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2-Methyl-1,3-dithietanes bearing electron withdrawing groups on the methylene carbon atom were synthesized and their reactivities were studied. These compounds readily underwent a ring-opening reaction with a variety of nucleophilic reagents such as amines, alcoholate and thiolate anions to yield thioamides, thionoesters and dithioesters, respectively. The products were applied for synthesis of heterocycles such as thiadiazoles, isothiazolones and pyrazoles.

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The small ring heterocyclic compounds are known to be susceptible to ring-opening due to the ring strain [1]. In spite of the versatility of 2-methylene-1,3-dithietanes, little attention has been devoted to the application of these compounds for synthesis [2]. We found some of them underwent ring-opening reactions with nucleophiles to afford thiocarbonyl compounds. The utility of thiocarbonyl compounds [3] for construction of various heterocycles prompted us to investigate the reaction.

The 2-methylene-1,3-dithietanes **1** were synthesized by the methods reported earlier [4].

This paper describes the synthesis of some thiocarbonyl and heterocyclic compounds from 2-methylene-1,3-dithietanes [4].

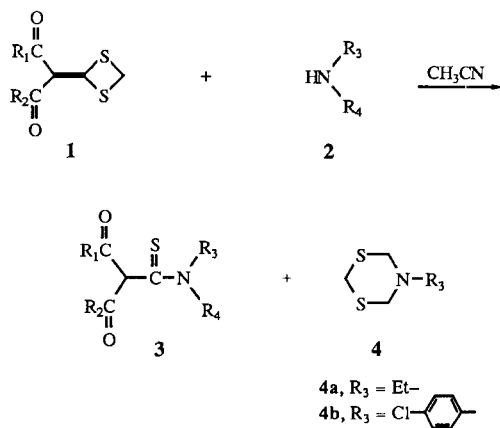
Results and Discussion.

1 The Reaction of 2-Methylene-1,3-dithietane with Nucleophiles.

1-1 Reaction with *N*-Nucleophiles.

The treatment of 2-(2,6-dioxo-4,4-dimethylcyclohexylidene)-1,3-dithietane (**1a**) with excess dimethylamine in acetonitrile at room temperature for 2 hours afforded 1-*N,N*-dimethylthiocarbamoyl-2,6-dioxo-4,4-dimethylcyclohexane (**3a**).

Scheme 1



Similarly the reaction of the other 2-methylene-1,3-dithietanes **1** with excess aliphatic amines afforded corres-

Table 1-1

Preparation of Thioamides **3**

	1	2	3		
3	R_1	R_2	R_3	R_4	Yield (%)
a	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$		CH_3	CH_3	100
b	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$		$-(\text{CH}_2)_5-$		74
c	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$		$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$		100
d	CH_3	$-\text{OC}_2\text{H}_5$	CH_3	CH_3	50
e	CH_3	$-\text{OC}_2\text{H}_5$	$-(\text{CH}_2)_5-$		77
f	CH_3	$-\text{NH}_2$	CH_3	CH_3	68
g	CH_3	$-\text{NH}_2$	$-(\text{CH}_2)_4-$		35
h	CH_3	$-\text{NH}_2$	$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$		21
i	CH_3	$-\text{NHC}_6\text{H}_5$	CH_3	CH_3	45

Table 1-2

Preparation of Thioamide **3**

3	R_1	R_2	R_3	R_4	Yield (%)
j	$-\text{OC}_2\text{H}_5$	$-\text{OC}_2\text{H}_5$	CH_3	CH_3	74
k	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$		H	C_2H_5	78
l	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$		H	H	92
m	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$		H	$-\text{C}_6\text{H}_4-\text{Cl}$	81
n	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$		H	$-\text{CH}_2\text{CH}(\text{OC}_2\text{H}_5)_2$	93

