydrazinecarboxamide (**2a**)*

Yield: 85%; mp = 174 °C. ^{1}H NMR ($CDCl_3$) δ: 4.12 (s, 4H), 6.70 (bs, 4H), 7.34 (m, 6H), 7.76 (m, 4H), 10.40 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ: 31.4, 126.0, 128.5, 129.4, 136.1, 145.2, 158.5. Anal. Calcd. for $C_{18}H_{20}N_6O_2S_2$ (416.52): C 51.90, H 4.84, N 20.18; found: C 51.97, H 4.91, N 20.16.

3.2.2. *2-[(Z)-2-[2-[(Z)-2-(Aminocarbonyl)hydrazono]-2-(4-methylphenyl)ethyl]disulfanyl-1-(4-methylphenyl)ethylidene]-1-hydrazinecarboxamide (**2b**)*

Yield: 56%; mp = 132 °C. ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 6H), 3.68 (s, 4H), 6.71 (bs, 4H), 7.16 (d, J = 7.8 Hz, 4H), 7.61 (d, J = 7.8 Hz, 4H), 10.48 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ: 20.1, 29.8, 125.2, 127.9, 132.1, 137.7, 147.9, 158.2. Anal. Calcd. for $C_{20}H_{24}N_6O_2S_2$ (444.57): C 54.03, H 5.44, N 18.90; found: C 54.12, H 5.57, N 18.95.

3.2.3. *2-[(Z)-2-(2-[(Z)-2-(Aminocarbonyl)hydrazono]-2-[1,1′-biphenyl]-4-ylethyldisulfanyl)-1-[1,1′-biphenyl]-4-ylethylidene]-1-hydrazinecarboxamide (**2c**)*

Yield: 64%; mp = 178 °C. ^{1}H NMR ($CDCl_3$) δ: 4.16 (s, 4H), 7.21-7.33 (m, 10H), 7.47 (d, J = 8.4 Hz, 4H), 7.70 (d, J = 8.4 Hz, 4H), 6.58-6.70 (bs, 4H), 10.42 (s, 2H); ^{13}C NMR ($CDCl_3$) δ: 30.4, 125.7, 125.8, 126.6, 127.9, 134.1,* 138.9, 140.2, 141.7, 157.9. Anal. Calcd. for $C_{30}H_{28}N_6O_2S_2$ (568.72): C 63.36, H 4.96, N 14.78; found: C 63.41, H 5.07, N 14.84. (*Two carbons merge here.)

3.2.4. *2-[(Z)-2-[2-[(Z)-2-(Aminocarbonyl)hydrazono]-2-(4-chlorophenyl)ethyl]disulfanyl-1-(4-chlorophenyl)ethylidene]-1-hydrazinecarboxamide (**2d**)*

Yield: 68%; mp = 168 °C. ^{1}H NMR ($CDCl_3$) δ: 4.16 (s, 4H), 6.65 (bs, 2H), 7.01 (bs, 2H), 7.22 (d, J = 8.4 Hz, 4H), 7.67 (d, J = 8.4 Hz, 4H), 10.50 (s, 2H); ^{13}6C NMR ($CDCl_3$) δ: 29.4, 126.5, 126.9, 132.8, 133.3, 140.0, 157.3. Anal. Calcd. for $C_{18}H_{18}Cl_2N_6O_2S_2$ (485.41): C 44.54, H 3.74, N 14.61; found: C 44.59, H 3.76, N 14.60.

3.3. *Reaction of 2-[(Z)-2-(2-[(Z)-2-(aminocarbonyl) hydrazono]-2-arylethyldisulfanyl)-1-arylethylidene]-1-hydrazinecarboxamide (2) with thionyl chloride*

The appropriate semicarbazone (0.001 mol) was added in portion to 10 ml of thionyl chloride while cooling to −5 °C with a freezing mixture. The reaction mixture was allowed to stir for about 3–4 h. The excess of thionyl chloride was decomposed using aqueous solution of sodium carbonate and the reaction mixture was extracted with chloroform. The product obtained upon

purification by column chromatography was found to be 4-aryl-1,2,3-thiadiazole. These 4-aryl substituted 1,2,3-thiadiazoles have already been reported. (**3a**): Yield = 42%; mp = 74 °C (76–78 °C) (*5*); (**3b**): Yield = 38%; mp = 72 (74–76 °C) (*12*); (**3c**): Yield = 46%; mp = 174–175 (176–177 °C) (*13*); (**3d**): Yield = 41%; mp = 133 (137 °C) (*11*).

