

## Heterocyclic Compounds. Part 6.<sup>1</sup> Synthesis of 1,3,4-Thiadiazolidines from the Reactions of Phenyl Hydrazones with Phenyl Isothiocyanate and Carbon Disulphide

By Jiro Motoyoshiya, Makoto Nishijima, Iwao Yamamoto,\* and Haruo Gotoh, Department of Chemistry, Shinshu University at Ueda, Ueda, Nagano 386, Japan

Yukiteru Katsube, Department of Chemistry, Faculty of Engineering, Tottori University, Tottori-City 680 Japan

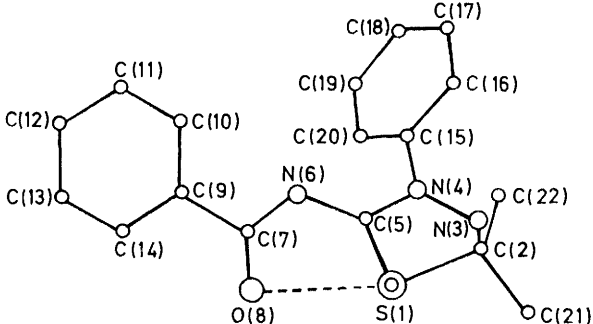
Yoshiki Ohshiro and Toshio Agawa, Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

The reactions of phenyl isothiocyanate with ketonephenylhydrazones in the presence of sodium hydride in dimethylformamide afforded 4-phenyl-5-phenylimino-1,3,4-thiadiazolidines (2a–e) in good yields. Aldehyde phenylhydrazones, however, gave the thiosemicarbazone (8). Reactions using carbon disulphide instead of isothiocyanates under similar conditions yielded 4-phenyl-1,3,4-thiadiazolidine-5-thiones (3a–e). The mechanisms of formation and <sup>13</sup>C n.m.r. spectra of the products are also described.

1,3-DIPOLAR reactions are one of the most versatile means for synthesis of 5-membered heterocycles.<sup>2</sup> Recently Saxena *et al.*<sup>3</sup> and Grigg *et al.*<sup>4</sup> showed that hydrazones undergo 1,3-dipolar cycloaddition reactions *via* mesoionic azomethine ylide tautomers. Previously, we reported the synthesis of 1,3,4-oxatriazepines from

TABLE I

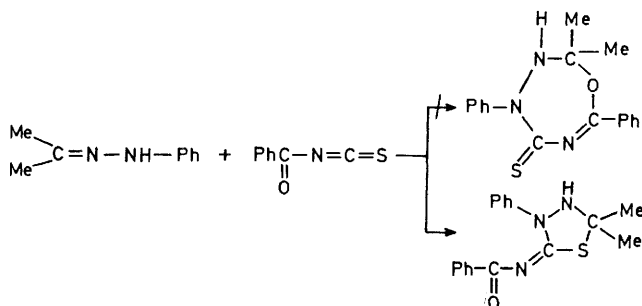
Selected bond lengths and angles of 5-benzoylimino-2,2-dimethyl-1,3,4-thiadiazolidine for non-hydrogen atoms



S(1)–C(2)	1.89	S(1)–C(5)	1.75
C(2)–N(3)	1.44	C(2)–C(21)	1.56
C(2)–C(22)	1.51	N(3)–N(4)	1.44
N(4)–C(5)	1.36	N(4)–C(15)	1.41
C(5)–N(6)	1.34	N(6)–C(7)	1.37
C(7)–O(8)	1.22	C(7)–C(9)	1.51
S(1)–O(8)	2.76		
	(°)		(°)
C(2)–S(1)–C(5)	89	S(1)–C(2)–N(3)	104
S(1)–C(2)–C(21)	108	S(1)–C(2)–C(22)	109
N(3)–C(2)–C(21)	109	N(3)–C(2)–C(22)	113
C(21)–C(2)–C(22)	114	C(2)–N(3)–N(4)	108
N(3)–N(4)–C(5)	115	N(3)–N(4)–C(15)	118
C(5)–N(4)–C(15)	127	S(1)–C(5)–N(4)	112
S(1)–C(5)–N(6)	129	N(4)–C(5)–N(6)	119
C(5)–N(6)–C(7)	116	N(6)–C(7)–O(8)	126
N(6)–C(7)–C(9)	113	O(8)–C(7)–C(9)	121
O(8)–S(1)–C(2)	158	O(8)–S(1)–C(5)	70