Table 2-1
Analytical and Spectral Data of Thioamides **3**

Compound	mp (°C)	Formula	Analysis (%)			IR v cm ⁻¹ (nujol)	¹ H-NMR [a] δ ppm (TMS)
			Calcd.	(found)			
			C	H	N		
3a	211-213	C ₁₁ H ₁₇ NO ₂ S	58.12 (58.31)	7.54 7.58	6.16 6.22	1575	1.12 (s, 6H), 2.40 (s, 4H), 3.35 (s, 6H, br), 11.04 (s, 1H) [A]
3b	146-148	C ₁₄ H ₂₁ NO ₂ S	62.89 (62.88)	7.92 7.99	5.24 5.25	1595	1.10 (s, 6H), 1.73 (s, 6H), 2.40 (s, 4H), 3.87 (s, 4H, br), 10.76 (s, 1H) [A]
3c	137-138	C ₁₃ H ₁₉ NO ₃ S	57.97 (58.00)	7.11 7.10	5.20 5.16	1600	1.03 (s, 6H), 2.40 (s, 4H), 3.83 (s, 8H, br), 10.90 (s, 1H) [A]
3d	(liquid)	C ₉ H ₁₅ NO ₃ S	49.75 (49.70)	6.96 6.90	6.45 6.50	1640 1715	1.30 (t, 3H, J = 7 Hz), 2.05 (s, 3H), 3.25 (s, 3H), 3.55 (s, 3H) [A]
3e	(liquid)	C ₁₂ H ₁₉ NO ₃ S	56.01 (56.03)	7.44 7.67	5.44 5.31		1.30 (t, 3H, J = 7.5 Hz), 1.73 (s, 6H), 2.07 (s, 3H), 3.63 (s, 2H), 4.33 (m, 4H), 12.63 (s, 1H) [A]
3f	145-147	C ₇ H ₁₂ N ₂ O ₂ S	44.66 (44.54)	6.43 6.43	14.88 14.68		1.90 (s, 3H), 3.30 (s, 3H), 3.52 (s, 3H), 6.60 (s, 2H, br), 14.95 (s, 1H) [B]
3g	122-124	C ₉ H ₁₄ N ₂ O ₂ S	50.45 (50.47)	6.59 6.60	13.07 13.10		3.50 (s, 3H), 2.00-2.30 (m, 4H), 3.50-4.00 (m, 4H) [A]
3h	173-175	C ₉ H ₁₄ N ₂ O ₃ S	46.94 (46.99)	6.13 6.06	12.16 12.13		1.94 (s, 3H), 3.50-3.90 (m, 8H), 5.70-5.90 (s, 2H, br) [A]

Table 2-2
Analytical and Spectral Data of Thioamides **3**

Compound	mp (°C)	Formula	Analysis (%)			IR v cm ⁻¹ (nujol)	¹ H-NMR [a] δ ppm (TMS)
			Calcd.	(found)			
			C	H	N		
3i	142-143	C ₁₃ H ₁₆ N ₂ O ₂ S	59.07 (59.10)	6.10 6.15	10.60 10.57	1615	1.90 (s, 3H), 3.35 (s, 3H), 3.58 (s, 3H), 7.10-7.40 (m, 5H) [A]
3j	(liquid)	C ₁₀ H ₁₇ NO ₄ S	48.57 (48.40)	6.93 6.96	5.66 5.60	1730	1.30 (t, 6H, J = 7 Hz), 3.25 (s, 3H), 3.50 (s, 3H), 4.30 (q, 4H, J = 7 Hz), 5.00 (s, 1H) [A]
3k	(liquid)	C ₁₁ H ₁₇ NO ₂ S	58.12 (58.15)	7.54 7.60	6.16 6.23	1625	1.16 (s, 6H), 1.36 (t, 3H, J = 7 Hz), 2.42 (s, 2H), 2.60 (s, 2H), 3.70 (dt, 2H, J = 7, 4.4 Hz), 12.20 (1H, br), 17.20 (s, 1H) [A]
3l	155-156	C ₉ H ₁₃ NO ₂ S	54.25 (54.24)	6.58 6.63	7.03 6.96	1530 1590	1.10 (s, 6H), 2.42 (s, 2H), 2.62 (s, 2H), 11.10 (s, 2H, br), 16.70 (s, 1H) [A]
3m	141.5-143	C ₁₅ H ₁₆ NO ₂ SCI	58.15 (57.95)	5.21 5.30	4.52 4.60	1550 1620	1.12 (s, 6H), 2.50 (s, 2H), 2.68 (s, 2H), 7.41 (s, 4H), 14.00 (s, 1H, br), 17.30 (s, 1H, br) [A]
3n	(liquid)	C ₁₅ H ₂₅ NO ₄ S	57.12 (57.00)	7.99 7.90	4.44 4.46	1530 1630	1.10 (s, 6H), 1.28 (t, 6H, J = 7Hz), 2.42 (s, 2H), 2.60 (s, 2H), 3.50-3.90 (m, 6H), 4.76 (t, 1H, J = 7Hz), 12.40 (s, 1H, br), 17.00 (s, 1H) [A]

[a] Measured solvent: [A] = deuteriochloroform. [B] = DMSO-d₆.

ponding thioamides **3** (Scheme 1) in yields of 35-100%, as summarized in Table 1. The reaction was not complete even after a prolonged reaction time when an equivalent amount of the amine was applied, thus it was shown that the presence of excess amine is necessary in this reaction.

The reaction of **1a** with excess ethylamine in acetonitrile at room temperature gave a mixture of thioamide

3k and dihydro-1,3,5-dithiazine **4a** (Scheme 1). The formation of **4a** is explicable by a three step process; Michael addition of ethylamine to the sp²-carbon of 1,3-dithietane, ring-opening of the adduct to afford thioamide **3k** with concomitant liberation of thioformaldehyde and condensation of the latter with ethylamine to yield dihydro-1,3,5-dithiazine **4a**.

The treatment of 1,3-dithietane **1a** with aqueous ammonia in a similar manner afforded thioamide **3l**.