3.4. *Reaction of 2-[(Z)-2-(2-[(Z)-2-(aminocarbonyl) hydrazono]-2-arylethyldisulfanyl)-1-arylethylidene]-1-hydrazinecarboxamide (2) with selenium dioxide*

To a solution of the appropriate semicarbazone (0.001 mol) dissolved in dry THF by gentle warming, 0.01 mol (1.10 g) of powdered selenium dioxide was added in portion. The reaction mixture was heated to reflux on a water bath for 2 h. The reaction mixture was filtered and the filtrate was poured onto crushed ice, extracted with chloroform. The product obtained upon purification by column chromatography was found to be 4-aryl-1,2,3-thiadiazole.

3.5. *General procedure for the reaction of 2-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-1-aryl-1-ethanone (1) with hydroxylamine*

To a solution of appropriate ketone **1** (0.005 mol), hydroxylamine hydrochloride (0.035 mol) and sodium acetate (0.035 mol) in a dioxane–water mixture (50 ml, 3:2 v/v), a catalytic amount of tetrabutylammonium bromide was added. The reaction mixture was stirred at room temperature for 3 days, poured onto crushed ice, extracted with chloroform and evaporated to dryness. The ethyl acetate insoluble portion was recrystallized from ethanol to give the respective bis-oximes.

3.5.1. *2-[2-(Hydroxyimino)-2-phenylethyl]disulfanyl-1-phenyl-1-ethanone oxime (**4a**)*

Yield: 74%; mp = 128 °C. ^{1}H NMR ($CDCl_3$) δ: 4.21 (s, 4H), 7.37-7.39 (m, 6H), 7.76-7.72 (m, 4H), 10.93 (s,2H); ^{13}C NMR ($CDCl_3$) δ: 32.2, 126.2, 128.4, 129.0, 135.4, 152.9. Anal. Calcd. for $C_{16}H_{16}N_2O_2S_2$ (332.44): C 57.81, H 4.85, N 8.43; found: C 56.95, H 4.76, N 8.38.

3.5.2. *2-[2-(Hydroxyimino)-2-(4-methylphenyl)ethyl]disulfanyl-1-(4-methylphenyl)-1-ethanone oxime (**4b**)*

Yield: 67%; mp = 150 °C. ^{1}H NMR ($CDCl_3$) δ: 2.43 (s, 6H), 4.28 (s, 4H), 7.29 (d, J = 8.1 Hz, 4H), 7.73 (d, J = 8.1 Hz, 4H), 10.90 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ: 20.3, 32.2, 126.1, 129.0, 132.3, 138.8, 152.7. Anal. Calcd. for $C_{18}H_{20}N_2O_2S_2$ (360.50): C 59.97, H 5.59, N 7.77; found: C 59.84, H 5.62, N 7.69.

3.5.3. *1-[1,1′-Biphenyl]-4-yl-2-[2-[1,1′-biphenyl]-4-yl-2-(hydroxyimino)ethyl]disulfanyl-1-ethanone oxime (**4c**)*

Yield: 78%; mp = 179 °C. ^{1}H NMR ($CDCl_3$) δ: 4.14 (s, 4H), 7.32–7.45 (m, 8H),7.57–7.61 (m, 6H), 7.77 (d, J = 8.1 Hz, 4H), 10.90 (s, 2H); ^{13}C NMR ($CDCl_3$) δ: 32.4, 126.5, 126.7, 127.5, 128.8, 129.1, 133.8, 139.8, 141.0, 152.2. Anal. Calcd. for $C_{28}H_{24}N_2O_2S_2$ (484.63): C 69.39, H 4.99, N 5.78; found: C 69.12, H 4.87, N 5.73.