the reactions of benzoyl isothiocyanate with phenylhydrazone derivatives.<sup>1</sup> Durant<sup>5</sup> has also reported the interaction of benzoyl isothiocyanate with alkylhydrazones. The structure of the above compounds were presumed to be seven-membered oxatriazepines on the

basis of their i.r., n.m.r., and mass spectra and some chemical properties. But an X-ray analysis (Table I)<sup>6</sup> clearly showed that the structure of the product from the reaction of acetone phenylhydrazone with benzoyl



isothiocyanate is 5-benzoylimino-2,2-dimethyl-4-phenyl-1,3,4-thiadiazolidine, and not the seven-membered oxatriazepine.

We now extend these findings to the reactions of phenylhydrazones with phenyl isothiocyanate and carbon disulphide, and report a convenient synthesis of 1,3,4-thiadiazolidines. 1,3,4-Thiadiazolidine-5-thiones are well known compounds,<sup>7,8</sup> and Heugebaert *et al.*<sup>8</sup> prepared 4-alkyl derivatives from *N*-alkylhydrazones and carbon disulphide. However, they failed to synthesize 4-aryl compounds.

### RESULTS AND DISCUSSION

**Reactions with Phenyl Isothiocyanate.**—Phenyl isothiocyanate did not react with phenylhydrazones in the absence of catalyst at room temperature or in boiling benzene. Hydrazones have an active hydrogen on a nitrogen atom and therefore it is expected that reaction might proceed in the presence of base. The mixture of phenyl isothiocyanate and the phenylhydrazone (1a), however, did not give any crystalline products in the presence of catalytic amounts of triethylamine in boiling benzene, nor in the presence of sodium hydroxide in boiling dioxan. On the contrary, sodium hydride proved an effective catalyst for these reactions. In the presence of sodium hydride, phenyl isothiocyanate and the phenyl-

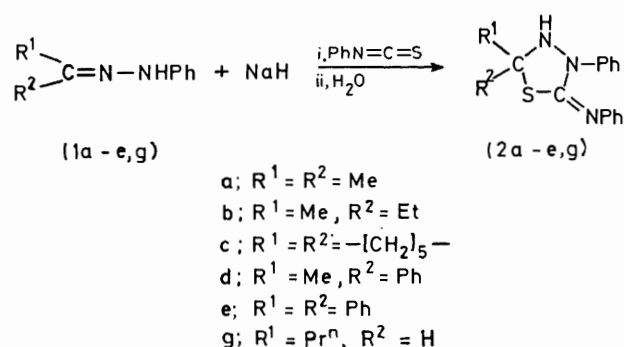
TABLE 2

## 2,2-Disubstituted-4-phenyl-5-phenylimino-1,3,4-thiadiazolidines (2a—f)

Products	R <sup>1</sup>	R <sup>2</sup>	Yield (%) <sup>a</sup>	M.p. (°C)	ν <sub>max.</sub> (cm <sup>-1</sup> ) NH	N.m.r. (δ) <sup>b</sup>			M <sup>+</sup>
						R <sup>1</sup>	R <sup>2</sup>	NH	
(2a)	Me	Me	90	160—160.5	3 160	1.4 (s)	1.4 (s)	5.1 (s)	283
(2b)	Me	Et	63	121—122	3 120	1.4 (s)	1.0 (t)	5.0 (s)	297
(2c)	-[CH <sub>2</sub> ] <sub>5</sub> -		97	156.5—157	3 160	1.2—2.1 (m)		4.8 (s)	323
(2d) <sup>c</sup>	Me	Ph	55	120—121	3 100	1.7 (s)	6.8—7.3 (m)	5.4 (s)	345
(2e)	Ph	Ph	73	145—147	3 190	7.2—7.6 (m)		5.5 (s)	407
(2f)	Pr <sup>n</sup>	H	82	123.5—124	3 120	0.7—2.9 (m)	2.5 (t)	5.0 (br)	297

<sup>a</sup> Based on hydrazones. <sup>b</sup> In CDCl<sub>3</sub>. <sup>c</sup> Reactions carried out at -5 °C.