The reaction of **1a** with 4-chloroaniline under the same conditions as above did not proceed. However, on conducting the reaction at reflux temperature in acetonitrile, thioamide **3m** and dihydro-1,3,5-dithiazine **4b** were obtained.

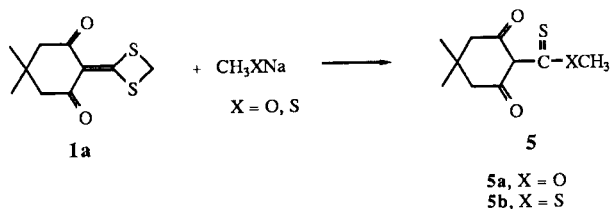
The 2-methylene-1,3-dithietanes **1**, thus, easily reacted with amines to afford thioamides in good yields as summarized in Tables 1 and 2.

This new ring-opening reaction provides an attractive synthetic route to thioamides bearing electron-withdrawing groups on the methylene carbon atom. Thioamides of secondary amines like **3a~j** can be obtained by other methods, for example by the reaction of aryl sulfonyl thioformamides with active-methylene compounds [5]. However, the present method represents an improvement over the methods reported earlier with respect to the yields and versatility.

1-2 Reaction with *O* and *S*-Nucleophiles.

Treatment of **1a** with sodium methylate in methanol at room temperature afforded thionoester **5a** in a yield of 99%, the treatment of **1a** with sodium methanethiolate afforded dithioester **5b** in a yield of 77% (Scheme 2).

Scheme 2



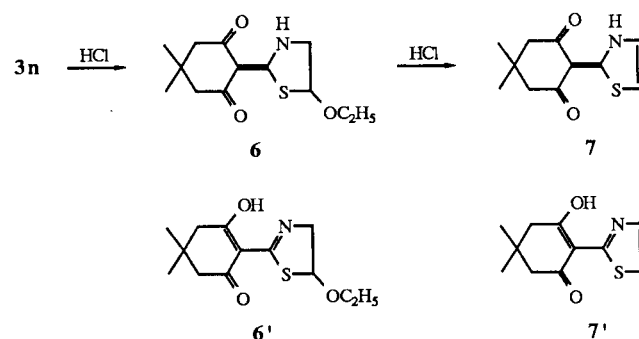
2 The Synthetic Application of 2-Methylene-1,3-dithietanes **1** for Heterocycles.

2-1 Thiazolidines, Thiazolines.

When thioamide **3n** obtained from **1a** and 2,2-diethoxyethylamine was treated with hydrochloric acid at room temperature, thiazolidines **6** was obtained. The ^1H nmr spectrum of the product showed a broad signal (1H) of an acidic hydrogen at δ 12.00.

The reaction of **6** with hydrochloric acid upon heating afforded thiazolines **7** (Scheme 3). The ^1H nmr spectrum of the product also exhibited a broad signal of an acidic hydrogen centered at δ 14.80. The broadness of the acidic hydrogen signals in their ^1H nmr spectra are attributable to the presence of their tautomers.

