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Photocyclization Reaction of some 2-Methyl-4-phenyl- Substituted Aldehyde Thiosemicarbazones. Mechanistic Aspects

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Abstract—Irradiation of 2-methyl-4-phenyl- substituted benzaldehyde thiosemicarbazones led with good yields to the corresponding Δ^2-1,2,4-triazoline-5-thione derivatives through the formation of stable 1,2,4-triazolidine-5-thione intermediates. The relative quantum yields of photocyclization at 313 nm were analysed by means of the Hammett equation and ρ values determined. We interpreted the results in terms of the mechanism of photocyclization of 2-methyl-4-phenyl-substituted benzaldehyde thiosemicarbazones.

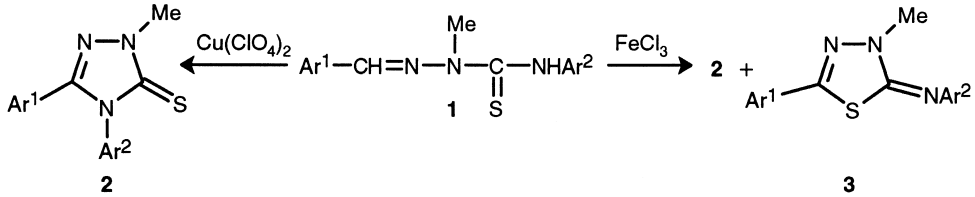
Introduction

Semi- and thiosemi-carbazones as well as 1,2,4-triazole, 1,3,4-oxadiazole and 1,3,4-thiadiazole rings, which can be obtained by oxidative cyclization, have received attention by pharmacologists. Semicarbazones have been considered as peptide isosteres and as possible urea peptide mimetics,[1] while thiosemicarbazones and their copper complexes have been used as antimalarial agents.[2,3] Further, 1,2,4-triazoline-5-ones and 1,2,4-triazoline-5-thiones have shown biological activity and have been used as anti-inflammatories, cardiotonics, or dopamine β-hydroxilase inhibitors,[4] as well as fungicides and herbicides.[5]

Several oxidizing agents can be used for the cyclization of semi- and thiosemi-carbazones and the regiochemistry of the cyclization reaction depends on conditions adopted for the reaction as well as the structure of the starting substrate.[6–11] For example, we have found that the oxidation of 2-methyl-4-phenyl thiosemicarbazones **1** with ferric chloride solutions gave 1,2,4-triazoline **2** and/or 1,3,4-thiadiazoline **3** heterocycles, the second being favoured by electron-withdrawing groups linked to the –CH=N–N< hydrazone moiety (Scheme 1).[6,9]

In contrast, only the 1,2,4-triazolines **2** were obtained when cupric perchlorate in methanol was used as oxidizing agent, but low concentrations of both the reagents (<0.01 M) had to be used in order to avoid the formation of stable complexes.[10]

Recently[11] we have investigated the photochemical behaviour of some substituted aldehyde thiosemicarbazones in methanol at 254 nm. We have found that the aldehyde residue influences the photoheterocyclization. In fact, thiosemicarbazones of glyoxyl methyl ester **4** cyclized to furnish the 3-thioxo-1,2,4-triazin-5-one **5** while, but when the group bonded to the –CH=N–N< hydrazone moiety was a methyl or phenyl group, only the 1,2,4-triazoline **2** was obtained. For comparison, the oxidative cyclization with ferric chloride solutions gave, in the former case only the 1,3,4-thiadiazolinic product **6** while, in the latter case,



2 1 3

Scheme 1.

Keywords: photocyclization; benzaldehyde thiosemicarbazones; Hammett equation; 1,2,4-triazoles.