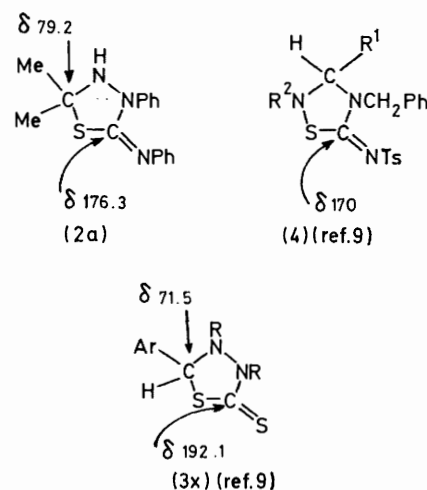
hydrazones (1a—e) were stirred in dimethylformamide (DMF) at room temperature or at -5 °C for 1 h to afford the 1,3,4-thiadiazolidines (2a—e) in good yields (Table 2). The progress of the reaction was readily distinguished by the change in colour of the solution.



The structures of the thiadiazolidines (2a—e) were determined by spectral data (Table 2) and <sup>13</sup>C n.m.r. spectra (Table 3). The <sup>13</sup>C n.m.r. spectrum of (2a) showed the two expected ring-carbon absorptions at δ 79.2 and 176.3 p.p.m., which were fully consistent with the values reported. L'abbe and his co-workers<sup>9</sup> reported that the S—C—N ring carbon absorbed at δ 71.5 p.p.m. for 1,3,4-thiadiazolidine (3x), and that the absorption of C=NTs ring carbon of 5-tosylimino-1,2,4-thiadiazolidines (4) appeared at ca. δ 170 p.p.m. In addition, the mass spectra of the products (2a—e) also satisfied the presumed structures of the 1,3,4-thiadiazolidines. For

instance, product (2a) showed a molecular ion peak at *m/e* 283 and fragments at *m/e* 268 (*M*<sup>+</sup> - CH<sub>3</sub>), 148 (*M*<sup>+</sup> - PhNCS), and 194 (PhNCNPh). The peak at *m/e* 194 suggests the ring structure, but not other structures such as the thiosemicarbazone (6a). The other products (2a—e) also testified to the ring structure.

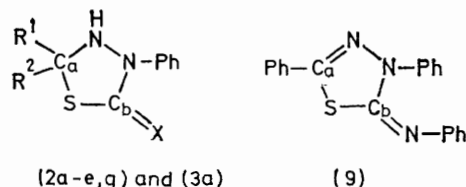
Based on these results, it is presumed that the re-



actions of phenyl isothiocyanate with ketone phenylhydrazones could proceed *via* a pathway as shown in the Scheme; *i.e.*, the anion of the hydrazones (5) formed initially would be attacked by the centre carbon of the isothiocyanate to form an intermediate ion (6), followed by cyclization to result in the 1,3,4-thiadiazolidine

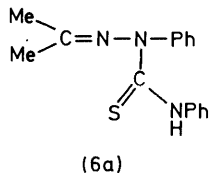
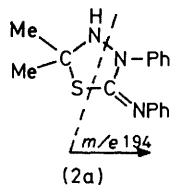
TABLE 3

Selected <sup>13</sup>C n.m.r. chemical shifts of (2a—e), (9), and (3a)



