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Note

Synthesis and characterization of 5-(cyclohexylsulfanyl)-4-aryl-1,2,3-selena/thiadiazoles

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The synthesis and characterization of new 5-(cyclohexylsulfanyl)-4-aryl-1,2,3-selena/thiadiazoles, obtained from the α-sulfanyl semicarbazones are described. The structures of these compounds have been established by ^{1}H NMR, ^{13}C NMR and single crystal X-ray diffraction.

Keywords: Cyclohexyl heteroaryl sulphide, 1,2,3-selenadiazoles, 1,2,3-thiadiazoles, ^{1}H NMR, ^{13}C NMR, X-ray diffraction

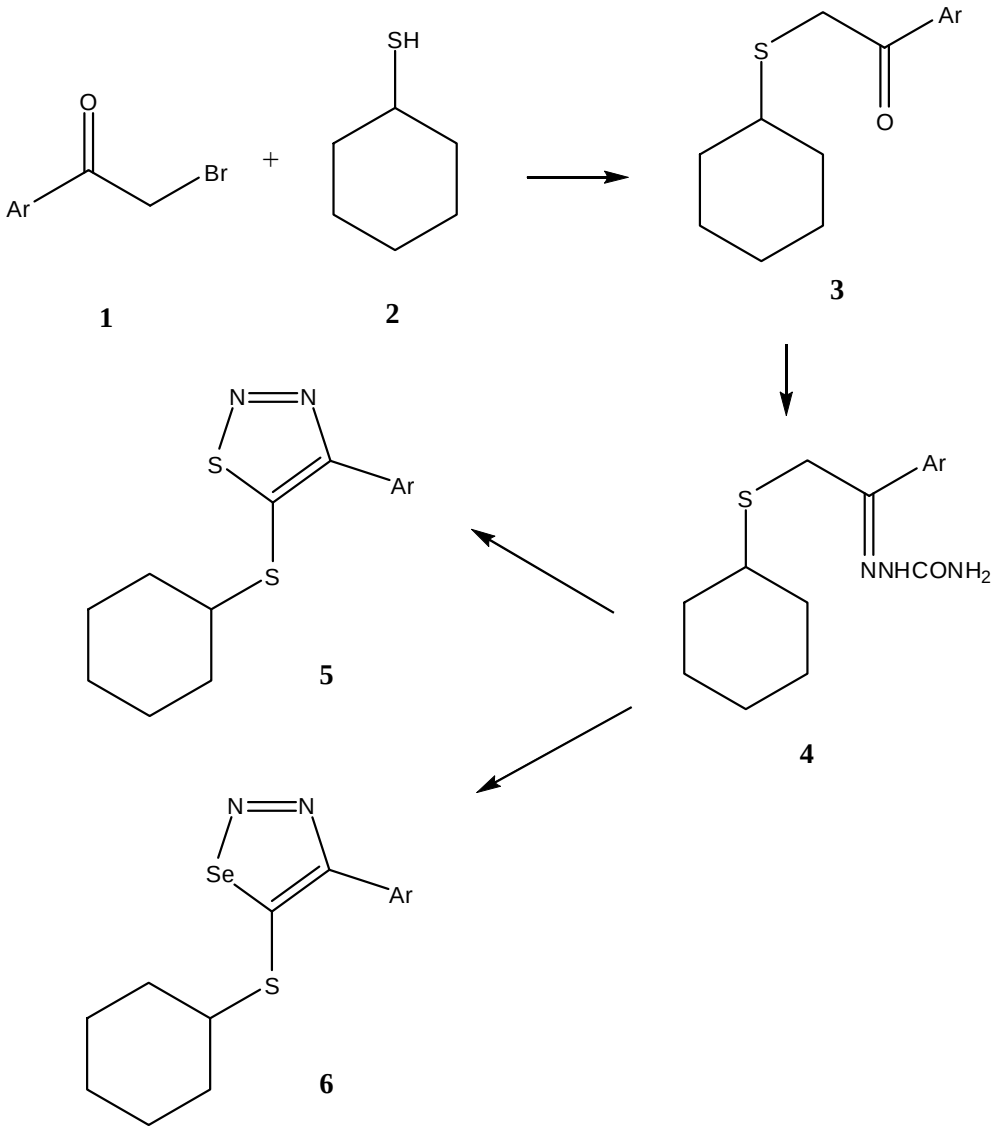
Sulfur linked heterocyclic compounds have received considerable attention recently because of their pharmacological importance[1-3]. 1,2,3-Selenadiazoles are versatile intermediates for the preparation of highly strained alkynes[4,5] and other selenium compounds[6-8]. Recently, it has been shown that 1,2,3-selenadiazoles react with olefins in the presence and absence of free radical initiator[9-11]. Compounds containing 1,2,3-selenadiazole moieties are well known for their pharmacological properties like antifungal and antibacterial activity[12-14].

