Photochemical Cyclization of Some Aldehyde Thiosemicarbazones

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The photochemical behaviour of some substituted aldehyde thiosemicarbazones **1a-k** has been investigated in methanol at 254 nm. Thiosemicarbazones of glyoxil methyl ester **1a-f** cyclized to furnish the 3-thioxo-1,2,4-triazin-5-one **2** ring system. The remaining thiosemicarbazones **1g-j** gave 1,2,4-triazoline **4** derivatives.

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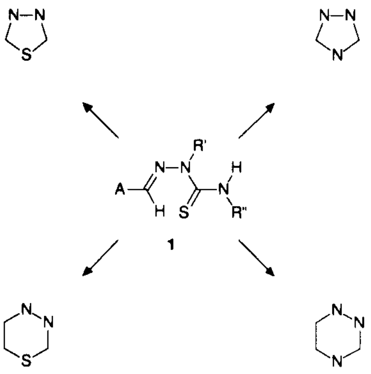
Aldehyde semi- and thiosemicarbazones are polyfunctionalyzed compounds which easily cyclize [1] by action of bases, acids or oxidants; therefore they are useful and versatile synthons for the preparation of five- or six-membered heterocyclic compounds.

In Scheme 1 are reported the rings that can be obtained by heterocyclization of aldehyde thiosemicarbazones **1**.

Scheme 1

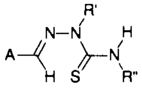


The formation of six-membered rings is, of course, possible only if the residue A contains a group $C=X$ or a carbon-halogen single bond conjugated with the carbon-nitrogen double bond.

The course of the cyclization reaction can be affected [2] by the nature of the cyclizing agent as well as by structure of the thiosemicarbazones **1**.

We have recently [3] studied the oxidation of some substituted aldehyde thiosemicarbazones **1** with ethanolic solutions of ferric chloride. The data obtained showed that the five membered heterocyclic ring formation depends on the structure of the starting thiosemicarbazones.

In the course of the above mentioned studies we noticed that in some cases **1** reacted in ethanol solution set aside for few hours. In order to gain information about this "spontaneous" transformation the thermal and photochemical behaviours of aldehyde thiosemicarbazones **1a-k** have been studied in methanol solution and under the below specified reaction conditions.



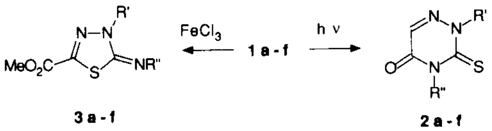
1a-k

a:	A = COOMe	R' = Ph	R" = Ph
b:	A = COOMe	R' = Me	R" = Ph
c:	A = COOMe	R' = H	R" = Ph
d:	A = COOMe	R' = Me	R" = Me
e:	A = COOMe	R' = Me	R" = H
f:	A = COOMe	R' = H	R" = H
g:	A = COPh	R' = Me	R" = Ph
h:	A = Me	R' = Me	R" = Ph
i:	A = Ph	R' = Me	R" = Ph
j:	A = Ph	R' = Me	R" = Me
k:	A = COPh	R' = Me	R" = H

Irradiation has been carried out in anhydrous methanol at 254 nm, by using low pressure Hg lamps (17W) in an immersion apparatus. Thermal reactions have been carried out by heating at reflux in the same solvent (anhydrous methanol) as for the photochemical reactions. The course of the reactions was followed by tlc analysis. The results obtained showed that thiosemicarbazones **1** were more reactive under photochemical than under thermal conditions. However the structure of the products obtained from the thiosemicarbazone cyclization is independent of the adopted reaction condition, either photochemical or thermal. Considering that irradiation of thiosemicarbazones **1** induced cyclizations (see before) in higher yields than those obtained by heating the thiosemicarbazones **1** for the same time, we report (see Table and Experimental) only the results of the photochemical reactions. Good or satisfactory yields were generally obtained by the photochemical experiments with the exception of the reactions of N-4 unsubstituted thiosemicarbazones **1e**, **f**, **k** which either gave cyclization in poor yields or did not react at all.