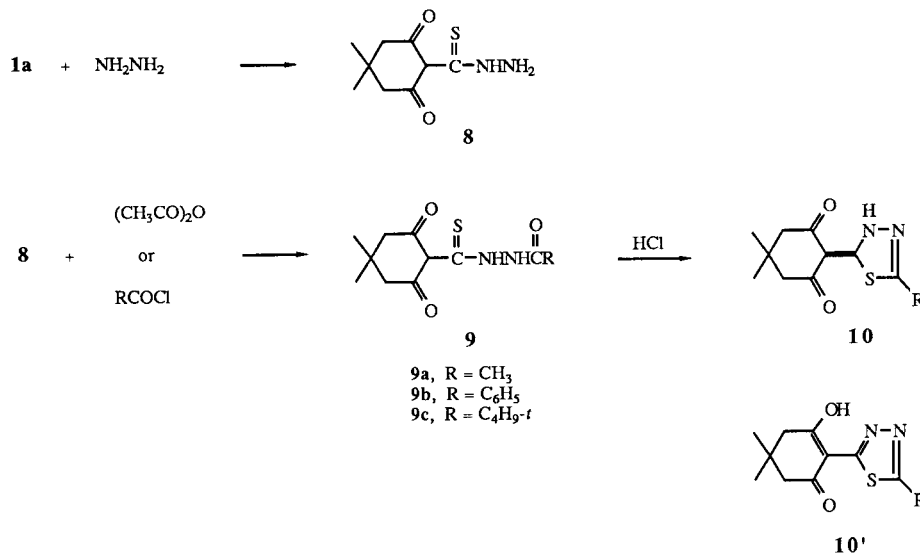
Scheme 3



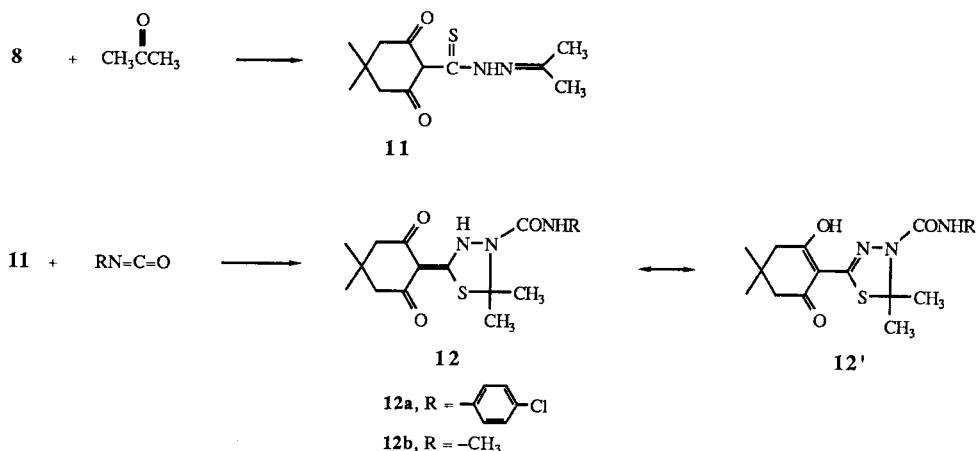
2-2 Thiadiazolidines.

The treatment of **1a** with hydrazine yielded thiohydrazide **8** which on acylation with acetic anhydride or acyl chloride afforded acyl derivatives **9a~c**. The cyclization of **9a~c** with hydrochloric acid led to thiadiazolidines in

Scheme 4



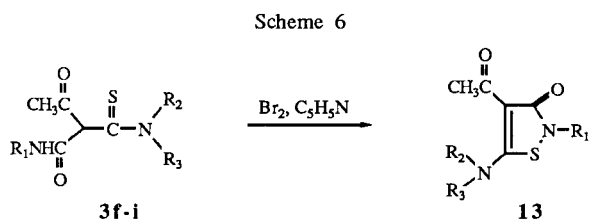
Scheme 5



almost quantitative yields. These products could contain tautomeric mixtures of **10a~c** and **10'a~c** in similar manner described for **6** and **7** (Scheme 4). On application of the method of Nakayama *et al.* [6a,b], hydrazone **11** was heated with isocyanate in chloroform to result in thiadiazolidines **12a,b** in excellent yields (Scheme 5).

2-3 Isothiazolones.

The oxidation of thioamides **3f~i** with bromine in pyridine at room temperature yielded 3-isothiazolones **13** (Scheme 6), as summarized in Tables 3 and 4.



2-4 5-Mercaptopyrazoles and 5-Methylthiopyrazoles.

As reported previously [7] the reaction of **1b** with excess methylhydrazine in acetonitrile at reflux temperature for 3

hours yielded 1,3-dimethyl-4-ethoxycarbonyl-5-mercaptopyrazole **14a** in good yield (Scheme 7).

Table 3

Preparation of isothiazolones **13**

		$\xrightarrow{\text{Br}_2, \text{C}_5\text{H}_5\text{N}}$			
13	R ₁	R ₂	R ₃	Yield (%)	
a	H	CH ₃	CH ₃	99	
b	H	-(CH ₂) ₄ -		99	
c	H	-(CH ₂) ₂ O(CH ₂) ₂ -		35	
d	C ₆ H ₅ -	CH ₃	CH ₃	26	