The sulfur analogue of 1,2,3-selenadiazole *viz*. 1,2,3-thiadiazole is known to undergo Dimroth[15] and Cornforth[16,17] rearrangements leading to 1,2,3-triazoles. Compounds with a 1,2,3-thiadiazole moiety have been found to exhibit various pharmacological properties such as antifungal, pesticidal and antibacterial activity[18,19]. 4,5-Bis(*p*-methoxyphenyl)-1,2,3-thiadiazole possesses platelet aggregation inhibitory activity in humans[20] and certain 1,2,3-thiadiazole derivatives are useful for the therapeutic and prophylactic treatment of viral, bacterial, fungal, and parasitic infections in humans and animals[21].

In continuation to the work on the synthesis of sulfur-linked 1,2,3-selena/thiadiazoles[22], it has been planned to synthesize a different type of sulfide linked to 1,2,3-selena/thiadiazole and a cycloalkyl system. These sulfides may exhibit significant biological activity due to the presence of the sulfide unit and the hetroaryl system. The starting materials for the targeted 4-aryl-5-cyclohexylthio-1,2,3-selena/thiadiazoles are thioketones with an active methylene group α to the carbonyl group. Such thioketones **3,** synthesised by reacting the appropriately substituted phenacyl bromides **1** and cyclohexanethiol **2,** were then converted to the respective semicarbazones **4** by a conventional method. All the semicarbazones formed are homogeneous, having only one of the two possible geometrical isomers. The ^{1}H NMR spectrum of **4a** exhibits a singlet at δ 3.76 for the side chain methylene hydrogens. The methine hydrogen of the cyclohexyl ring appears at δ 2.5 as a triplet of triplet with coupling constants 10.5 Hz and 2.7 Hz indicating that the side chain sulphur is equatorially oriented in a cyclohexyl system.

Among the methods of synthesis for 1,2,3-thiadiazoles[23,24], the Hurd-Mori reaction was adopted in the present investigation. Thus, the semicarbazone **4** was stirred with thionyl chloride at -5°C for 90 min and upon working up, the pure thiadiazoles **5** were obtained (**Scheme I**). The ^{1}H and ^{13}C NMR data of semicarbazones **4** and thiadiazoles **5** are given in the **Table I**. The two sp^2 carbons of 1,2,3-thiadiazole ring appear around δ 147 and 157, the former being the one attached to sulfur and the latter, the one attached to nitrogen. There is no substantial change in the coupling pattern, indicating the absence of any conformational change in the cyclohexyl system.