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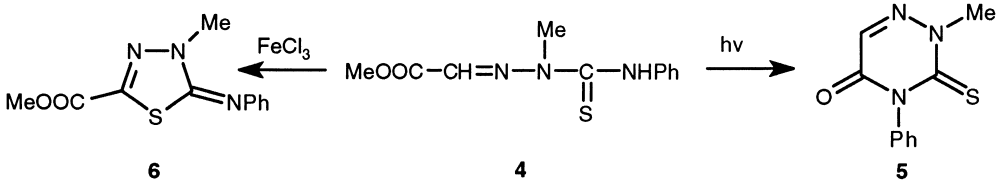


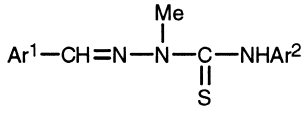
6 4 5

Scheme 2.

usually a mixture of 1,2,4-triazoline and 1,3,4-thiadiazoline rings (Scheme 2).[6]

Moreover the yields of the photoreactions strongly depend on the nature of the group bonded to the N(4) atom, being better when it is an aryl group; in fact the photocyclization of **1c** gave **2** in 70% yield after 8 h, while the 2,4-dimethyl-thiosemicarbazone of benzaldehyde did not react after 40 h of irradiation.[11]

In order to gain more information about the photochemical behaviour of thiosemicarbazones, we have studied the photocyclization reaction at various wavelengths (254, 313 and 366 nm) of some 2-methyl-4-phenyl benzaldehyde thiosemicarbazones **1a**–**i**. Compounds **1a**–**i** were chosen in such a way as to have a change of electronic density on both the carbon–nitrogen double bond and the N(4). Furthermore, the effect of substituents on cyclization at 313 nm has been also investigated.



1a-i

1	Ar^1	Ar^2
a	4-$MeOC_6H_4$	C_6H_5
b	4-MeC_6H_4	C_6H_5
c	C_6H_5	C_6H_5
d	4-ClC_6H_4	C_6H_5
e	4-BrC_6H_4	C_6H_5
f	4-$CF_3C_6H_4$	C_6H_5
g	C_6H_5	4-$MeOC_6H_4$
h	C_6H_5	4-MeC_6H_4
i	C_6H_5	4-ClC_6H_4

Results and Discussion

UV spectra of compounds **1a**–**i** showed an absorption maximum around 300 nm and a minimum around 250 nm. In Table 1 are reported λ_{max} and ϵ values at λ_{max}, 254, 313 and 366 nm.

Preparative Photolysis

Since all the compounds **1a**–**i** showed an adsorption maximum around 300 nm, we have irradiated at 313 nm in order to improve the yields of the reactions. In Table 2 are reported data obtained for the irradiation at 313 nm for compounds **1a**–**i**. These results confirmed an excellent efficiency, leading to an almost quantitative formation of the Δ^2-1,2,4-triazoline-5-thione derivatives **1a**–**i**. Irradiation at 254 nm of compound **1c** gave **2c** in lower yield (53%).[11] Some quenching experiments were carried out in the presence of a large excess of penta-1,3-diene (piperylene) as a triplet quencher. The disappearance of compounds **1a**–**i** was not quenched (both at 254 and 313 nm). This result suggested that, in the primary photochemical process, singlet excited states should be involved.

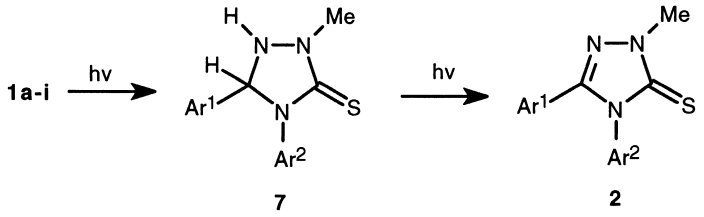
Monitoring the reaction solution of **1c** at 313 nm by HPLC or TLC, we observed an intermediate species, the concentration of which at first increased to a maximum and then decreased while the concentration of **2c** increased. Differently from what was observed at 313 nm, the reaction of **1c** at 254 nm proceeded without formation of the intermediate species, but the photoproduct **2c** was formed directly. However, when the solution of **1c** was degassed by argon bubbling (15 min) and then irradiated at 254 nm, a small amount of the intermediate species was detected (by HPLC). We were able to isolate the intermediate species **7c** in good yield (80%) by irradiation of a diluted solution of **1c** (100 mg in 200 mL of MeOH) degassed by argon bubbling and then irradiated at 313 nm for 60 min. The structure of compound **7c** was proved by the usual