Scheme 7

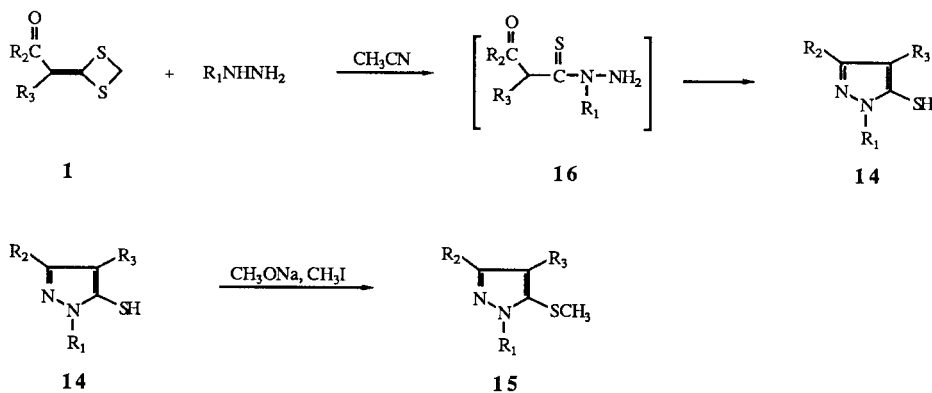


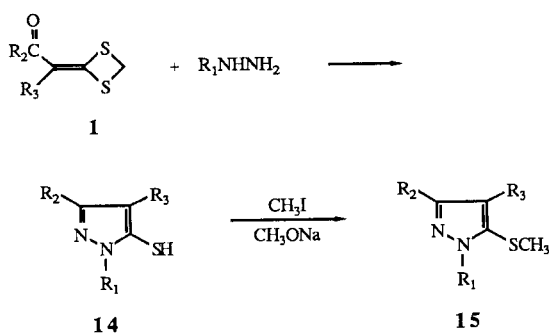
Table 4

Analytical and Spectral Data of Isothiazolones

Compound	mp (°C)	Formula	Analysis (%)			IR ν cm ⁻¹ (nujol)	¹ H-NMR [a] δ ppm (TMS)
			Calcd.	(Found)			
			C	H	N		
13a	144.5-145.5	C ₇ H ₁₀ N ₂ O ₂ S	45.15 (45.44)	5.41 5.44	15.04 15.08	1610 1655	2.55 (s, 3H), 3.05 (s, 6H) 10.00 (s, 1H) [A]
13b	177-179	C ₉ H ₁₂ N ₂ O ₂ S	50.92 (51.05)	5.70 5.72	13.20 13.11	1615 1650	1.80-2.20 (m, 4H), 2.60 (s, 3H), 3.20-3.50 (m, 4H), 8.50 (s, 1H, br) [A]
13c	184-186	C ₉ H ₁₂ N ₂ O ₃ S	47.36 (47.08)	5.30 5.25	12.27 12.28	1650	2.48 (s, 3H), 3.23-3.33 (m, 4H), 3.77-3.90 (m, 4H) [B]
13d	84-86	C ₁₃ H ₁₄ N ₂ O ₂ S	59.52 (59.22)	5.38 5.39	10.68 10.61	1590 1640	2.62 (s, 3H), 3.08 (s, 6H), 7.20-7.60 (m, 5H) [A]

[a] Measured solvent: [A] = deuteriochloroform. [B] = DMSO-d₆

Table 5

Preparation of Mercapto and Methylthiopyrazoles **14** and **15**

formation of thiohydrazides **16** as intermediates and subsequent intramolecular cyclization to afford pyrazoles **14**.

In summary, this study reports some examples of the synthesis of thiocarbonyl compounds from 2-methylene-1,3-dithietanes and the transformation of the compounds to a variety of heterocyclic compounds.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were recorded with a Shimadzu IR-420 spectrophotometer. The ¹H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using tetramethylsilane as an internal standard.

Reaction of **1a** with Secondary Amines. General Procedure for Preparation of **3**.

To a solution of 2-(5,5-dimethyl-1,3-dioxocyclohexane-2-ylidene)-1,3-dithietane (**1a**, 20 mmoles) in acetonitrile (10 ml) was added piperidine (40 mmoles) dropwise over 30 minutes. The reaction mixture was stirred at room temperature for 3 hours. The resulting precipitate was collected by filtration and recrystallized from acetonitrile to afford **3b**. Results are summarized in Tables 1 and 2.

Reaction of **1a** with Ethylamine. Preparation of **3k** and **4a**.

To a solution of **1a** (5.0 g, 20 mmoles) in acetonitrile (30 ml) was added ethylamine (70%, aqueous solution, 2.8 g, 47 mmoles) at room temperature. The reaction mixture was stirred for 3 hours at room temperature. The resulting precipitates were collected by filtration and desolved in water (30 ml). The solution was acidified with 1 N hydrochloric acid and extracted with dichloromethane. The organic layer was collected, washed with water, then dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure to dryness to yield 3.5 g of **3k** as an amorphous powder Tables 1 and 2. The filtrate from the reaction mixtures was concentrated under reduced pressure and the residue was chromatographed on a silica gel column using *n*-hexane/ethyl acetate (2:1) as an eluent to yield 600

The reason why the formation of the 3-mercapto isomers were excluded is as follows; **14a** was converted to 5-methylthiopyrazole **15a** by the reaction with iodomethane, summarized in Tables 5 and 6 [8]. 1,3-Dimethyl-4-ethoxycarbonyl-5-methylthiopyrazoles (**15'**) was prepared by other methods [9,10,11]. The physical properties and spectral data of **15a** were consistent with those of **15'**.

In a similar manner, the other 1,3-dithietanes **1** were converted to 5-mercaptothiopyrazoles and 5-methylthiopyrazoles (Scheme 7). The results were summarized in Tables 5 and 6.