Irradiation of the glyoxil methyl ester thiosemicarbazones **1a-f** gave a photoinduced heterocyclization leading to six membered triazine ring **2**. It should be remembered that oxidative cyclization of **1a-f** with ferric chloride solutions exclusively furnished the corresponding 1,3,4-thiadiazoles **3a-f**.

Scheme 2



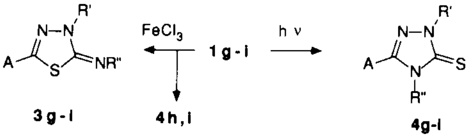
The formation of the triazine ring **2** is independent of the nature of the R′ and R″ groups of the thiosemicarbazone chain, the R′ and R″ groups influencing only the reaction yield. In our opinion the reaction consists of a nucleophilic attack of the N-4 nitrogen atom of the thiosemicarbazone chain on the carbon atom of the carbomethoxy group followed by the departure of the leaving alkoxy group from a cyclic intermediate, subsequent deprotonation of the N-4 nitrogen atom and eventually by the formation of a double bond between carbon and oxygen atoms. Irradiation could be determinant to induce the breaking off of the carbon-alkoxy bond, by activating the N-4 nitrogen atom or the carbon-oxygen double bond of the carbomethoxy group. However, the order of reactivity observed under photochemical conditions: NHPh > NHMe ≫ NH_2 seems to suggest that activation of the N-4 nitrogen atom is the important step of the photochemical heterocyclization of the thiosemicarbazones **1a-f**. This hypothesis is also confirmed by the results of the thermal cyclization, for which it has been observed, as mentioned above, a low reactivity and a reactivity order parallel to the basicity of the amino groups *i.e.* NHMe > NH_2 > NHPh [4].

An analysis of the effect of the nature of R′ group on reactivity has shown that the effect of this group on the reaction yield is less important than that of the R″ group, the methyl group being, among those examinated, the most efficient group.

The influence of the aldehydic residue A on the photoheterocyclization has also been investigated in thiosemicarbazones **1g-i**. These compounds have the same thiosemicarbazidic chain structure, characterized by a methyl group on N-2, a terminal NHPh group and a residue A having different electronic effects: electron-withdrawing the benzoyl group, electron-repelling the methyl group and the electronic effect of the phenyl group depending on its position with respect to the reaction centre and the reaction type. These different behaviours can be displaied by the σ_p^+ (-0.18) and σ_p^- (0.08) values [5] of the phenyl group.

Irradiation of thiosemicarbazones **1g-i** gave a photoinduced heterocyclization leading to a five membered triazoline ring **4** [6], irrespective of the electronic effects of the A group.

Scheme 3



Substitution of H for methyl or phenyl group, R″, in compounds **1** determined a dramatic lowering of the reaction yield or even a complete loss of reactivity. The above results show that the mechanism of the photoinduced cyclization is not influenced by the electronic density on the aldehydic carbon. According to the afore interpretation the activation of N-4 nitrogen atom is the main factor affecting the photocyclization of thiosemicarbazones **1**.

It should be noticed that the oxidative cyclization of **1g** exclusively furnished 1,3,4-thiadiazoline **3** ring, while under the same reaction condition **1h** and **1i** gave both 1,2,4-triazoline **4** and 1,3,4-thiadiazoline **3** rings. Therefore photochemical, in contrast with chemical oxidative conditions, seem able to give highly regiospecific heterocyclization or to change the regiochemistry of the reaction.

In conclusion the data obtained indicate that: i) the terminal group of the thiosemicarbazone chain operates as a chromophore; ii) the nature of the heterocyclic ring synthesized depends only on the chemical structure of the residue A, while the electronic properties of A, in contrast to what was observed for the oxidative cyclization reaction, are unimportant.