Table 1. λ_{max} and ϵ values at λ_{max}, 254, 313 and 366 nm for **1a**–**i**

Compound	λ_{max}	ϵ_{max}	ϵ_{254}	ϵ_{313}	ϵ_{366}
1a	328	37 900	8100	27 500	2300
1b	321	38 100	5700	32 900	800
1c	318	35 300	5400	32 800	900
1d	323	36 400	6300	29 600	1600
1e	325	40 400	7200	31 600	1000
1f	326	35 900	6500	29 400	2300
1g	317	36 900	8300	35 200	1400
1h	317	36 700	7100	34 600	1100
1I	318	33 200	8400	31 100	900

Table 2. Yields and reaction time for the photochemical cyclization of **1a**–**i**

Compound	**2** (%)	Irradiation time (h)
1a	95	14
1b	95	16
1c	95	16
1d	95	19
1e	95	20
1f	85	40
1g	95	16
1h	95	21
1I	95	30



Scheme 3.

Table 3. λ_{max} and ϵ values at λ_{max}, 254, 313 and 366 nm for **7b**–**c**,**e**

Compound	λ_{max}	ϵ_{max}	ϵ_{254}	ϵ_{313}	ϵ_{366}
7b	259	13 000	12 500	2700	60
7c	259	13 000	12 500	2500	40
7e	254	10 100	10 100	3600	200

spectroscopic techniques, in particular the signal at δ 5.96 in the ^{1}H NMR spectrum and that at δ 79.7 in the ^{13}C NMR spectrum were attributed to the C–H of the heterocycle. In order to distinguish photochemical and thermal processes, a sample of **7c** was irradiated in methanol at 313 nm giving directly the corresponding Δ^2-1,2,4-triazoline-5-thione **2c**, showing that the formation of **2c** was the final result of two consecutive photochemical reactions. In fact, compound **1c** was thermally stable at 40°C and compound **7c** was converted into **2c** at 40°C after 50 h (Scheme 3).

In the irradiation at 254 nm we did not isolate compound **7c** because of the high ratio $\epsilon_{7c}/\epsilon_{1c}$ (12 500/5400), whereas we were able to do so at 313 nm ($\epsilon_{7c}/\epsilon_{1c}$=2500/32 800) (see Table 3).

In order to realize a method for the synthesis of compounds **7** we have carried out photochemical reactions at 366 nm (at this wavelength compounds **7** do not have appreciable absorption) in anhydrous methanol, degassing the solutions by argon bubbling. Irradiation of compounds **1b**,**c**,**e** gave compounds **7b**,**c**,**e** in high yields (90%).

Also compounds **7b**,**e** showed absorption maxima around 254 nm and low absorption at 366 nm (see Table 3).

