Substituent Effect on Oxidative Cyclization of Aldehyde Thiosemicarbazones with Ferric Chloride

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The reactivity of aldehyde thiosemicarbazones **1** with ferric chloride solutions was examined. When compounds **1** are not substituted on the N-2 nitrogen atom formation of 1,3,4-thiadiazole **3** heterocyclic ring was observed. In contrast 1,2,4-triazoline **4** and/or 1,3,4-thiadiazoline **5** heterocyclic rings were afforded when N-2 nitrogen atom carried a methyl or a phenyl group. The reaction mechanism is also discussed.

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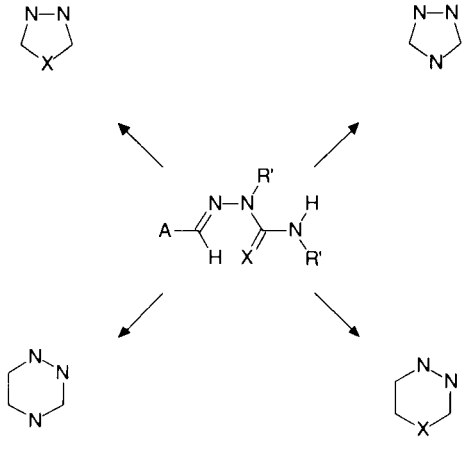
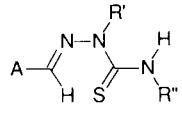
Aldehyde semi- and thiosemicarbazones are polyfunctionalyzed compounds which easily cyclize [1] by action of bases, acids or oxidants: therefore they are useful synthons for the preparation of five- or six-membered heterocyclic compounds. Studies [2] on the cyclization reaction have shown that the nature of the cyclizing agent can affect the structure of the obtained heterocyclic compounds (Scheme 1).

Scheme 1



In order to gain information on the course of this reaction and in an attempt to find the reason for the different types of cyclization observed, we have collected literature data (see Table) together with further experimental data concerning the study of the behaviour of some substituted aldehyde thiosemicarbazones **1a-l** with an ethanolic solution of ferric chloride.

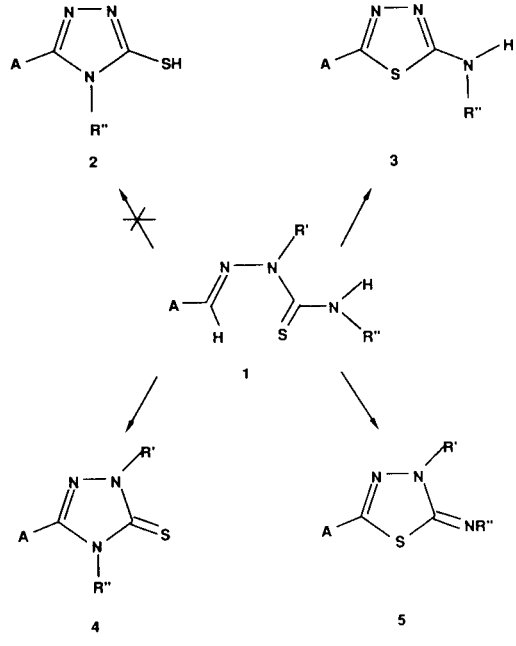
In principle **1a-l** can give by oxidative cyclization derivatives of 1,3,4-triazole **2**, of 1,3,4-thiadiazole **3**, of 1,2,4-triazoline-5-thione **4**, and of Δ^2-1,3,4-thiadiazoline **5** (see Scheme 2). Data reported in Table show that only the formation of compounds **2** has not been observed and that the cyclization reactions are usually regiospecific (yields indicated) and the course of the cyclization seems to depend of the structure of the starting thiosemicarbazones.



1 a - l

a:	A = COOEt	R' = Me	R" = H
b:	A = Me	R' = Me	R" = H
c:	A = COOEt	R' = Me	R" = Me
d:	A = Me	R' = Me	R" = Me
e:	A = Ph	R' = Me	R" = Me
f:	A = p-NO_2-C_6H_4	R' = Me	R" = Me
g:	A = COOEt	R' = Me	R" = Ph
h:	A = Me	R' = Me	R" = Ph
i:	A = Ph	R' = Me	R" = Ph
j:	A = COOMe	R' = Ph	R" = Ph
k:	A = PhCO	R' = Ph	R" = Ph
l:	A = Me	R' = Ph	R" = Ph

Scheme 2



In fact aldehyde thiosemicarbazones unsubstituted at N-2 (in **1**, R' = H) are always converted into 2-amino-