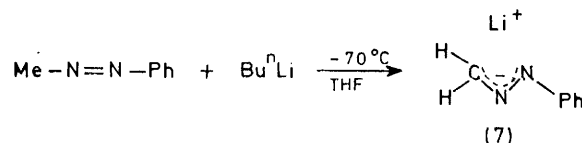
Compounds	R <sup>1</sup>	R <sup>2</sup>	X	δ (p.p.m.)		Solvent
				C <sub>a</sub>	C <sub>b</sub>	
(2a)	Me	Me	NPh	79.2	176.3	[ <sup>2</sup> H <sub>6</sub> ]DMSO
(2b)	Me	Et	NPh	82.2	177.4	CDCl <sub>3</sub>
(2c)	-[CH <sub>2</sub> ] <sub>5</sub> -		NPh	81.8	177.6	CDCl <sub>3</sub>
(2d)	Me	Ph	NPh	82.4	177.0	CDCl <sub>3</sub>
(2e)	Ph	Ph	NPh	88.5	177.1	CDCl <sub>3</sub>
(2g)	Pr <sup>n</sup>	H	NPh	76.6	175.8	[ <sup>2</sup> H <sub>6</sub> ]DMSO
(3a)	Me	Me	S	73.1	194.2	[ <sup>2</sup> H <sub>6</sub> ]DMSO
(9)			NPh	149.9	168.6	CDCl <sub>3</sub>

(2a—e). The anion (5) is similar to Kauffmann's anion (7),<sup>10</sup> which was obtained from methylazobenzene and *n*-butyl-lithium. They reported that the anion (7)



reacted with carbonyl compounds at the CH<sub>2</sub> group. On the contrary, phenyl isothiocyanate attacked the hydrazone anion (5) at N-1 preferentially, *i.e.*, the

*i.r.* (NH stretch at 3 320 cm<sup>-1</sup>) and n.m.r. spectra (NH proton resonated at δ 10.2). The thiosemicarbazone (8) was heated in benzene-hexane (*ca.* 2:1) to give the thiadiazoline (9) in 38% yield. The thiadiazoline (9)



did not show any NH absorption in either its *i.r.* or n.m.r. spectrum and its mass spectrum contained a molecular ion peak at *m/e* 329. On the contrary, a reaction of *n*-butylaldehyde phenylhydrazone gave the thiadi-

TABLE 4  
2,2-Disubstituted-4-phenyl-1,3,4-thiadiazolidine-5-thiones (3a—e)

Products	R <sup>1</sup>	R <sup>2</sup>	Yield (%) <sup>a</sup>	M.p. (°C)	ν <sub>max</sub> (cm <sup>-1</sup> ) NH	N.m.r. (δ) <sup>b</sup>			M <sup>+</sup>
						R <sup>1</sup>	R <sup>2</sup>	NH	
(3a)	Me	Me	76	122—123	3 140	1.72 (s)	1.72 (s)	6.0 (s)	224
(3b)	Me	Et	61	89—90	3 120	1.69 (s)	1.05 (t)	5.85 (s)	238
(3c)	-[CH <sub>2</sub> ] <sub>5</sub> -		80	139—141	3 150	2.0 (q)		5.9 (s)	264
(3d)	Me	Ph	63	107—107.5	3 130	2.03 (s)	7.23—7.85 (m)	6.12 (s)	286
(3e)	Ph	Ph	50	163—164	3 160	7.30—7.85 (m) <sup>c</sup>		8.35 (s) <sup>c</sup>	348

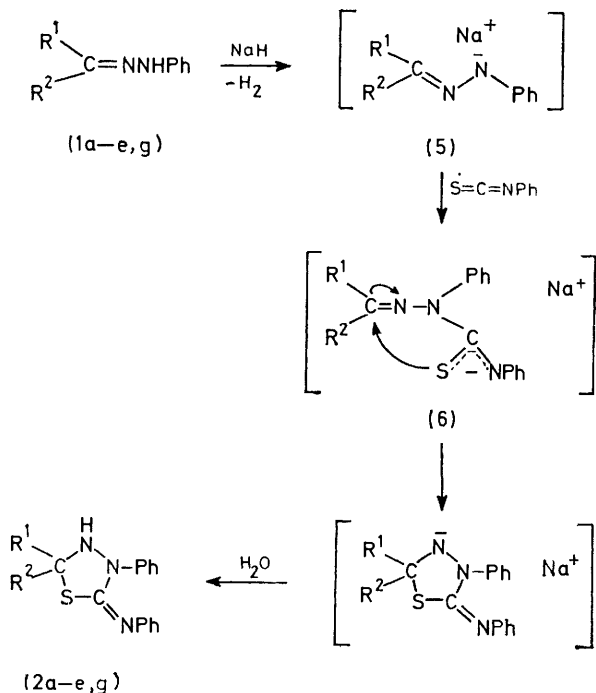
<sup>a</sup> Based on hydrazones. <sup>b</sup> In CDCl<sub>3</sub>. <sup>c</sup> In [²H<sub>6</sub>]DMSO.