At last the photocyclization reaction of glyoxil methyl ester thiosemicarbazones, in virtue of the satisfactory yields obtained, can be considered a suitable and general preparative method of the 3-thioxo-4-phenyl-5-one-1,2,4-triazine system **2**.

Table

Irradiation of Thiosemicarbazones 1a-k at 254 nm in Methanol

Compound	$\log(\varepsilon_{254})$	Time hours	Starting material (%)	Product	(%)
1a	4.08	6	(/)	**2a**	(61)
1b	3.75	6	(/)	**2b**	(88)
1c	3.89	9	(24)	**2c**	(44)
1d	3.37	11	(37)	**2d**	(42)
1e	3.67	11	(86)	**2e**	(5)
1f	4.04	11	(85)	**2f**	(4)
1g	4.08	5	(/)	**4g**	(53)
1h	4.11	8	(/)	**4h**	(70)
1i	3.88	20	(/)	**4i**	(53)
1j	3.61	40	(99)	**4j**	(traces)
1k	3.71	40	(100)		

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus; ir spectra (nujol mulls) were determined with a Perkin-Elmer 257 instrument, uv spectra (in ethanol) with a Varian Superscan 3 spectrophotometer, ^{1}H-nmr spectra (60 MHz) with a

Varian EM 360 spectrometer (TMS as the internal standard), ^{13}C-nmr spectra with a Varian Gemini 300 spectrometer and mass spectra with a VG 7070E spectrometer. Flash chromatography was performed on Merck silica gel (0,040-0,063 mm).

Thiosemicarbazones were prepared as reported [3].

Structures of the irradiation products were assigned by a comparison with authentic samples (mp, ir, uv), or on the basis of analytical and spectroscopic data (ir, nmr, ms).

Photochemical Reactions.

General Procedure.

A solution of the thiosemicarbazones (1 g) in anhydrous methanol (100 ml), in a quartz tube, was degassed by nitrogen bubbling (20 minutes), and then irradiated at 254 nm in an immersion well apparatus by a low-pressure mercury lamp (Helios Italquartz, 17 W). The solvent was removed under reduced pressure and the residue was subjected to chromatography by using mixtures of cycloexane-ethyl acetate in varying volume ratios as eluent.

Irradiation of Compound **1a**.

Irradiation for 6 hours gave 2,4-diphenyl-3-thioxo-1,2,4-triazin-5-one (**2a**) (61% by chromatography 5/1). Compound **2a** had mp 156°; ir: 1700 cm^{-1} (C=O), 1590 cm^{-1} (C=N), 1170 cm^{-1} (C=S); ^{1}H-nmr (deuteriochloroform): δ 7.1-7.6 (m, aromatic, 10 H), 7.8 (s, H-6, 1 H); ^{13}C-nmr (deuteriochloroform): δ 127.67, 128.54, 129.94, 130.11, 130.18, 130.64, 137.76, 138.87, 144.91, 152.77, 176.96; uv: λ max nm (log ϵ) 275 (4.04); ms: m/z 281 (M$^+$).

Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94; S, 11.40. Found: C, 63.85; H, 3.89; N, 14.89; S, 11.36.

Irradiation of Compound **1b**.

Irradiation for 6 hours gave 2-methyl-4-phenyl-3-thioxo-1,2,4-triazin-5-one (**2b**) (88% by crystallization from carbon tetrachloride). Compound **2b** had mp 151°; ir: 1690 cm^{-1} (C=O), 1590 cm^{-1} (C=N), 1180 cm^{-1} (C=S); ^{1}H-nmr (deuteriochloroform): δ 3.95 (s, N-CH$_3$, 3 H), 7.0-7.6 (m, aromatic, 5 H), 7.65 (s, H-6, 1 H); ^{13}C-nmr (deuteriochloroform): δ 47.60, 128.41, 130.08, 130.56, 137.87, 138.70, 152.98, 176.02; uv: λ max nm (log ϵ): 267 (4.21), sh 315 (3.63); ms: m/z 219 (M$^+$).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16; S, 14.62. Found: C, 54.90; H, 4.07; N, 19.24; S, 14.57.