Table

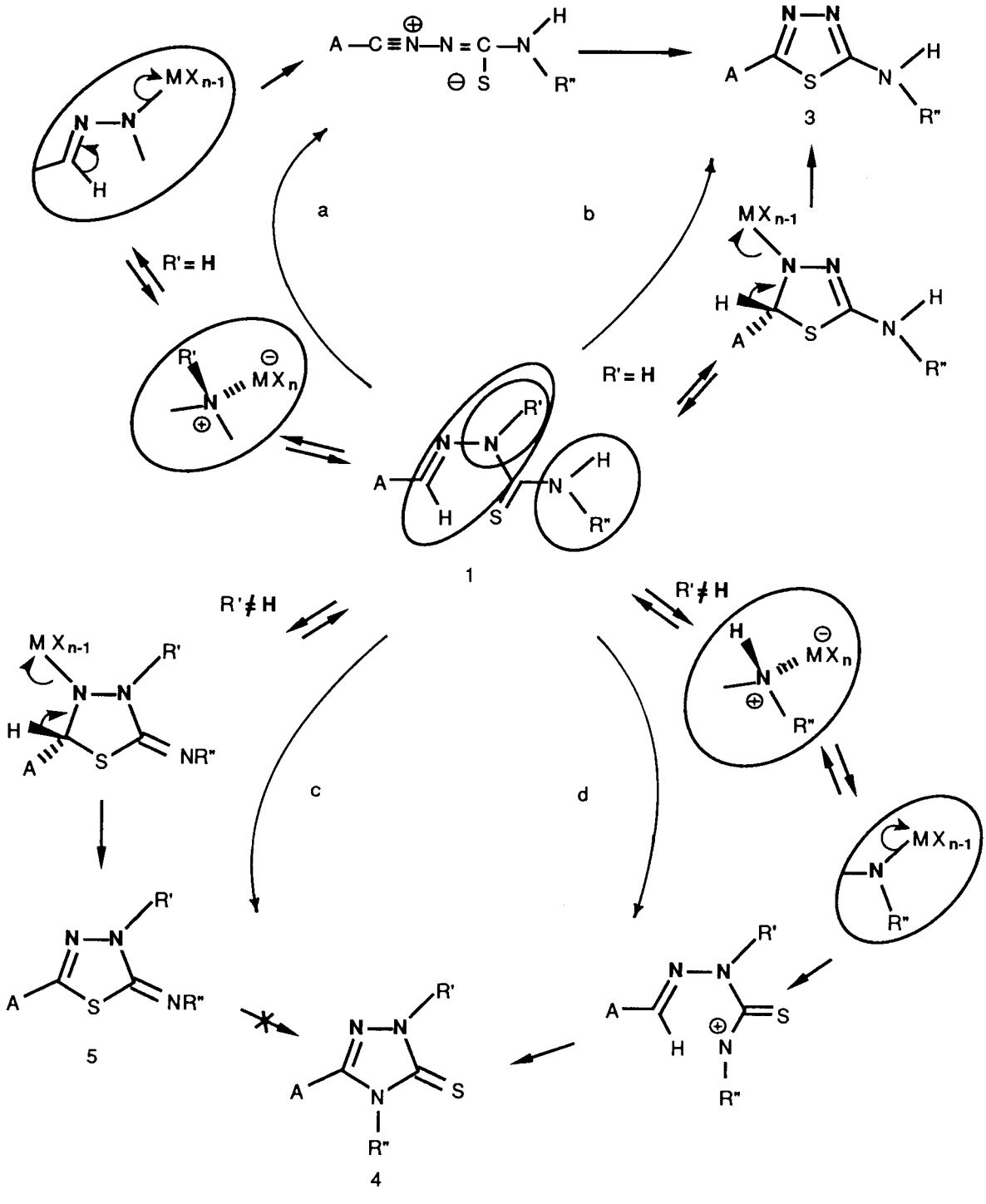
Results of cyclization of tiosemicarbazones **1** with $FeCl_3$

A	R'	R''			ref.
COOR	H	H	1	0	[7]
PhCO	H	H	1	0	[8]
Ph	H	H	1	0	[9]
COOR	H	Me	1	0	[10]
PhCO	H	Me	1	0	[8]
Ph	H	Me	1	0	[9]
COOR	H	Ph	1	0	[10]
PhCO	H	Ph	1	0	[8]
Ph	H	Ph	1	0	[9]
COOEt	Me	H	1	0	this work
PhCO	Me	H	1	0	[8]
Me	Me	H	5	3	this work
COOEt	Me	Me	1	0	this work
PhCO	Me	Me	1	0	[8]
Me	Me	Me	6	1	this work
Ph	Me	Me	1	4	this work
p-NO_2-C_6H_4	Me	Me	1	1	this work
COOEt	Me	Ph	1	0	this work
PhCO	Me	Ph	1	0	[11]
Me	Me	Ph	1	1	this work
Ph	Me	Ph	2	5	this work
COOMe	Ph	Ph	1	0	this work
PhCO	Ph	Ph	1	0	this work
Me	Ph	Ph	0	1	this work
Ph	Ph	Ph	0	1	[12]