This reaction is considered to proceed through the

Table 6

Analytical and Spectral Data of Mercapto and Methylthiopyrazoles **14** and **15**

Compound 14		Compound 15						
mp (°C)	¹ -NMR [a] δ ppm (TMS)	mp (°C)	Formula	Analysis (%) Calcd. (Found)			¹ -NMR [a] δ ppm (TMS)	
				C	H	N		
a	64-66	1.35 (t, 3H, J = 7 Hz, 2.37 (s, 3H), 3.67 (s, 3H), 4.30 (q, 2H, J = 7 Hz), 6.55 (s, 1H, br) [A]	33-34	C ₉ H ₁₄ N ₂ O ₂ S	50.45 (50.44)	6.59 (6.70)	13.07 (13.11)	1.40 (t, 3H, J = 7 Hz) 2.45 (s, 6H), 3.92 (s, 3H), 4.35 (q, 2H, J = 7 Hz) [A]
b	212-214	2.45 (s, 3H), 3.92 (s, 3H), 7.05-7.70 (q, 2H, J = 7 Hz), 7.20-7.70 (m, 5H) [B]	194.5-195.5	C ₇ H ₁₁ N ₃ OS	45.39 (45.54)	5.99 (5.91)	22.68 (22.59)	2.37 (s, 3H), 2.50 (s, 3H), 3.92 (s, 3H), 6.00 (s, 1H, br), 7.30 (s, 1H) [A]
c	(oil)	2.37 (s, 3H), 3.92 (s, 3H), 7.05-7.70 (m, 5H) [A]	98.5-100.5	C ₁₃ H ₁₅ N ₃ OS	59.74 (59.80)	5.79 (5.88)	16.08 (16.00)	2.37 (s, 3H), 2.52 (s, 3H), 3.92 (s, 3H), 7.05-7.70 (s, 5H), 9.45 (s, 1H, br) [A]
d	(oil)	1.15 (t, 3H, J = 7 Hz), 3.85 (s, 3H), 4.20 (q, 2H, J = 7 Hz), 7.20-7.60 (m, 5H) [A]	(oil)	C ₁₄ H ₁₆ N ₂ O ₂ S	60.85 (60.88)	5.84 (5.84)	10.14 (10.15)	1.18 (t, 3H, J = 7 Hz), 2.50 (s, 3H), 4.00 (s, 3H), 4.24 (q, 2H, J = 7 Hz), 7.20-7.60 (m, 5H) [A]

[a] Measured solvent: [A] = deuteriochloroform. [B] = DMSO-d₆.

mg of **4a** as an oil; ¹H-nmr (deuteriochloroform): 1.08 (t, 3H, J = 8 Hz), 3.08 (q, 2H, J = 8 Hz), 4.10 (s, 2H), 4.45 (s, 4H).

Anal. Calcd. for C₈H₁₁NS₂: C, 40.23; H, 7.43; N, 9.38. Found: C, 40.37; H, 7.68; N, 9.45.

Reaction of **1b** with *p*-Chloroaniline. Preparation of **4b**.

Compound **4b** was afforded by the reaction of **1a** and *p*-chloroaniline as crystals; mp 155-156°; ir (nujol): 1590, 1495 cm⁻¹; ¹H nmr (deuteriochloroform): 4.29 (s, 2H), 4.95 (s, 4H), 7.15 (dd, 4H, J = 8, 11.6 Hz), 17.30 (s, 1H, br).

Anal. Calcd. for C₉H₁₀NSCl: C, 46.64; H, 4.35; N, 6.04. Found: C, 46.44; H, 4.35; N, 5.99.

Reaction of **1a** with Sodium Methylate. Preparation of **5a**.

To a solution of **1a** (2.0 g, 8.8 mmoles) in anhydrous methanol (30 ml) was added sodium methylate (28% in methanol, 1.0 g, 19 mmoles). The reaction mixture was stirred for 1.5 hours at room temperature. The insoluble material was filtered and the filtrate was concentrated under reduced pressure. The residue was suspended in water (30 ml), acidified with dilute hydrochloric acid and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, then evaporated to dryness. The residue was chromatographed on a silica gel column using hexane/ethyl acetate (5:1) as an eluent to give **5a** (1.9 g) as crystals, yield 99%, mp 69-70°; ¹H nmr (deuteriochloroform): 1.10 (s, 6H), 2.38 (s, 2H), 2.60 (s, 2H), 4.20 (s, 3H), 14.80 (s, 1H); ir (nujol): ν 1530, 1665 cm⁻¹.

Anal. Calcd. for C₁₀H₁₄O₃S: C, 56.05; H, 6.59. Found: C, 56.08; H, 6.62.

Reaction of **1a** with Sodium Methanethiolate. Synthesis of **5b**.

To a solution of **1a** (3.0 g, 13 mmoles) in acetonitrile (30 ml) was added sodium methanethiolate (1.8 g, 26 mmoles). The reaction mixture was stirred at room temperature for 4 hours, then concentrated under reduced pressure. After adding water (30 ml) to the residue, the solution was acidified with dilute hydrochloric acid to pH 2. The resulting precipitate was collected by filtration and chromatographed on a silica gel column using hexane/ethyl

acetate (5:1) as an eluent, then recrystallized from ethanol to afford **5b** (2.0 g) as pale yellow crystals, yield 77%, mp 104-105°; ir (nujol): ν 1520, 1645 cm⁻¹; ¹H nmr (deuteriochloroform): 1.10 (s, 6H), 2.49 (s, 2H), 2.68 (s, 2H), 17.35 (s, 1H).

Anal. Calcd. for C₁₀H₁₄O₂S₂: C, 52.14; H, 6.13. Found: C, 52.17; H, 6.18.