It is well known that the treatment of semicarbazones having α-methelene group with selenium dioxide leads to the formation of 1,2,3-selenadiazoles[25,26]. A mixture of semicarbazone and selenium dioxide in 1:5 mole ratio in tetrahydrofuran at reflux yielded the selenadiazole **6** (**Scheme I**). The compound **6f** could not be obtained in pure form. The ^{1}H and ^{13}C NMR spectral data of all the synthesized selenadiazoles are given in **Table I**. The sp^2 carbons of hetroaryl rings appear very close to each other around δ 156. The methylene carbon, which appeared around δ 51 in the case of the thiadiazole, shows a downfield shift by 5 ppm. However, the corresponding hydrogen shows an upfield shift, appearing at δ 3. The results of



1 **2** **3** **4** **5** **6**

a: Ar = Phenyl
b: Ar = 4-Methylphenyl
c: Ar = 4-Phenylphenyl
d: Ar= 4-Chlorophenyl
e: Ar = 2-Naphthyl
f: Ar = 1-Naphthyl

Scheme I

X-ray analysis[27] of **6d** unambiguously prove its structure. The ORTEP and packing diagrams are given in **Figure 1** and **Figure 2**. The crystal data are presented in **Table II**.

In conclusion, the synthesis and spectral characterization of a new set of 1,2,3-selena/thiadiazoles, 5-(cyclohexylsulfanyl)-4-aryl-1,2,3-selena/thiadiazoles with cyclohexylthio group at five position have been achieved.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Bruker 300 MHz instrument in DMSO-d_6/$CDCl_3$ using TMS as internal standard. Chemical

Table I — Yield, ^{1}H and ^{13}C NMR spectral data for **4**, **5** and **6**[*]

