A Study of the Behaviour of 2,4-Substituted Thiosemicarbazides toward Orthoesters: Formation of Mesoionic Compounds

Francesco Buccheri, Giuseppe Cusmano, Michelangelo Gruttadauria, Renato Noto and Giuseppe Werber *

Dipartimento di Chimica Organica "E. Paternò", Università di Palermo, Via Archirafi 26, 90123 Palermo, Italy

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The reactions beetwen 2,4-disubstituted thiosemicarbazides and orthoesters in refluxing xylene led to the formation of the 1,2,4-triazoline-5-thione ring and to the 1,2,4-triazolium-5-thiolate ring. The formation of the mesoionic componds is due to rearrangement of the easily available 2,4-disubstituted thiosemicarbazides to 1,4-disubstituted thiosemicarbazides under the reaction conditions adopted. This method can be usefully used for the synthesis of mesoionic compounds, especially in the case of the 2-methyl-4-phenylthiosemicarbazide.

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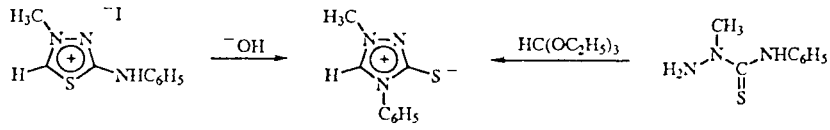
Mesoionic compounds are very important for industrial purposes, especially in the photographic field [1]; triazolium thiolates decrease fog formation in a color diffusion transfer process for instant photography without decreasing the sensitivity or the development speed [2], they accelerate hydroquinone development of chlorobromide and bromoiodide emulsions [3]. In a previous paper [4] we reported that the 2-methyl-4-phenyl-1,2,4-triazolium-5-thiolate (**1a**), obtained by treatment with alkaline hydroxide solution of the iodide **2**, could be also obtained starting from 2-methyl-4-phenyl-thiosemicarbazide (**3**) and triethyl orthoformate [5]. However we did not give any mechanistic interpretation of the latter reaction.