3.6. *General procedure for the reaction of 2-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-1-phenyl-1-ethanone (1a) with phenylhydrazine*

To a solution of ketone **1a** (0.005 mol), phenylhydrazine hydrochloride (0.035 mol) and sodium acetate (0.035 mol) in a dioxane–water mixture (50 ml, 3:2 v/v), a catalytic amount of

tetrabutylammonium bromide was added. The reaction mixture was stirred at room temperature for 3 days, poured onto crushed ice, extracted with chloroform and evaporated to dryness. The ethyl acetate insoluble portion was recrystallized from ethanol to give bis-phenylhydrazone. Yield: 58%; mp = 146 °C. ^{1}H NMR ($CDCl_3$) δ: 3.04 (s, 4H), 6.86 (td, J = 7.5, 1.2 Hz, 2H), 6.88 (d, J = 7.5 Hz, 4H), 7.21 (t, J = 7.5 Hz, 4H), 7.30–7.49 (m, 6H), 7.80 (d, J = 8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ: 21.4, 113.4, 120.4, 125.4, 128.4, 128.8, 129.1, 137.4, 143.0, 144.8. Anal. Calcd. for $C_{28}H_{26}N_4S_2$ (482.67): C 69.68, H 5.43, N 11.61; found: C 69.70, H 5.49, N 11.64.

3.7. *General procedure for the reaction of 2-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-1-phenyl-1-ethanone (1a) with hydrazine*

A mixture of ketone **1a** (0.005 mol), hydrazinium sulfate (0.035 mol) and sodium acetate (0.035 mol) in 30 ml of ethanol was heated to reflux condition for about 3 h. The reaction mixture was then poured onto crushed ice, extracted with chloroform and evaporated to dryness. The ethyl acetate insoluble portion was recrystallized from ethanol to give 3,6-diphenyl-2,7-dihydro-1,4,5-thiadizepine.[18] Yield: 62%; mp = 179 °C. ^{1}H NMR ($CDCl_3$) δ: 3.30 (d, J = 13.2 Hz, 2H), 3.66 (d, J = 13.2 Hz, 2H), 7.46 (m, 6H), 7.90 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 26.4, 127.1, 128.8, 130.2, 135.0, 151.8. GC-mass (m/z): 266.6 (100%), 232.2 (41%), 163.2 (93%). Anal. Calcd. for $C_{16}H_{14}N_2S$ (266.36): C 72.15, H 5.30, N 10.52; found: C 72.17, H 5.36, N 10.55.

3.8. *General procedure for the reaction of 2-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-1-phenyl-1-ethanone (1a) with ethylene diamine/o-phenylenediamine/ethanolamine/o-aminophenol*

To a solution of ketone **1a** (0.005 mol) and appropriate dinucleophile (0.035 mol) in 30 ml of ethyl alcohol was heated to reflux condition for about 3 h. The reaction mixture was then poured onto crushed ice, extracted with chloroform and evaporated to dryness. The ethyl acetate insoluble portion was recrystallized from ethanol to give 1-phenyl-2-(thiazolidin-2-ylidene)ethanone, **7a**. Yield: 75%; mp = 165 °C (reported = 168 °C) (*17*). ^{1}H NMR ($CDCl_3$) δ: 3.28 (t, J = 7.2 Hz, 2H), 3.95 (t, J = 7.2 Hz, 2H), 5.99 (s, 1H), 7.42 (m, 3H), 7.85 (m, 2H), 10.7 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ: 29.7, 49.7, 87.0, 127.0, 128.2, 130.8, 139.6, 169.8, 186.4. GC-mass (m/z): 204.7 (100%), 176.5 (86%), 144.8 (40%), 104.8 (52%). Anal. Calcd. for $C_{16}H_{14}N_2S$ (205.28): C 64.36, H 5.40, N 6.82; found: C 64.40, H 5.45, N 6.83.

Acknowledgements

The authors thank DST, New Delhi, for assistance under the IRHPA program for the NMR facility.