negative charge of the anion (5) might be localized on the nitrogen atom as shown in the Scheme.

In contrast to the cases of ketone phenylhydrazones, aldehyde phenylhydrazones did not always give thiadi-

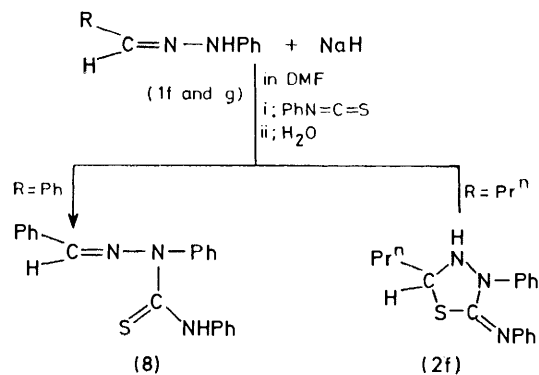
azolidine (2f) in 82% yield. The structure of (2f) was determined on the basis of its spectral data (Tables 2 and 3).

*Reactions with Carbon Disulphide.*—Heugebaert and

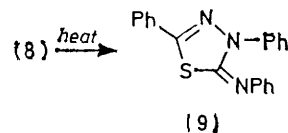


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azolindines; that is, the substituents of the aldehydes affected the course of the reaction. In the case of benzaldehyde phenylhydrazone (1f), the product was the thiosemicarbazone (8) which was identified by its

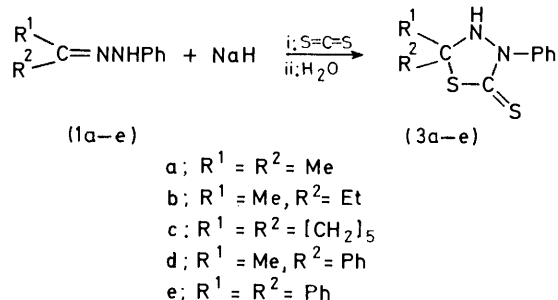


his co-workers<sup>8</sup> reported that phenylhydrazones did not react with carbon disulphide because of the low electron density of the aryl-substituted nitrogen and because it is difficult to synthesize 1,3,4-thiadiazolidines



having an aryl substituent at the 4-position. In contrast to their results, 4-arylthiadiazolidines are readily obtained by our method. In the presence of sodium hydride, the phenylhydrazones (1a—e) readily reacted with carbon disulphide in DMF at room temperature to afford 2,2-disubstituted-4-phenyl-1,3,4-thiadiazolidine-5-

thiones (3a–e) in good yields. The results are summarized in Table 4. The C=S ring carbon absorbed at  $\delta$  194.2 p.p.m., and the other ring carbon atom resonated



at  $\delta$  73.1 p.p.m. These chemical shifts are comparable to those in the literature,<sup>9</sup> and are fully consistent with the 1,3,4-thiadiazolidine-5-thione structure.

#### EXPERIMENTAL

M.p.s were taken with a Mitamura capillary micro-apparatus. I.r. spectra were obtained using a JASCO IR-E spectrometer. <sup>1</sup>H N.m.r. spectra were recorded with a JEOL JNM-C-60HL spectrometer, and <sup>13</sup>C spectra with a JNM-FX90Q spectrometer using tetramethylsilane as internal reference. Mass spectra were obtained with a JEOL JMS-01SG-2 spectrometer on-line to a JEOL JEC-6 spectrum computer.