2-(2,6-Dioxo-4,4-dimethylcyclohexylidene)-5-ethoxythiazolidine (**6**).

A mixture of **3n** (1.0 g, 3.2 mmoles) and concentrated hydrochloric acid (20 ml) was stirred at room temperature for 2 hours. The reaction mixture was extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield **6** (0.7 g) as crystals, yield 82%, mp 168-170°; ir (nujol): ν 1580, 1630, 3150 cm⁻¹; ¹H nmr (deuteriochloroform): 1.08 (s, 6H), 1.20 (t, 3H, J = 7 Hz), 2.40 (s, 4H), 3.50-4.10 (m, 4H), 5.30 (d, 1H, br), 12.00 (s, 1H, br).

Anal. Calcd. for C₁₃H₁₉NO₃S: C, 57.97; H, 7.10; N, 5.20. Found: C, 57.62; H, 6.92; N, 5.15.

2-(2,6-Dioxo-4,4-dimethylcyclohexylidene)-3*H*-thiazoline (**7**).

A suspension of **6** (1.4 g, 5.2 mmoles) in concentrated hydrochloric acid was heated under reflux for 7.5 hours. The reaction mixture was extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed on a silica gel column using hexane/ethyl acetate (1:2) as an eluent to give **7** (0.8 g) as crystals, yield 70%, mp 193-194°; ir (nujol): ν 1565, 1610, 3100, 3150 cm⁻¹; ¹H nmr (deuteriochloroform): 1.10 (s, 6H), 2.50 (s, 4H), 7.00 (d, 1H, J = 3 Hz), 7.40 (1H, br), 14.80 (s, 1H, br).

Anal. Calcd. for C₁₁H₁₃NO₂S: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.05; H, 5.78; N, 6.20.

2,6-Dioxo-4,4-dimethylcyclohexylthiocarbonylhydrazide (**8**).

To a solution of **1a** (5.0 g, 22 mmoles) in acetonitrile (30 ml) was added hydrazine monohydrate (3.3 g, 22 mmoles) at 5-8°.

The reaction mixture was stirred for 2.5 hours at 10-15°. The resulting precipitate was collected by filtration and then suspended in water (30 ml). The suspension was acidified with dilute hydrochloric acid and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. The residue was chromatographed on a silica gel column using hexane/ethyl acetate (5:1) as an eluent to give **8** (2.0 g) as crystals, yield 43%, mp 119-121.5°; ir (nujol): ν 1625, 3220, 3320 cm^{-1} ; ^1H nmr (deuteriochloroform): 1.56 (s, 6H), 2.42 (s, 2H), 2.59 (s, 2H), 5.00 (s, 2H, br), 13.30 (s, 1H, br), 16.30 (s, 1H).

Anal. Calcd. for $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 50.44; H, 6.59; N, 13.07. Found: C, 49.95; H, 6.61; N, 12.88.

Acylation of **8**. General Procedure for the Preparation of **9**.

To a mixture of **8** (4.7 mmoles), triethylamine (4.7 mmoles) and chloroform (20 ml) was added acetic anhydride (4.7 mmoles) at 5°. The reaction mixture was stirred for 1 hour at the same temperature, then 4 hours at room temperature and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column using hexane/ethyl acetate (1:2) as an eluent to afford **9**.

Compound **9a**.

This compound was obtained in a yield of 69%, mp 124-125.5°; ir (nujol): 1630, 1655, 3080, 3150 cm^{-1} ; ^1H nmr (deuteriochloroform): 1.10 (s, 6H), 2.18 (s, 3H), 2.48 (s, 2H), 2.62 (s, 2H), 9.70 (d, 1H, br), 15.00 (d, 1H, br), 15.80 (s, 1H).

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$: C, 51.54; H, 6.29; N, 10.93. Found: C, 51.27; H, 6.16; N, 11.20.

Compound **9b**.

This compound was obtained in a yield of 76%, mp 239-242°; ^1H nmr (deuteriochloroform): 1.20 (s, 6H), 2.38 (s, 2H), 2.60 (s, 2H), 7.20-8.00 (m, 5H), 11.90 (s, 1H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.33; H, 5.79; N, 8.80.

Compound **9c**.

This compound was obtained in a yield of 70%, mp 85-88°; ir (nujol): ν 1620, 1655, 1675, 3330 cm^{-1} ; ^1H nmr (deuteriochloroform): 1.10 (s, 6H), 1.32 (s, 9H), 2.50 (s, 2H), 2.60 (s, 2H), 5.40 (s, 1H, br) 15.00 (s, 1H, br).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$: C, 56.35; H, 7.43; N, 9.39. Found: C, 56.40; H, 7.50; N, 9.40.

General Procedure for the Preparation of **10**.

A mixture of **9** (2.0 mmoles) and concentrated hydrochloric acid (15 ml) was stirred at room temperature for 2 hours. The reaction mixture was extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. The residue was recrystallized from ethanol to afford **10** as crystals.