References

(1) (a) Arsenyan, P.; Oberte, K.; Pudova, O.; Lukevics, E. *Chem. Heterocycl. Compd.* **2002,** *38,* 1437–1447. (b) Morzherin, Y.Y.; Glukhareva, T.V.; Bakulev, V.A. *Chem. Heterocycl. Compd.* **2003,** *39,* 679–706.
(2) (a) Moawad, E.B.; Yousif, M.Y.; Metwally, M.A. *Pharmazie* **1989,** *44,* 820–822. (b) Kuroda, K.; Uchikurohane, T.; Tajima, S.; Tsubata, K. US Patent, US 6,166,054; *Chem. Abstr.* **2001,** *134,* 38255.
(3) (a) El-Kashef, H.S.; E-Bayoumy, B.; Aly, T.I. *Egypt J. Pharm. Sci.* **1986,** *27,* 27–30. (b) Sasaki, T. Japan Patent, 70,27,573; *Chem. Abstr.* **1971,** *74,* 3629.
(4) (a) El-Bahaie, S.; Assy, M.G.; Hassanien, M.M. *Pharmazie* **1990,** *45,* 791–793. (b) Padmavathi, V.; Sumathi, R.P.; Padmaja, A. *J. Ecobiol.* **2002,** *14,* 9–12.
(5) Thomas, E.W.; Nishizawa, E.E.; Zimmermann, D.C.; Williams, D.J. *J. Med. Chem.* **1985,** *28,* 442–446.
(6) Al-Smadi, M.; Ratrout, S. *Molecules* **2004,** *9,* 957–967.
(7) (a) Hurd, C.D.; Mori, R.I. *J. Am. Chem. Soc.* **1955,** *77,* 5359–5364. (b) Lalezari, I.; Shafiee, A.; Yalpani, M. *J. Org. Chem.* **1973,** *38,* 338–340.

(8) (a) Saravanan, S.; Muthusubramanian, S. *Phosphorous Sulfur Silicon Relat. Elem.* **2004,** *179,* 2411–2421. (b) Saravanan, S.; Nithya, A.; Muthusubramanian, S. *J. Heterocycl. Chem.* **2006,** *43,* 149–155. (c) Saravanan, S.; Athimoolam, S.; Muthusubramanian, S. *ARKIVOC* **2007,** (*i*), 22–33. (d) Saravanan, S.; Muthusubramanian, S.; Vasantha, S.; Sivakolunthu, S.; Raghavaiah, P. *J. Sulfur Chem.* **2007,** *28,* 181–199.
(9) Hollecker, M.; Marshall, D.L.; Harvey, A.L. *Br. J. Pharmacol.* **1993,** *110,* 790–794.
(10) Sudharsanam, R.; Chandrasekaran, S.; Das, P.K. *J. Mater. Chem.* **2002,** *12,* 2904–2908.
(11) Flowers, W.T.; Robinson, J.F.; Taylor, D.R.; Tipping, A.E. *J. Chem. Soc. Perkin Trans.* **1981,** *1,* 349–355.
(12) Butler, R.N.; O'Donoghue, D.A. *J. Chem. Soc. Perkin Trans.* **1982,** *1,* 1223–1227.
(13) Hu, Y.; Baudart, S.; Porco, J.A. *J. Org. Chem.* **1999,** *64,* 1049–1051.
(14) Warburton, W.K. *Chem. Rev.* **1957,** *57,* 1011–1120.
(15) Silberrad, O. *J. Chem. Soc. Trans.* **1922,** *121,* 1015–1022.
(16) Nakayama, J.; Konishi, T.; Ishii, A.; Hoshino, M. *Bull. Chem. Soc. Jpn.* **1989,** *62,* 2608–2612.
(17) Dixit, A.N.; Reddy, K.V.; Deshmukh, A.R.A.S.; Rajappa, S.; Ganguly, B.; Chandrasekar, J. *Tetrahedron,* **1995,** *51,* 1437–1448.
(18) Fujita, E. *J. Chem. Soc. Perkin Trans.* **1981,** *1,* 914–919.