Compd	R	Yield (%)	m.p. (ºC)	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
4a	Phenyl	92	122	1.20-1.60 (m, 6H), 1.75-1.84 (m, 2H), 1.96-2.01 (m, 2H), 2.50 (tt, *J* = 10.5, 2.7 Hz, 1H), 3.76 (s, 2H), 5.37 (bs, 1H), 6.20 (bs, 1H), 7.36-7.43 (m, 3H), 7.67-7.71 (m, 2H), 8.75 (s, 1H)spfksdopfk	25.6, 25.9, 26.0, 33.3, 44.8, 126.1, 128.6, 129.4, 137.1, 145.3, 157.4.
4b	4-Methylphenyl	88	159	1.22-1.62 (m, 6H), 1.73-1.76 (m, 2H), 1.95-1.99 (m, 2H), 2.36 (s, 3H), 2.70.-2.78 (m, 1H), 3.73 (s, 2H), 5.45 (b,1H), 6.19 (bs, 1H), 7.21 (d, *J* = 8.1, Hz, 2H), 7.57-7.59 (m, d, *J* = 8.1 Hz, 2H), 8.76 (s, 1H)	21.2, 25.6, 25.7, 25.8, 33.2, 44.7, 125.9, 129.2, 134.2, 139.4, 145.4, 157.5.
4d	4-Chlorophenyl	93	169	1.2-1.6 (m, 6H), 1.75-1.83 (m, 2H), 1.96-2.00 (m, 2H), 2.75 (tt, *J* = 10.5, 3.3 Hz, 1H), 3.72 (s, 2H), 5.42 (bs, 1H), 6.15 (bs, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.7 Hz), 8.82 (s, 1H)	25.6, 25.7, 25.9, 33.3, 44.9, 127.3, 128.8, 135.3, 135.5, 144.2 157.3.
5a	Phenyl	42	--[**]	1.22-1.65 (m, 6H), 1.70-1.85 (m, 2H), 2.05-2.15 (m, 2H), 3.11-3.20 (m, 1H), 7.40-7.53 (m, 2H), 7.96 (dd, *J* = 10.1, 1.5 Hz, 2H)	25.3, 25.6, 33.0 51.6, 128.6, 128.7, 128.8 130.9 147.4, 157.5.
5b	4-Methylphenyl	50	--[**]	1.18-1.60 (m, 6H), 1.73-1.77 (m, 2H), 2.03-2.08 (m, 2H), 2.39 (s, 3H), 3.10 (tt, *J* = 7.2, 3 Hz, 1H), 7.20-7.30 (m, 2H), 7.80-7.89 (m, 2H)	21.4, 25.4, 25.6, 33.0, 51.5, 128.4, 129.2, 129.5, 138.8, 146.7, 157.5.
5c	4-Phenylphenyl	48	61	1.25-1.69 (m, 6H), 1.80-1.84 (m, 2H), 2.12-2.16 (m, 2H), 3.20 (tt, *J* = 10.2, 3.6 Hz, 1H), 7.48 (t, *J* = 9 Hz, 2H), 7.68 (d, *J* = 9 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 8.09 (d, *J* =8.4 Hz, 2H)	25.3, 25.,6, 33.0 51.7, 127.0, 127.2, 127.6, 128.9, 129.4, 129.9, 140.3, 141.5, 147.3, 157.0.
5d	4-Chlorophenyl	49	50	1.20-1.69 (m, 6H), 1.77-1.80 (m, 2H), 2.07-2.11 (m, 2H), 3.15 (t, *J* = 10.2, 3.3 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H)	25.2, 25.6, 32.9, 51.8, 128.8, 129.4, 129.8, 134.7, 147.7, 156.2.
5e	2-Naphthyl	46	--[**]	1.24-1.45 (m, 6H), 1.70-1.73 (m, 2H), 2.00-2.10 (m, 2H), 3.12 (tt, *J* = 9.9, 4.2 Hz, 1H), 7.47-7.60 (m, 5H), 7.93-7.80 (m, 2H)	25.3, 25.7, 33.0, 51.8, 125.2, 125.6, 126.3, 126.8, 127.9, 128.5, 128.9, 130.0, 131.9, 133.9, 150.6, 157.5.
5f	1-Naphthyl	44	--[**]	1.23-1.69 (m, 6H), 1.79-1.83 (m, 2H), 2.11-2.15 (m, 2H), 3.16-3.25 (m, 1H), 7.51-7.57 (m, 2H), 7.88-7.99 (m, 3H), 8.14-8.18 (m, 1H), 8.45 (s, 1H)	25.3, 25.6, 33.0, 51.7, 126.0, 126.4, 126.7, 127.7, 128.1, 128.3, 128.4, 128.4, 133.1, 133.1, 147.6, 157.4.
6a	Phenyl	43	--[**]	1.27-1.66 (m, 6H), 1.781.82 (m, 2H), 2.13-2.18 (m, 2H), 2.95-3.04 (m, 1H), 7.43(tt, *J* = 7.5, 2.7 Hz, 1H), 7.49-7.54 (m, 2H), 7.91-7.95 (m, 2H)	25.4, 25.7, 33.1, 56.0, 128.5, 128.6, 129.2, 131.9, 155.9 156.3.
6b	4-Methylphenyl	42	--[**]	1.28-1.83 (m, 6H), 1.79-1.83 (9m, 2H), 2.14-2.19 (m, 2H), 2.44 (s,3H), 2.96-3.00 (tt, *J* = 10.5, 3.6 Hz, 1H), 7.27-7.34 (d, *J* = 8.1 Hz), 7.80 (d, *J* = 8.1 Hz)	21.3, 25.3, 25.6, 33.1, 55.9, 129.0 (2 C merging 1 CH and 1 Q), 129.1, 138.4, 155.5, 156.1.
6c	4-Phenylphenyl	43	53	1.28-1.63 (m, 6H), 1.81 (m, 2H), 2.17-2.20 (m, 2H), 2.98-3.05 (m, 1H), 7.35-7.50 (m, 3H), 7.65-7.75 (m, 3H), 7.99-8.02 (m, 2H)	25.3, 25.7, 33.1, 56.2, 127.1, 127.2, 127.5, 128.8, 129.5, 130.9, 140.4, 144.1, 155.1, 156.2.
6d	4-Chlorophenyl	48	109	1.24-1.65 (m, 6H), 1.78-1.82 (m, 2H), 2.13-2.17 (m, 2H), 2.95-3.04 (tt, *J* = 10.2, 3.6 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H)	25.3, 25.6, 33.1, 56.3, 128.7, 129.8, 130.4, 134.2, 154.8, 156.6.
6e	2-Naphthyl	46	--[**]	1.23-1.66 (m, 2H), 1.80-1.83 (m, 2H), 2.17-2.21 (m, 2H), 2.99-3.08 (m, 1H), 7.52-7.57 (m, 2H), 7.88-7.99 (m, 3H), 8.06-8.12 (m, 1H), 8.36 (m, 1H)	25.3, 25.7, 33.2, 56.2, 126.4, 126.4, 126.8 127.7, 128.2, 128.4, 128.6, 129.4, 132.1, 132.9, 156.0, 156.6.