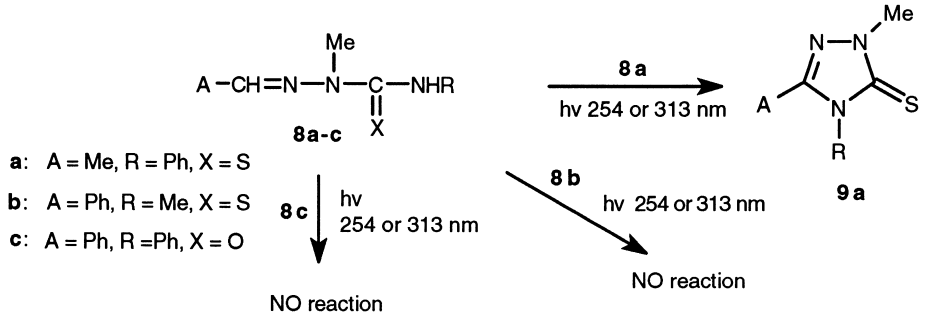
Mechanistic Consideration

The first step of the photoreaction of compounds **1** could be depicted as the cyclization to the 1,2,4-triazolidine-5-thione derivatives **7**, the second step as the photooxidation of **7** to give the Δ^2-1,2,4-triazoline-5-thione derivatives **2**. The first step takes place faster at 313 nm in comparison with the irradiation at 254 nm (higher absorption of compounds **1**), whereas the second step takes place faster at 254 nm (higher absorption of compounds **7**). For the photocyclization at 254 nm of the thiosemicarbazones **1**, it was noted[11] that the photochemically active chromophore was the phenylamino group, i.e. the activation of N(4) nitrogen atom is the main factor affecting the photocyclization of thiosemicarbazones. By contrast the presence of a phenyl group linked on the –CH=N–N< hydrazone moiety does not seem to be essential.

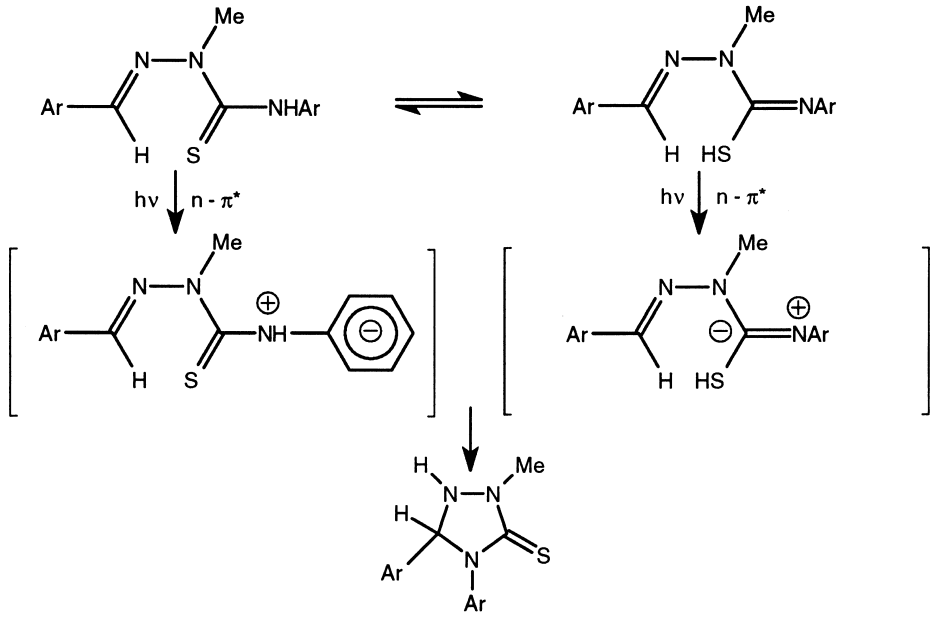
This result was also confirmed by irradiation at 313 nm of compound **8a** that gave the corresponding Δ^2-1,2,4-triazoline-5-thione **9** in good yield (90%), in fact this leaves out a meaningful contribution of the aldehydic residue chromophore to the primary photochemical process. Compound **8b** did not show photochemical reactivity at 254 or 313 nm. Moreover, the influence of the sulphur atom on photochemical process was ascertained by irradiation of compound **8c** at 254 and 313 nm. Both the reactions did not take place (Scheme 4).

These results clearly indicate that the photochemically active chromophore should be the CSNHPh group that can undergo three different types of transitions based on the presence of the three donor centres, π–π^* of the aryl group, n–π^* of the nitrogen atom and n–π^* of the sulphur atom. Moreover it is well known that thiosemicarbazones can undergo an enolization reaction as depicted in Scheme 5.[12]

In order to gain deeper insight into the photochemical processes we have analysed the rate of reaction on irradiation of compounds **1a**–**d**,**f**–**i** at 313 nm. In Table 4 are



Scheme 4.