1,3,4-thiadiazoles **3**, independently of the substituents present on the amino group (R'' = H, Me, Ph) and of the nature of the residue linked at the aldehydic carbon (**A** = Ph, PhCO, CO_2R). The presence of a substituent at N-2 (in **1**, R' = Me, Ph) causes the cyclization of **1** to compounds **4** and/or **5** depending of the nature of the residue linked to the aldehydic carbon. When **A** is an electron-withdrawing group (**A** = PhCO, CO_2R), **1** is oxidized exclusively to 1,3,4-thiadiazoline derivative **5**. In contrast when **A** is phenyl the oxidation yielded a mixture of 1,2,4-triazoline **4** and 1,3,4-thiadiazoline derivatives **5** with predominance of the former derivative. At last, when **A** is a methyl group both 1,2,4-triazoline **4** and 1,3,4-thiadiazoline derivatives **5** are obtained from cyclization of **1**. The composition of the mixture depends on the substituents present on the amino group. Thus when this is a phenylamino group predominance of the 1,2,4-triazoline derivative **4** is observed. In contrast, when the amino group is unsubstituted or mono methyl substituted 1,3,4-thiadiazoline (**5**) prevails. To confirm the influence of the nature of the structure **A** on the course of the cyclization reaction we have studied the behaviour of *p*-nitrobenzaldehyde 2,4-dimethylthiosemicarbazone (**1f**) in comparison with that of benzaldehyde 2,4-dimethylthiosemicarbazone **1e** (with this compounds the formation of a 1,2,4-triazoline derivative **4** has been observed). In fact using the Hammett substituent constants [3] to evaluate the electronic effect of a substituent one can observe that *p*-nitrophenyl substituent would behave as a weak electron-withdrawing substituent (σ = 0.23) [4], *i.e.* with an electronic effect intermediate between that of a phenyl group (σ = -0.01) [4] and those of a carbomethoxy or a benzoyl group (σ = 0.45 and 0.43 respectively) [4]. In line with the previous indications we have observed that *p*-nitrobenzaldehyde 2,4-dimethylthiosemicarbazone cyclizes giving both 1,3,4-thiadiazoline and 1,2,4-triazoline derivatives with comparable yields. The regioselectivity observed in all of the studied cyclization reactions but that of **1** probably depends on kinetic and not on thermodynamic factors as the following data indicate. For example benzaldehyde 2-methyl-4-phenylthiosemicarbazone (**1i**) cyclizes into 3,4-diphenyl-1-methyl-1,2,-4-triazoline-5-thione (**4i**): this product can come directly from **1i** (kinetic control) or through the intermediate formation of 2-phenyl-4-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**5i**) (thermodynamic control). It is possible to exclude the thermodynamic control in the formation of **4**, because **5** remains unchanged by treatment with an alcoholic solution of ferric chloride or of hydrochloric acid, *i.e.* in the condition of the cyclization. In order to understand the mechanism of cyclization it must be observed that substrates **1** exist in cyclic structures in acidic solution, the equilibrium composition depends on both the structure of the thiosemicarbazones **1** and the acid concentration. In fact nmr spectra, recorded at various acid concentration, of some compounds **1** containing an **A** group strongly electron-withdrawing indicate that the cyclic structure is largely predominant one [5]. In contrast, if **A** is a phenyl or methyl group the cyclic structure is predominant only at high acid concentration (TFA > 5*M*).

The different pathways through which the oxidation of thiosemicarbazones **1** may occur are shown in the Scheme 3. Probably the early stage of the reaction involves the reversible electrophilic attack of the hard acid iron(III) on the hardest basic site among N-2 and N-4 of the open chain structure or on N-4 of the cyclic structure. If there is no substituent at N-2 then the reaction may proceed or through a variety of pathways (way **a**) to the nitrilimine intermediate that can undergo a 1,5-electrocyclization or to a 5 *endo* dig type process [6] when the open chain structure is predominant or through way **b** when thiosemicarbazone is in the cyclic structure. If the nitrogen atom in the position 2 carries a substituent (methyl or phenyl group) then the above stage could in principle still occur giving demethylation or dephenylation but surely alternative pathways result faster. Therefore the reaction may proceed through way **c** for substrates that exist in cyclic structure. If open chain structure is predominant then way **d** becomes important and in some cases represents the preferred course of the reaction.

Scheme 3



EXPERIMENTAL

All melting points (Kofler) are uncorrected. The spectra were recorded as follows: ir (nujol mull), Perkin-Elmer 1310 Spectrophotometer; ^{1}H-nmr, Varian EM 360 spectrometer (TMS as the internal reference). All compounds had analytical data consistent with the assigned structures.