Compound **10a**.

This compound was obtained in a yield of 99%; mp 224-224.5°; ir (nujol): ν 1575, 2850, 3100 cm^{-1} ; ^1H nmr (deuteriochloroform): 1.10 (s, 6H), 2.48 (s, 4H), 2.68 (s, 3H), 14.40 (s, 1H).

Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 55.44; H, 5.92; N, 11.76. Found: C, 55.42; H, 5.92; N, 11.65.

Compound **10b**.

This compound was obtained in a yield of 99%; mp 175-175.5°; ir (nujol): ν 1580, 1622, 3200 cm^{-1} ; ^1H nmr (deuteriochloroform): 1.15 (s, 6H), 2.53 (s, 4H), 7.40-8.05 (m, 5H), 14.46 (s, 1H, br), 15.00 (s, 1H, br).

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.46; H, 5.31; N, 9.11.

Compound **10c**.

This compound was obtained in a yield of 99%, mp 152-153.5°; ir (nujol): ν 1570, 1620, 1670, 3200 cm^{-1} ; ^1H nmr (deuteriochloroform): 1.10 (s, 6H), 1.48 (s, 9H), 2.50 (s, 4H), 14.46 (s, 1H, br).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 59.97; H, 7.19; N, 9.99. Found: C, 59.97; H, 7.19; N, 9.93.

2-Isopropylidenehydrazino-2,6-Dioxo-4,4-dimethylcyclohexyl Thioketone (**11**).

A mixture of **8** (3.0 g, 14 mmoles) and acetone (10 ml) was stirred at room temperature for 2 hours. The resulting precipitate was collected by filtration, recrystallized from ethanol to afford **11** (2.7 g) as pale yellow crystals, yield 76%, mp 199-200°; ir (nujol): ν 1570, 1620, 3150, 3200 cm^{-1} ; ^1H nmr (deuteriochloroform): 1.05 (s, 6H), 1.67 (s, 6H), 2.40 (s, 4H), 4.78 (s, 1H, br), 12.50 (s, 1H, br).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 56.67; H, 7.13; N, 11.01. Found: C, 56.81; H, 7.12; N, 10.97.

General Procedure for Preparation of **12**.

A mixture of **11** (4.7 mmoles) and 4-chlorophenyl isocyanate (4.7 mmoles) in chloroform (30 ml) was stirred for 15 hours at room temperature. The reaction mixture was concentrated under reduced pressure, the residue was chromatographed on a silica gel column using hexane/ethyl acetate (4:1) as an eluent to afford **12** as crystals.

Compound **12a**.

This compound was obtained in a yield of 99%, mp 178-180°; ir (nujol): ν 1590, 1655, 3350 cm^{-1} ; ^1H nmr (deuteriochloroform): 1.12 (s, 6H), 1.98 (s, 6H), 2.38 (s, 2H), 2.60 (s, 2H), 7.30-7.40 (m, 4H), 12.20 (s, 1H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_3\text{O}_3\text{SCl}$: C, 55.94; H, 5.44; N, 10.30. Found: C, 55.87; H, 5.50; N, 10.15.

Compound **12b**.

This compound was obtained in a yield of 91%, mp 152-154°; ir (nujol): ν 1580, 1650, 3400 cm^{-1} ; ^1H nmr (deuteriochloroform): 1.20 (s, 6H), 1.95 (s, 6H), 2.85 (d, 3H, J = 5 Hz), 5.25 (s, 1H, br), 12.80 (s, 1H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$: C, 54.00; H, 6.80; N, 13.49. Found: C, 53.76; H, 6.22; N, 13.20.

General Procedure for the Preparation of **13**.

To a solution of **3h** (8.7 mmoles) in pyridine (20 ml) was added a solution of bromine (8.7 mmoles) in ethyl acetate (10 ml) at room temperature. The reaction mixture was stirred at room temperature for 30 minutes, poured into ice water (50 ml) and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford **13** as crystals. Results are summarized in Tables 3 and 4.

General Procedure for the Preparation of **14**.

To a solution of **1** (21 mmoles) in acetonitrile (30 ml) was added methyl hydrazine (43 mmoles) at room temperature. The reaction mixture was heated under reflux for 3 hours, concentrated under reduced pressure. The residue was added water (30 ml), acidified with dilute hydrochloric acid to pH 2 and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. The residue was chromatographed on a silica gel column using hexane/ethyl acetate (2:1) as an eluent to afford **14** as crystals. Results are summarized in Tables 5 and 6.

General Procedure for the Preparation of **15**.

To a solution of **14** (2.9 mmoles) in methanol (30 ml) was added sodium methoxide (28% in methanol, 3.0 mmoles) and then iodomethane (3.5 mmoles) at room temperature. The reaction mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was added water (30 ml), acidified with dilute hydrochloric acid to pH 2 and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulfate, evaporated to dryness to afford **15** as crystals. Results are summarized in Tables 5 and 6.

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