Scheme 5.

Table 4. Disappearance (%) and relative quantum yields (Φ_S/Φ_H) for the photochemical cyclization of **1a**–**d**,**f**–**i**

Compound	Disappearance of **1** (%)	Φ_S/Φ_H	Compound	Disappearance of **1** (%)	Φ_S/Φ_H
1a	34	2.125	**1g**	5.6	0.350
1b	26	1.625	**1h**	8.8	0.550
1c	16	1.000	**1c**	16	1.000
1d	8.5	0.431	**1i**	47	2.906

reported the relative quantum yields [Φ_S/Φ_H; Φ_S indicates the quantum yield for compounds with substituted phenyl ring, Φ_H indicates the quantum yield for compound with unsubstituted phenyl ring (**1c**)].

In order to quantify the above substituent effects we have attempted to correlate the data reported in Table 4 with σ substituent constant[13] in terms of Hammett's equation and obtained the following good correlations:

1. $\log \Phi_S/\Phi_H = -0.01(0.01) - 1.32(0.05)\sigma$ (r=0.998) for substitution on the phenyl ring bonded to –CH=N–N< hydrazone moiety;
2. $\log \Phi_S/\Phi_H = 0.03(0.02) + 1.86(0.11)\sigma$ (r=0.996) for substitution on the phenyl ring bonded to N(4) atom (Fig. 1).

The negative value calculated for susceptibility constant ρ of the former correlation shows that the above substituents influence the cyclization reaction of thiosemicarbazones **1** in a similar manner irrespective of the fact that the reaction is carried out with a metallic salt as oxidizing agent or under photochemical conditions.

Such substituent effects are rationalized assuming that the –CH=N–N< hydrazone moiety acts as an internal nucleophile. On the contrary, the effect of a substituent bonded to phenyl group linked to N(4) nitrogen atom depends on the conditions adopted for the cyclization reactions. In fact, a negative value for susceptibility constant ρ was calculated for the oxidative reaction induced by ferric chloride[9] while a non-linear trend was observed when cupric perchlorate was used as oxidizing agent.[10] So the positive value calculated for susceptibility constant ρ in the present study represents a further and different substituent effect.

This is not surprising, indeed it is plausible that the substituent effects on the *N*-phenyl thioamide moiety can be different according to reaction conditions. In the case of oxidation induced by metallic salts the relative importance of various steps determines the observed substituent effects. In the photochemical cyclization reaction, the collected data seem to suggest that the primary photochemical process involves a n–π^* transition of the N(4) nitrogen atom that leads to an electrophilic N(4) nitrogen atom in its singlet state responsible for the cyclization to give the dihydro

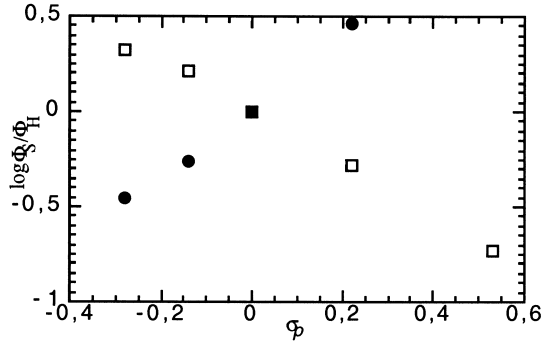


Figure 1. Plots of log Φ_S/Φ_H versus σ_p for the photochemical cyclization of **1a**–**f** (squares) and **1c**,**g**–**i** (circles).

derivatives **7**.[14,15] The electron-withdrawing substituents support the formation of the above singlet excited state and consequently favour the electrophilic attack delocalizing the increase of the electron density on the aromatic ring as a consequence of $n-\pi^*$ transition.