The 2-methyl- [13], 2,4-dimethyl- [14], 2-methyl-4-phenyl- [15], 2,4-diphenyl-thiosemicarbazide [16] and the thiosemicarbazones **1b** [17], **1e** [14], **1i** [18] were prepared by the methods described in the literature.

Typical Procedure for the Preparation of Thiosemicarbazones.

2-Methylthiosemicarbazone of Ethyl Glyoxylate (**1a**).

To a stirred hot solution of 2-methylthiosemicarbazide (4.2 g, 40 mmoles) in water (40 ml), acidified with acetic acid (2 ml), an ethanol solution of ethyl glyoxylate [7] (5.1 g, 50 mmoles in 5 ml of ethanol) was added portionwise. After a few hours the 2-methylthiosemicarbazone **1a** (6 g, 79% yield) was collected, washed with water then crystallized from methanol had mp 112-113°; ir: 3510, 3420, 3310, 3160 cm^{-1} (N-H), 1710 cm^{-1} (C=O), 1630, 1600 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 1.30 (t, 3H, CH_2CH_3, J = 7.1 Hz), 3.71 (s, 3H, NCH_3), 4.28 (q, 2H, CH_2CH_3, J = 7.1 Hz), 6.91 (s, 1H, CH), 8.05 (bs, 2H, NH_2), 6.3-7.6 (m, 12H, ArH).

Anal. Calcd. for $C_6H_{11}N_3O_2S$: C, 38.08; H, 5.86; N, 22.20. Found: C, 37.95; H, 5.90; N, 22.23.

2,4-Dimethylthiosemicarbazone of Ethyl Glyoxylate (**1c**).

This compound (5.05 g, 62% yield) was prepared by the above procedure from 2,4-dimethylthiosemicarbazide (4.8 g, 40 mmoles in 30 ml of water) and ethyl glyoxylate (5.1 g, 50 mmoles, in 15 ml of ethanol), mp 127-128° (benzene-ligroin); ir: 3340 cm^{-1} (N-H), 1725 cm^{-1} (C=O), 1590 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 1.33 (t, 3H, CH_2CH_3, J = 7.0 Hz), 3.15 (d, 3H, $NHCH_3$, J = 4.8 Hz), 3.73 (s, 3H, NCH_3), 4.27 (q, 2H, CH_2CH_3, J = 7.0 Hz), 6.88 (s, 1H, CH), 8.35 (bs, 1H, $NHCH_3$).

Anal. Calcd. for $C_7H_{13}N_3O_2S$: C, 41.36; H, 6.45; N, 20.67. Found: C, 41.45; H, 6.49; N, 20.75.

2,4-Dimethylthiosemicarbazone of Acetaldehyde (**1d**).

This compound was prepared by the above procedure from 2,4-dimethylthiosemicarbazide (2.4 g, 20 mmoles, in 30 ml of ethanol) and acetaldehyde (2.25 ml, 40 mmoles). After standing overnight, the solvent was evaporated under reduced pressure and the solid residue chromatographed on silica gel column (eluent cyclohexane/ethyl acetate 2:1) gave 2.64 g (91% yield) of **1d**, mp 59-60°; ir: 3280 cm^{-1} (N-H); ^1H nmr (deuteriochloroform): δ 2.02 (d, 3H, $CHCH_3$, J = 5.0 Hz), 3.12 (d, 3H, $NHCH_3$, J = 4.6 Hz), 3.65 (s, 3H, NCH_3), 7.05 (q, 1H, $CHCH_3$, J = 5.0 Hz), 8.12 (bs, 1H, $NHCH_3$).

Anal. Calcd. for $C_5H_{11}N_3S$: C, 41.35; H, 7.63; N, 28.93. Found: C, 41.39; H, 7.60; N, 28.85.

2,4-Dimethylthiosemicarbazone of *p*-Nitrobenzaldehyde (**1f**).

This compound (4.9 g, 97% yield) was prepared by the above procedure from 2,4-dimethylthiosemicarbazide (2.4 g, 20 mmoles, in 30 ml of hot water) and *p*-nitrobenzaldehyde (3 g, 20 mmoles in 30 ml of hot ethanol). The crude **1f** washed with ethanol had mp 265-266°; ir: 3370 cm^{-1} (N-H), 1585 cm^{-1} (C=N).

Anal. Calcd. for $C_{10}H_{12}N_4O_2S$: C, 47.61; H, 4.79; N, 22.21. Found: C, 47.55; H, 4.83; N, 22.17.

2-Methyl-4-phenylthiosemicarbazone of Ethyl Glyoxylate (**1g**).