* **6f** could not be obtained in pure form; **4c** (Yield 89%; m.p. 171°C), **4e** (Yield 91%; high melting) and **4f** (Yield 86%; high melting) are not sufficiently soluble in common NMR solvents to record the NMR spectra.

** Viscous liquid

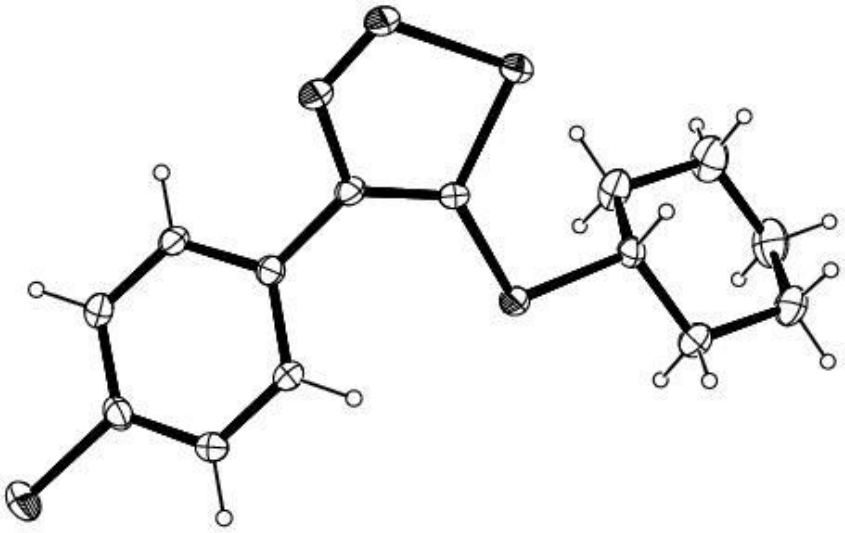


Figure 1 — ORTEP diagram of 4-(4-chlorophenyl)-5-(cyclohexylsulfanyl)-1,2,3-selenadiazole **6d**

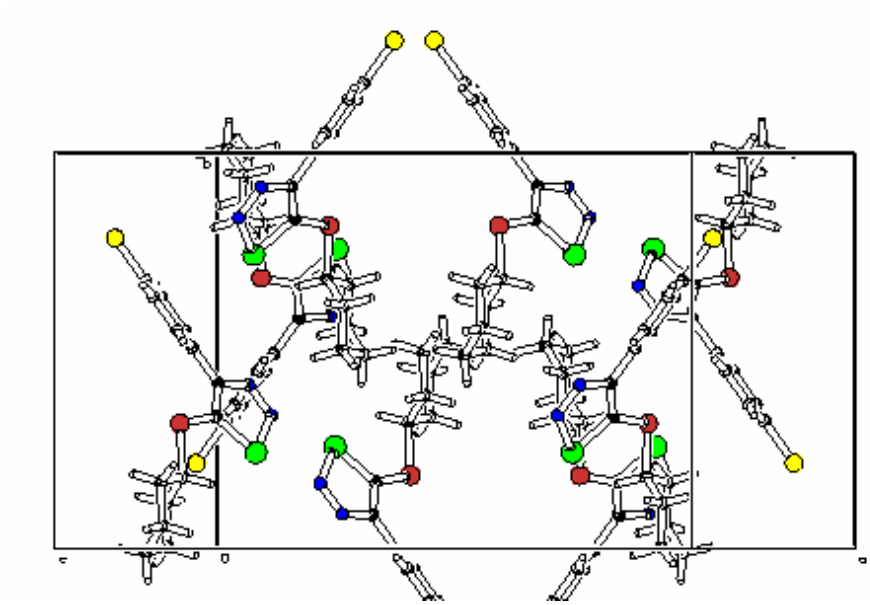


Figure 2 — Packing diagram of 4-(4-chlorophenyl)-5-(cyclohexylsulfanyl)-1,2,3-selenadiazole **6d**