Conclusions

Our study has clarified the photochemical processes involved in the cyclization of some thiosemicarbazones derivatives, showing that this reaction is the result of two consecutive photochemical processes and how the substituents bonded to the two phenyl rings can affect the cyclization. We have also realized an interesting method for the synthesis of the 1,2,4-triazolidine-5-thiones **7**. Some 3-monosubstituted 1,2,4-triazolidine-5-thiones were observed during the recording of mass-spectra of thiosemicarbazones.[16] They may be produced in the gas phase after multiple collisions of the vaporized sample molecules with hot surfaces of the ion source prior to the ionization. Our method allows us to prepare these compounds in a very simple way.

Experimental

Materials and methods

Photochemical reactions were carried out in anhydrous methanol by using a Rayonet RPR-100 photoreactor fitted with 16 lamps irradiating at $\lambda=254$ nm (in quartz vessels), $\lambda=313$ and 366 nm (in pyrex vessels) and a merry-go-round apparatus. HPLC analyses were performed by using a C-18 SIL-X-10 Perkin–Elmer column (25 cm×4.6 mm diameter) eluting with water/acetonitrile 20:80, flow 1 mL/min at $\lambda=280$ nm. UV spectra were recorded with a Jasco 7800 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-E series 250 MHz spectrometer with TMS as internal standard. Photoproducts **2a**–**i**[9] and **9a**[6] were compared with authentic samples. Compounds **1a**–**i**,[9] **8a**,**b**[6] and **8c**[8] were prepared as reported.

General procedure for photochemical reactions

A sample of the thiosemicarbazones **1a**–**i** and **8a** (250 mg; 0.7–0.9 mmol) in methanol (150–200 mL) was apportioned into three or four pyrex tubes and then irradiated ($\lambda=313$ nm) for the time indicated. Removal of the solvent under reduced pressure gave the triazolines **2a**–**i** and **9a**.

Analytical photoreactions

On the basis of ϵ values at $\lambda=313$ nm (see Table 1), solutions of substrates **1a**–**d**,**f**–**i** were made to have the same absorbance. Solutions of each thiosemicarbazone **1a**–**d**,**f**–**i** in 10 mL of methanol were irradiated simultaneously for 45 min in a merry-go-round apparatus and the resulting photolysates were analysed quantitatively by HPLC in order to determine the disappearance of compounds **1**.

Synthesis of 1,2,4-triazolidine-5-thiones

A sample (100 mg) of **1b**, **1c** or **1e**, respectively, in methanol (100 mL) was degassed by argon bubbling (15 min) and then irradiated for 90 min (for **1b**,**c**) or 210 min (for **1e**) at 366 nm. Removal of the solvent under reduced pressure gave the triazolidines **7b**,**c** and **7e** (>90%) that were not purified (less than 5% of the corresponding thiosemicarbazones and triazolines were detected by ^{1}H NMR).

Compound **7c**: ^{1}H NMR (250 MHz) ($CDCl_3$) δ: 3.47 (s, 3H, NCH_3), 4.50 (s br, 1H, NH), 5.96 (s, 1H, CH), 7.20–7.50 (m, 10H, ArH); ^{13}C NMR δ: 36.1, 79.7, 126.0, 126.1, 127.0, 127.4, 127.7, 128.3, 129.1, 130.0, 130.4, 135.3, 138.7, 180.5.

Compound **7b**: ^{1}H NMR (250 MHz) ($CDCl_3$) δ: 2.30 (s, 3H, CH_3), 3.44 (s, 3H, NCH_3), 4.55 (s br, 1H, NH), 5.89 (s, 1H, CH), 7.12 (d, $J=7.8$ Hz, 2H, *p*-MeC_6H_4), 7.15–7.29 (m, 7H, ArH).

Compound **7e**: ^{1}H NMR (250 MHz) ($CDCl_3$) δ: 3.26 (s, 3H, NCH_3), 4.43 (s br, 1H, NH), 5.74 (s, 1H, CH), 6.97–7.22 (m, 7H, ArH), 7.29 (d, $J=8.8$ Hz, 2H, *p*-BrC_6H_4).

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