This compound (3.3 g, 62% yield) was prepared by the above procedure from 2-methyl-4-phenylthiosemicarbazide (3.6 g, 20 mmoles, in 35 ml of hot ethanol) and ethyl glyoxylate (2.55 g, 25 mmoles, in 5 ml of ethanol) by refluxing for 5 minutes and diluting with 20 ml of water. The crude **1g** washed with hot water, after crystallization from carbon tetrachloride-ligroin had mp 99-100°; ir: 3300 cm^{-1} (N-H), 1710 cm^{-1} (C=O), 1580 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 1.35 (t, 3H, CH_2CH_3, J = 7.0 Hz), 3.78 (s, 3H, NCH_3), 4.30 (q, 2H, CH_2CH_3, J = 7.0 Hz), 6.90 (s, 1H, CH), 7.0-7.7 (m, 5H, ArH), 10.12 (bs, 1H, NH).

Anal. Calcd. for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.84. Found: C, 54.24; H, 5.74; N, 15.91.

2-Methyl-4-phenylthiosemicarbazone of Acetaldehyde (**1h**).

This compound (3.2 g, 77% yield) was prepared by the above procedure from 2-methyl-4-phenylthiosemicarbazide (3.6 g, 20 mmoles, in 50 ml of ethanol) and acetaldehyde (2.25 ml, 40 mmoles). The crude **1h** after crystallization from ethylacetate had mp 109-110°; ir: 3280 cm^{-1} (N-H), 1590 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 2.06 (d, 3H, $CHCH_3$, J = 5.2 Hz), 3.72 (s, 3H, NCH_3), 7.0-7.7 (m, 6H, $CHCH_3$ and ArH), 9.86 (bs, 1H, NH).

Anal. Calcd. for $C_{10}H_{13}N_3S$: C, 57.94; H, 6.32; N, 20.27. Found: C, 58.02; H, 6.36; N, 20.33.

2,4-Diphenylthiosemicarbazone of Methyl Glyoxylate (**1j**).

To a solution of 2,4-diphenylthiosemicarbazide (2.4 g, 10 mmoles, in 75 ml of chloroform) a solution of glyoxylic acid monohydrate (1, 9 g, 20 mmoles, in 7.5 ml of ethanol) was added. After standing overnight, an excess of ether solution of diazomethane was added. Solvents were evaporated and the obtained red oil was treated with ethanol. The resultant solid was collected by filtration, washed with water then crystallized from ethanol to give 1.8 g (57% yield) of the 2,4-diphenylthiosemicarbazone **1j**, mp 146-147°; ir: 3300 cm^{-1} (N-H), 1735 cm^{-1} (C=O), 1590, 1580 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 3.70 (s, 3H, OCH_3), 6.35 (s, 1H, CH), 6.9-7.7 (m, 10H, ArH), 10.02 (bs, 1H, NH).

Anal. Calcd. for $C_{16}H_{15}N_3O_2S$: C, 61.37; H, 4.82; N, 13.41. Found: C, 61.35; H, 4.90; N, 13.33.

2,4-Diphenylthiosemicarbazone of Phenylglyoxal (**1k**).

This compound (1.7 g, 47% yield) was prepared by the above procedure from 2,4-diphenylthiosemicarbazide (2.4 g, 10 mmoles, in 35 ml of hot ethanol) and phenylglyoxal monohydrate (1.65 g, 11 mmoles, in 10 ml of ethanol), mp 166-167° (acetonitrile); ir: 3290 cm^{-1} (N-H), 1645 cm^{-1} (C=O), 1590, 1570, 1525 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 6.90 (s, 1H, CH), 6.9-8.0 (m, 15H, ArH), 9.90 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{17}N_3OS$: C, 70.17; H, 4.77; N, 11.69. Found: C, 70.25; H, 4.78; N, 11.58.

2,4-Diphenylthiosemicarbazone of Acetaldehyde (**1l**).

This compound was prepared by the above procedure from 2,4-diphenylthiosemicarbazide (2.4 g, 10 mmoles, in 25 ml of tetrahydrofuran) and acetaldehyde (1.1 ml, 20 mmoles). After standing overnight, the solvent was evaporated under reduced pressure and the residue chromatographed on silica gel column (eluent cyclohexane/ethyl acetate 4:1) gave 1.15 g (43% yield) of **1l**, mp 122-123° (benzene-ligroin); ir: 3320 cm^{-1} (N-H), 1590 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 1.92 (d, 3H, $CHCH_3$, J = 5.2 Hz), 6.48 (q, 1H, $CHCH_3$, J = 5.2 Hz), 6.9-7.8 (m, 10H, ArH), 9.91 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{15}N_3S$: C, 66.88; H, 5.61; N, 15.60. Found: C, 67.05; H, 5.60; N, 15.52.

Oxidative Cyclization of Thiosemicarbazones **1a-l**.