Irradiation of Compound **1c**.

Irradiation for 9 hours gave 4-phenyl-3-thioxo-1,2,4-triazin-5(2*H*)-one (**2c**) (44% by chromatography with dichloromethane), and starting material (24%). Compound **2c** had mp 233-235°; ir: 3040, 3140, 3190 cm^{-1} (N-H), 1650, 1670 cm^{-1} (C=O), 1590 cm^{-1} (C=N), 1200 cm^{-1} (C=S); ^{1}H-nmr (deuteriochloroform): δ 7.1-7.6 (m, aromatic, 5 H), 7.85 (s, H-6, 1 H), 13.8 (br s, NH, 1 H); ^{13}C-nmr (deuteriochloroform): δ 127.98, 128.92, 129.30, 136.36, 138.80, 152.42, 175.70; uv: λ max nm (log ϵ) 271 (4.11), sh 312 (3.51); ms: m/z 205 (M$^+$).

Anal. Calcd. for $C_9H_7N_3OS$: C, 52.67; H, 3.44; N, 20.47; S, 15.62. Found: C, 52.57; H, 3.36; N, 20.55; S, 15.68.

Irradiation of Compound **1d**.

Irradiation for 11 hours gave 2,4-dimethyl-3-thioxo-1,2,4-triazin-5-one (**2d**) (42% by chromatography with 3/1), and starting material (37%). Compound **2d** had mp 118°, lit [7] mp 115-116°; ir: 1700 cm^{-1} (C=O), 1124 cm^{-1} (C=S); ^{1}H-nmr (deuteriochloroform): δ 3.6 (s, N-CH$_3$, 3 H), 3.9 (s, N-CH$_3$, 3 H), 7.5 (s, H-6, 1 H); ^{13}C-nmr (deuteriochloroform): δ 33.71, 47.54, 137.06, 152.87, 177.82.

Irradiation of Compound **1e**.

Irradiation for 11 hours gave 2-methyl-3-thioxo-1,2,4-triazin-5(4*H*)-one (**2e**) (5% by chromatography with 2/1), and starting material (86%). Compound **2e** had mp 215-217°, lit [8] mp 216-218°; ^{13}C-nmr (DMSO-d$_6$): δ 44.49, 140.21, 152.53, 173.20.

Irradiation of Compound **1f**.

Irradiation for 11 hours gave 3-thioxo-1,2,4-triazin-5-one (**2f**) (4% by chromatography with 2/1), and starting material (85%). Compound **2f** had mp 228-232°, lit [9] mp 227-228°; ^{13}C-nmr (DMSO-d$_6$): δ 140.12, 152.78, 173.78.

Irradiation of Compound **1g**.

Irradiation for 5 hours gave 1-methyl-4-phenyl-1,2,4-triazoline-5-thione (**4g**) (53% by chromatography with 5/1). Compound **4g** had mp 111-112° [10].

Irradiation of Compound **1h**.

Irradiation for 8 hours gave 1,3-dimethyl-4-phenyl-1,2,4-triazoline-5-thione (**4h**) (70% by chromatography with 1/1). Compound **4h** had mp 74-75° [3].

Irradiation of Compound **1i**.

Irradiation for 20 hours gave 1-methyl-3,4-diphenyl-1,2,4-triazoline-5-thione (**4i**) (53% by chromatography with 3/1). Compound **4i** had mp 185-186° [3].

Irradiation of Compound **1j**.

Irradiation for 40 hours gave starting material and only traces of 1,4-dimethyl-3-phenyl-1,2,4-triazoline-5-thione (**4j**) (tlc).

Irradiation of Compound **1k**.

Starting material was exclusively recovered after irradiation for 40 hours.

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