shifts are given in δ (ppm) and coupling constants are given in Hertz. The single crystal X-ray data were collected on a Nonius MACH3 kappa diffractometer with Mo K_α radiation (λ = 0.71069 Å). The structure was solved by direct methods from SHELXA97 and refined by full matrix least squares on F^2 by SHELXTL97. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 648888. Copies of the data can be obtained, free of charge, by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK (e-mail: data_request@ccdc.cam.ac.uk; fax: +44 1223 336033). Column chromatography was carried out over silica gel (60-120 mesh) using petroleum ether-ethyl acetate as an eluent.

General procedure for the preparation of 2-[(*Z*)-2-(cyclohexylsulfanyl)-1-arylethylidene]-1-hydrazinecarboxamide, 4

To a warm ethanolic solution of 2-(cyclohexylsulfanyl)-1-phenyl-1-ethanone **3** (0.005 mole), aqueous solution of semicarbazide hydrochloride (3.90 g, 0.035 mole) and sodium acetate (2.87 g, 0.035 mole) was added carefully. The reaction mixture was

Table II — Crystal data and structural refinement for **6d**

Parameters	**6d**
Empirical formula	$C_{14}H_{15}ClN_2SSe$
Formula weight	357.75
Temperature	293 (2) K
Wavelength	0.71069 Å
Crystal system, Space group	Monoclinic, C2/c
Unit cell dimensions	a = 21.374 Å; α = 90.00 deg; b = 13.252 Å; β = 116.846 deg; c = 12.055 Å; γ = 90.00 deg.
Z, Volume	8, 3046.5 $Å^3$
Density (calculated)	1.560 mg/m^3
Absorption coefficient	2.765 mm^{-1}
F(000)	1440
Crystal size	0.24 × 0.21 × 0.18 mm
Theta range for data collection	2.14 to 24.99 deg.
Index ranges	0<=h<=25, -1<=k<=15, -14<=l<=12
Reflections collected	3005
Independent reflections	2678 [R(int) = 0.0234]
Absorption correction	Psi-scans
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2678 / 0 / 173
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R_1 = 0.0303, wR_2 = 0.0618
R indices (all data)	R_1 = 0.0679, wR_2 = 0.0734
Largest diff. peak and hole	0.262 and -0.274 e. $Å^{-3}$

refluxed for 2 hr, poured into crushed ice and filtered. The product was purified by recrystallization from ethanol to give the respective semicarbazones, **4**.

General procedure for the preparation of 5-(cyclohexylsulfanyl)-4-aryl-1,2,3-thiadiazole, 5

Semicarbazone (0.001 mole) was added to 10 mL of thionyl chloride and cooled to –5°C. The reaction-mixture was stirred for about 2 hr. The excess thionyl chloride was decomposed by pouring an aqueous solution of sodium carbonate and the resultant mixture was extracted with chloroform. The product was obtained upon purification by column chromatography over silica gel.

General procedure for the preparation of 5-(cyclohexylsulfanyl)-4-aryl-1,2,3-selenadiazole, 6

A solution of 0.001 mole of the appropriate semicarbazone was dissolved in dry THF by gentle warming and 0.01 mole (1.10 g) of powdered selenium dioxide was added portionwise. The reaction mixture was heated to reflux on a water bath for 1-2 hr. The selenium deposited on cooling was removed by filtration, and the filtrate was poured into crushed ice and extracted with chloroform. The desired product was obtained upon purification by column chromatography over silica gel.

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