To a 10 mmoles of thiosemicarbazones **1** (solution or suspension) in ethanol (50 ml) an ethanol solution (2 *M*) of ferric chloride hexahydrate (10 ml) was added. The mixture was refluxed for 5 minutes (**1a**, **1c**, **1d**, **1i**, **1j**, **1k**, **1l**) or 30 minutes (**1b**, **1e**, **1f**, **1g**, **1h**) then the solvent evaporated under reduced pressure.

Water (30 ml) was added and the mixture was extracted with chloroform. The organic layer was dried and the chloroform

removed under reduced pressure. Residue and aqueous solution were appropriately worked as below reported.

Oxidation of **1a**. 5-Imino-4-methyl-Δ^2-1,3,4-thiadiazoline-2-carboxylic Acid.

Unreacted substrate **1a** (0.3 g) was founded in the residue. The aqueous solution was made alkaline with aqueous 10% sodium hydroxide then filtered and extracted with chloroform. The organic layer dried and the solvent removed under reduced pressure gave 0.1 g (9% yield) of the 5-imino-4-methyl-Δ^2-1,3,4-thiadiazoline [8].

The alkaline solution was treated with hydrochloric acid (6*M*) to give 0.5 g (31% yield) of 5-imino-4-methyl-Δ^2-1,3,4-thiadiazoline-2-carboxylic acid which was purified by dissolution in aqueous 2.5% sodium hydroxide followed by reprecipitation with hydrochloric acid (6 *M*), mp 175° dec; ir: 3220 cm^{-1} (N-H), 1660 cm^{-1} (C=O), 1620, 1560 cm^{-1} (C=N).

Anal. Calcd. for $C_4H_5N_3O_2S$: C, 30.18; H, 3.17; N, 26.40. Found: C, 30.25; H, 3.22; N, 26.33.

The thiadiazoline structure of the above acid was confirmed by decarboxylation and subsequent benzoylation to give the 5-benzoylimino-4-methyl-Δ^2-1,3,4-thiadiazoline, mp 129-130° [19].

Oxidation of **1b**. 1,3-Dimethyl-1,2,4-triazoline-5-thione (**4b**) and 2,4-Dimethyl-5-imino-Δ^2-1,3,4-thiadiazoline (**5b**).

The solid residue (0.36 g, 28% yield) gave the 1,3-dimethyl-1,2,4-triazoline-5-thione (**4b**) which was crystallized from toluene, mp 169-171° [20]; ir: 3200-3000 cm^{-1} (N-H), 1590 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3), 3.69 (s, 3H, NCH_3), 13.00 (bs, 1H, NH).

The aqueous solution was made alkaline with aqueous 10% sodium hydroxide then filtered and extracted with chloroform. The organic layer treated as above gave an oil (0.58 g, 45% yield) which was purified by column chromatography (eluent cyclohexane/ethyl acetate 1:1) and the yellow oil obtained was identified as 2,4-dimethyl-5-imino-Δ^2-1,3,4-thiadiazoline (**5b**) [21]; ^1H nmr (deuteriochloroform): δ 2.24 (s, 3H, CH_3), 3.43 (s, 3H, NCH_3), 5.30 (s, 1H, NH).

The thiadiazoline structure was confirmed by benzoylation to the 5-benzoylimino-2,4-dimethyl-Δ^2-1,3,4-thiadiazoline which was purified by column chromatography (eluent cyclohexane/ethyl acetate 2:1), mp 150° (lit [22] mp 148-150°); ir: 1605 cm^{-1} (C=O), 1600, 1570 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 2.48 (s, 3H, CH_3), 3.97 (s, 3H, NCH_3), 7.3-7.6 (m, 3H, ArH), 8.25 (m, 2H, *o*-ArH).

Oxidation of **1c**. 2-Carboxyethyl-4-methyl-5-methylimino-Δ^2-1,3,4-thiadiazoline (**5c**).

The white solid residue (0.33 g 16% yield) crystallized from ligroin, mp 70° was identified as the 4-methyl-5-methylimino-Δ^2-1,3,4-thiadiazoline 2-carboxylic acid ethyl ester (**5c**); ir: 1730, 1705 cm^{-1} (C=O), 1640 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 1.38 (t, 3H, OCH_2CH_3, J = 7.0 Hz), 3.01 (s, 3H, $=NCH_3$), 3.59 (s, 3H, NCH_3), 4.40 (q, 2H, OCH_2CH_3, J = 7.0 Hz).

Anal. Calcd. for $C_7H_{11}N_3O_2S$: C, 41.78; H, 5.51; N, 20.88. Found: C, 41.84; H, 5.48; N, 20.85.