**2,2-Dimethyl-4-phenyl-5-phenylimino-1,3,4-thiadiazolidine (2a).**—To a suspension of an excess of sodium hydride (1.0 g, 50% oil) in dimethylformamide (DMF) (100 ml) was added acetone phenylhydrazone (1a) (1.48 g, 10 mmol) at room temperature. After 10 min phenyl isothiocyanate (1.35 g, 10 mmol) was added dropwise to the mixture (the colour of the solution changed from brown to pale yellow), and the resulting mixture was stirred for an additional 1 h at room temperature. A large excess of water (500 ml) was added and the mixture was extracted with two 150-ml portions of ethyl acetate; the extracts were combined, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated to give the *thiadiazolidine* (2a) (2.54 g, 90%) (Found:  $M^+$ , 283.115 7.  $\text{C}_{16}\text{H}_{17}\text{N}_3\text{S}$  requires  $M$ , 283.114 5). Physical and other spectral data are shown in Tables 2 and 4.

Similarly prepared were *2-ethyl-2-methyl-4-phenyl-5-phenylimino-1,3,4-thiadiazolidine* (2b) [from sodium hydride (1.0 g), (1b) (1.62 g, 10 mmol), and phenyl isothiocyanate (1.35 g, 10 mmol)] (1.87 g, 63%) (Found:  $M^+$ , 297.127 8.  $\text{C}_{17}\text{H}_{19}\text{N}_3\text{S}$  requires  $M$ , 297.129 1); *cyclohexanespiro-2'-(4'-phenyl-5'-phenylimino-1',3',4'-thiadiazolidine)* (2c) [from sodium hydride (1.0 g), (1c) (1.88 g, 10 mmol), and phenyl isothiocyanate (1.35 g, 10 mmol)] (3.13 g, 97%) (Found:  $M^+$ , 323.148 3.  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{S}$  requires  $M$ , 323.145 8); *2-methyl-2,4-diphenyl-5-phenylimino-1,3,4-thiadiazolidine* (2d) [from sodium hydride (1.0 g), (1d) (2.10 g, 10 mmol), and phenyl isothiocyanate (1.35 g, 10 mmol) at  $-5^\circ\text{C}$ ] (1.90 g, 55%) (Found:  $M^+$ , 345.130 6.  $\text{C}_{21}\text{H}_{19}\text{N}_3\text{S}$  requires  $M$ , 345.127 6); *2,2,4-triphenyl-5-phenylimino-1,3,4-thiadiazolidine* (2e) [from sodium hydride (1.0 g), (1e) (2.72 g, 10 mmol), and phenyl isothiocyanate (1.35 g, 10 mmol) at  $-5^\circ\text{C}$ ] (2.99 g, 73%) (Found:  $M^+$ , 407.145 1.  $\text{C}_{26}\text{H}_{21}\text{N}_3\text{S}$  requires  $M$ , 407.145 8); *4-phenyl-5-phenylimino-2-propyl-1,3,4-thiadiazolidine* (2g) [from sodium hydride (1.0 g), (1g) (1.62 g, 10 mmol), and phenyl isothiocyanate (1.35 g, 10 mmol) at room temper-

ature] (2.45 g, 82%) (Found:  $M^+$ , 297.130 2.  $\text{C}_{17}\text{H}_{19}\text{N}_3\text{S}$  requires  $M$ , 297.130 2).

**Benzaldehyde 2,4-Diphenylthiosemicarbazone (8) and 2,4-Diphenyl-5-phenylimino- $\Delta^2$ -1,3,4-thiadiazoline (9).**—A similar reaction of sodium hydride (1.0 g), compound (1 g) (1.96 g, 10 mmol), and phenyl isothiocyanate (1.35 g, 10 mmol) at room temperature gave as a single product, the *thiosemicarbazone* (8) (2.35 g, 71%), m.p. 162–163°;  $\nu_{\text{max}}$ , 3 320 (NH)  $\text{cm}^{-1}$ ;  $\delta(\text{CDCl}_3)$  7.15–7.91 (16 H, m, ArH and CH), and 10.16 (1 NH, br, H);  $m/e$  (75 eV) 331 ( $M^+$ ), 329, 196, 135, 92, and 77 (Found:  $M^+$ , 331.113.  $\text{C}_{20}\text{H}_{17}\text{N}_3\text{S}$  requires  $M$ , 331.114 4).