The aqueous solution was made alkaline with triethylamine then filtered and extracted with chloroform. The organic layer treated as above gave a white solid which was triturated in benzene and the resulting suspension filtered off. The solid (1.2 g, 69% yield) washed with ethanol, had mp 135-136° dec, and was identified as 4-methyl-5-methylimino-Δ^2-1,3,4-thiadiazoline 2-carboxylic acid [23]; ir: 2700 cm^{-1} (OH), 1660 cm^{-1} (C=O), 1640, 1600 cm^{-1} (C=N); ^1H nmr (deuterium oxide): δ 3.25 (s, 3H, $=NCH_3$), 3.93 (s, 3H, NCH_3).

Anal. Calcd. for $C_5H_7N_3O_2S$: C, 34.68; H, 4.07; N, 24.26. Found: C, 34.74; H, 4.12; N, 24.17.

The benzene solution was evaporated to give 0.1 g (8% yield) of crude 4-methyl-5-methylimino-Δ^2-1,3,4-thiadiazoline, mp 47-48° [8].

Oxidation of **1d**. 1,3,4-Trimethyl-1,2,4-triazoline-5-thione (**4d**) and 2,4-Dimethyl-5-methylimino-Δ^2-1,3,4-thiadiazoline (**5d**).

The solid residue (0.18 g, 13% yield) purified by column chromatography (eluent cyclohexane/ethyl acetate 1:1) gave 0.1 g of **4d**, mp 106-107° (lit [20b] mp 82°, [24] mp 105-106°, [25] mp 106-107°); ir: 1575 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 2.32 (s, 3H CH_3), 3.48 (s, 3H, NCH_3), 3.70 (s, 3H, NCH_3).

The aqueous solution was made alkaline with aqueous 10% sodium hydroxide then filtered and extracted with chloroform. The organic layer treated as above gave an oil (1.15 g, 80% yield) which was purified by column chromatography (eluent cyclohexane/ethyl acetate/methanol 1:1:0.2) to give the 2,4-dimethyl-5-methylimino-Δ^2-1,3,4-thiadiazoline (**5d**) [26]; ir: 1635 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3), 2.95 (s, 3H, $=NCH_3$), 3.43 (s, 3H, NCH_3).

Anal. Calcd. for $C_5H_9N_3S$: C, 41.93; H, 6.33; N, 29.34. Found: C, 42.06; H, 6.35; N, 29.39.

Oxidation of **1e**. 1,4-Dimethyl-3-phenyl-1,2,4-triazoline-5-thione (**4e**) and 4-Methyl-5-methylimino-2-phenyl-Δ^2-1,3,4-thiadiazoline (**5e**).

The reaction mixture was diluted with water then was allowed to stand at room temperature for 1 day. The collected compound **4e** (1.17 g, 57% yield) was crystallized from benzene-ligroin, mp 135-136° [24,27]; ir: 1545 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 3.65 (s, 3H, NCH_3), 3.86 (s, 3H, NCH_3), 7.55 (s, 5H, ArH).

An additional amount of **4e** (0.1 g, 5% yield) could be obtained when the filtrate was concentrated under reduced pressure. The aqueous solution was extracted with chloroform. The organic layer treated as above gave 0.4 g of **5e** hydrochloride. This was dissolved in water (10 ml) and the solution was made alkaline with triethylamine. The separated oil was extracted with chloroform then purified by column chromatography (eluent cyclohexane/ethyl acetate 1:1) 0.3 g (15% yield) and identified as **5e** [27,28]; ir: 1640 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 3.05 (s, 3H, $=NCH_3$), 3.57 (s, 3H, NCH_3), 7.2-7.7 (m, 5H, ArH).

Oxidation of **1f**. 1,4-Dimethyl-3-(*p*-nitrophenyl)-1,2,4-triazoline-5-thione (**4f**) and 4-Methyl-2-(*p*-nitrophenyl)-5-methylimino-Δ^2-1,3,4-thiadiazoline (**5f**).

After cooling overnight, 0.9 g (36% yield) of starting material **1f** was recovered by filtration. The solution was concentrated to *ca.* 12 ml under reduced pressure then ethanol (8 ml) and water (20 ml) were added. The triazoline **4f** (0.55 g, 22% yield) was collected, washed with aqueous ethanol (1:1) and after crystallization from ethanol had mp 186-188°; ir: 1600 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 3.72 (s, 3H, NCH_3), 3.87 (s, 3H, NCH_3), 7.6-8.5 (m, 4H, ArH).

Anal. Calcd. for $C_{10}H_{10}N_4O_2S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 48.07; H, 4.12; N, 22.44.

The concentrated mother liquors were extracted with chloroform, organic extracts were dried and solvent distilled off. The solid residue was crystallized from ethanol to yield 0.6 g (24% yield) of **5f**, mp 190-191° (lit [29] mp 203°); ir: 1635, 1590 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 3.09 (s, 3H, $=NCH_3$), 3.64 (s, 3H, NCH_3), 7.6-8.4 (m, 4H, ArH).

Oxidation of **1g**. 2-Carboxyethyl-4-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**5g**).

The reaction mixture was diluted with water and was allowed to stand at room temperature for 1 day, then the solvent was partially evaporated under reduced pressure. The solid precipitate (1.90 g) was collected and washed with aqueous ethanol (2:1) and after crystallization from ligroin gave 1.7 g (65% yield) of **5g**, mp 83-84°; ir: 1705 cm^{-1} (C=O), 1610, 1585 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 1.34 (t, 3H, OCH_2CH_3, J = 7.0 Hz), 3.77 (s, 3H, NCH_3), 4.35 (q, 2H, OCH_2CH_3, J = 7.0 Hz), 6.8-7.5 (m, 5H, ArH).

Anal. Calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.83; H, 5.02; N, 16.10.

An additional amount of **5g** (0.42 g, 16% yield) could be obtained by usual treatment of the mother liquors. The structure of **5g** was confirmed through the 4-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline [11] obtained by hydrolysis of **5g** and decarboxylation of corresponding acid.

Oxidation of **1h** 1,3-Dimethyl-4-phenyl-1,2,4-triazoline-5-thione (**4h**) and 2,4-Dimethyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**5h**).

The oil residue (1.1 g) was chromatographed on a column of silica gel (eluents cyclohexane and cyclohexane-ethyl acetate). Two products were collected. The former (0.45 g, 22% yield) was an oil identified as the 2,4-dimethyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**5h**) [26]; ir: 1610, 1585 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 2.12 (s, 3H, CH_3), 3.50 (s, 3H, NCH_3), 6.7-7.4 (m, 5H, ArH).

Anal. Calcd. for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47. Found: C, 58.72; H, 5.61; N, 20.30.

The latter was a solid (0.52 g, 25% yield), mp 74-75°, identified as the 1,3-dimethyl-4-phenyl-1,2,4-triazoline-5-thione (**4h**) [30,31]; ir: 1575 (C=N); ^1H nmr (deuteriochloroform): δ 2.16 (s, 3H, CH_3), 3.81 (s, 3H, NCH_3), 7.0-7.6 (m, 5H, ArH).

Oxidation of **1i** 3,4-Diphenyl-1-methyl-1,2,4-triazoline-5-thione (**4i**) and 4-Methyl-2-phenyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**5i**).

After cooling overnight, 1.65 g (62% yield) of crude triazoline **4i** was collected. The solid material washed with water and with ethanol, after crystallization from ethanol had mp 185-186° (lit [32] mp 182°, [33] mp 183.5-184°); ir: 1590 (weak) cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 3.95 (s, 3H, NCH_3), 7.2-7.6 (m, 10H, ArH).

Mother liquors were concentrated under reduced pressure then water (20 ml) was added and the solution was extracted with chloroform. The organic extracts were dried and the solvent distilled off to yield (0.95 g) of crude product, which was chromatographed on silica gel column (eluent cyclohexane/ethyl acetate 4:1). Triazoline **4i** (0.18 g, 7% yield) and thiadiazoline **5i** (0.70 g, 26% yield) were obtained. Compound **5i** crystallized from ligroin had mp 81-82° (lit [34] mp 79-81°); ir: 1610, 1585 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 3.72 (s, 3H, NCH_3), 6.8-7.7 (m, 10H, ArH).

Oxidation of **1j**. 2-Carboxymethyl-4-phenyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**5j**).

After cooling overnight, 2.45 g (79% yield) of the thiadiazoline **5j** was collected. Crystallized from ethanol it had mp 115-117°; ir: 1745 cm^{-1} (C=O), 1630, 1590 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 3.76 (s, 3H, OCH_3), 6.6-8.0 (m, 10H, ArH).

Anal. Calcd. for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.90; H, 4.18; N, 13.55.

Oxidation of **1k**. 2-Benzoyl-4-phenyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**5k**).

After cooling overnight, 3.23 g (90% yield) of crude thiadiazoline **5k** was collected. The solid material washed with ethanol after crystallization from acetonitrile had mp 133-134°; ir: 1640, 1630 cm^{-1} (C=O), 1615, 1580 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 6.7-8.1 (m, 13H, ArH), 8.25 (m, 2H, o-ArH of COPh).

Anal. Calcd. for $C_{21}H_{15}N_3OS$: C, 70.57; H, 4.23; N, 11.76. Found: C, 70.64; H, 4.31; N, 11.67.

Oxidation of **1l**. 1,4-Diphenyl-3-methyl-1,2,4-triazoline-5-thione (**4l**).

After cooling overnight, to the reaction mixture water was added then concentrated under reduced pressure to give 2.3 g (86% yield) of the triazoline **4l**, which after crystallization from ethanol had mp 132° (lit [31] mp 134°, [33] mp 131-132°); ir: 1590 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 2.20 (s, 3H, CH_3), 7.1-8.2 (m, 10H, ArH).

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