From the mother-liquor after recrystallization of (8) (2.35 g) was obtained the *thiadiazoline* (9) (0.89 g, 38%), m.p. 188–189°;  $\delta(\text{CDCl}_3)$  7.30–7.65 (11 H, m, ArH) and 8.12–8.34 (4 H, m, ArH);  $m/e$  329 ( $M^+$ ) (Found:  $M^+$ , 329.096 5.  $\text{C}_{20}\text{H}_{15}\text{N}_3\text{S}$  requires  $M$ , 329.098 8).

**2,2-Dimethyl-4-phenyl-1,3,4-thiadiazolidine-5-thione (3a).**—To a suspension of sodium hydride (1.0 g) in DMF (100 ml) was added acetone phenylhydrazone (1a) (1.48 g, 10 mmol) at room temperature. After 10 min carbon disulphide (0.76 g, 10 mmol) was added dropwise to the mixture, when the solution changed from brown to yellow-brown. The resulting mixture was stirred for 1 h after which a large excess of water (500 ml) was added and the mixture extracted with ethyl acetate (2  $\times$  150 ml). The extract was dried and evaporated to give the *thione* (3a) (1.7 g, 76%), m.p. 122–123°;  $m/e$  224 ( $M^+$ ), 209, and 148 (Found:  $M^+$ , 224.044 4.  $\text{C}_{10}\text{H}_{12}\text{N}_2\text{S}_2$  requires  $M$ , 224.044 3). Other spectral and physical data are shown in Table 3.

Similarly prepared were *2-ethyl-2-methyl-4-phenyl-1,3,4-thiadiazolidine-5-thione* (3b) [from (1b) (1.67 g, 10 mmol), sodium hydride (1.0 g), and carbon disulphide (0.91 g, 12 mmol) (1.46 g, 61%), m.p. 89–90°,  $m/e$  238 ( $M^+$ ), 209, 162, and 135 (Found:  $M^+$ , 238.057 1.  $\text{C}_{11}\text{H}_{14}\text{N}_2\text{S}_2$  requires  $M$ , 238.059 9); *cyclohexane spiro-2'-(4'-phenyl-1',3',4'-thiadiazolidine-5-thione)* (3c) [from sodium hydride (1.0 g), compound (1c) (1.88 g, 10 mmol), and carbon disulphide (0.91 g, 12 mmol)] (2.12 g, 80%), m.p. 139–141°,  $m/e$  264 ( $M^+$ ), 221, 188, and 135 (Found: C, 59.25; H, 6.05; N, 10.7.  $\text{C}_{13}\text{H}_{16}\text{N}_2\text{S}_2$  requires C, 59.1; H, 6.1; N, 10.6%); *2-methyl-2,4-diphenyl-1,3,4-thiadiazolidine-5-thione* (3d) [from sodium hydride (1.0 g), compound (1d) (2.10 mmol), 63%) and carbon disulphide (0.91 g, 12 mmol)] (1.80 g, m.p. 107–107.5,  $m/e$  286 ( $M^+$ ), 210, 209, and 118 (Found: C, 62.65; H, 4.8; N, 9.8.  $\text{C}_{15}\text{H}_{14}\text{N}_2\text{S}_2$  requires C, 62.95; H, 4.95; N, 9.8%); and *2,2,4-triphenyl-1,3,4-thiadiazolidine-5-thione* (3e) [from sodium hydride (1.0 g), compound (1e) (2.70 g, 10 mmol), and carbon disulphide (0.91 g, 12 mmol)], m.p. 163–164°,  $m/e$  348 ( $M^+$ ), 272, and 180 (Found:  $M^+$ , 348.075 9.  $\text{C}_{20}\text{H}_{16}\text{N}_2\text{S}_2$  requires  $M$ , 348.075 8).

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