Scheme 1



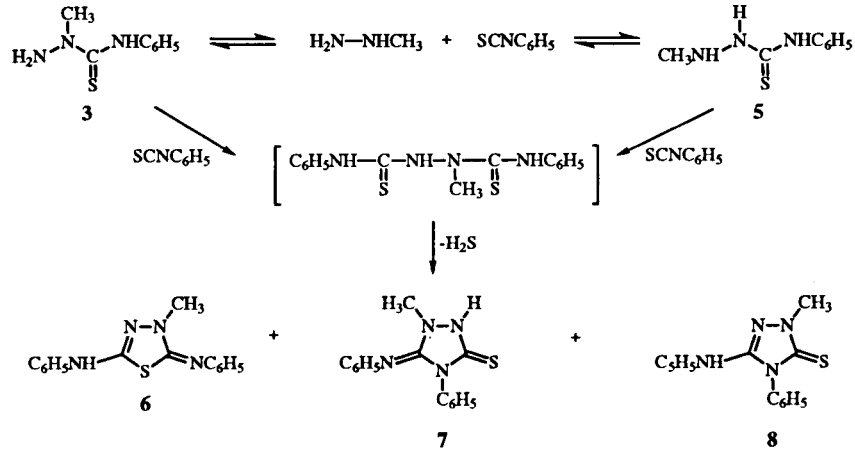
2 **1a** **3**

The major aspect of this work is now to establish the course of the reactions between 2-methyl-4-phenylthiosemicarbazide (**3**) or 2,4-dimethylthiosemicarbazide (**4**) with orthoesters and to develop a reliable method for the synthesis of 1,2,4-triazolium-5-thiolates; we focus our attention on the possibility of the rearrangement of 2,4-disubstituted-thiosemicarbazides to 1,4-disubstituted-thiosemicarbazides under the reaction conditions adopted. As a matter of fact the occurrence of compound **1a** in the reaction between 2-methyl-4-phenylthiosemicarbazide (**3**) and triethyl orthoformate could be explained only if the 1-methyl-4-phenylthiosemicarbazide (**5**) is present in the reaction mixture. It was reported already [8] that alkylhydrazines react with isothiocyanates to give mixtures of 2,4- and 1,4-substituted-thiosemicarbazides. In order to verify such an assertion we purified a sample of 2-methyl-4-phenylthiosemicarbazide, obtained from phenyl isothiocyanate and methylhydrazine, by column chromatography and we confirmed that only the 2-methyl-4-phenyl-thiosemicarbazide was present. Although, when the radical in the 2-position is primary, the thiosemicarbazides do not as a rule rearrange, even on melting [9], it was possible to rearrange the 2-methyl-4-phenylthiosemicarbazide to 1-methyl-4-phenylthiosemicarbazide by heating the thiosemicarbazide in xylene at *ca* 123°.

We believe that under these conditions the thiosemicarbazide is in equilibrium with its components that, at high temperature, react in a different fashion to give the 1-methyl-4-phenylthiosemicarbazide (**5**). Besides the thiosemicarbazides we obtained the 1,3,4-thiadiazole **6** from the reaction mixture.

It was reported [10] that compound **6** could be formed by condensation of two molecules of 2-methyl-4-phenylthiosemicarbazide with elimination of methylhydrazine and hydrogen sulfide or by reaction between phenyl isothiocyanate and 2-methyl-4-phenylthiosemicarbazide followed by cyclisation with elimination of hydrogen sulfide [11]. We believe that, due to the aforesaid equilibrium, the isothiocyanate reacts with the unchanged thiosemicarbazide or the rearranged substance followed by cyclisation with elimination of hydrogen sulfide to provide **6** and, in principle, compounds **7** and **8**. Other authors [12] claimed that compound **6** is formed as a consequence of the reaction between 2-methyl-4-phenylthiosemicarbazide and phenyl isothiocyanate formed in the degradation of the corresponding thiosemicarbazones of

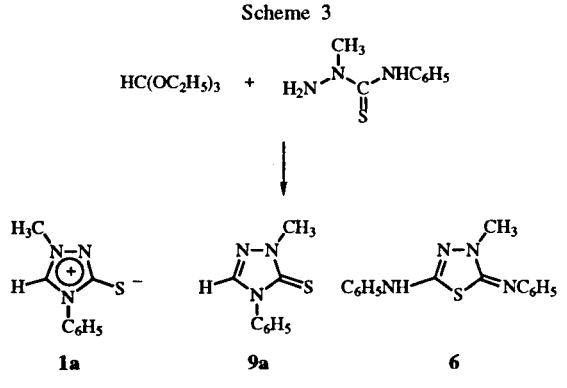
Scheme 2



γ-chloropropiophenone or γ-chlorobutyrophenone in refluxing ethanol. Our results show that compound **6** is simply owned from 2-methyl-4-phenylthiosemicarbazide (**3**) by heating.

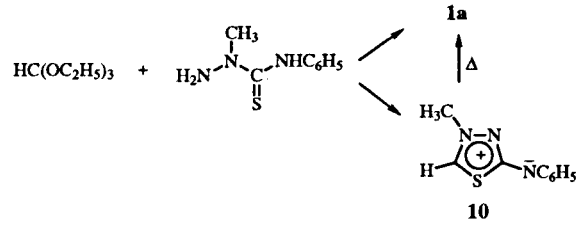
The reactions between the thiosemicarbazide or 4-substituted-thiosemicarbazides with aliphatic orthoesters already have been reported [13] and the composition of the products depends on the experimental conditions adopted and the orthoesters employed. 2-Methyl-4-phenylthiosemicarbazide had already been treated with triethyl orthoformate [5] and triethyl orthoacetate [14], but the results are incomplete, not reproducible, or are incorrect. Since the rearrangement of 2-methyl-4-phenylthiosemicarbazide was established, it was decided to perform the reaction between 2-methyl-4-phenylthiosemicarbazide with triethyl orthoformate in boiling xylene which yielded 2-methyl-4-phenyl-1,2,4-triazolium-5-thiolate (**1a**), 1-methyl-4-phenyl-1,2,4-triazoline-5-thione (**9a**) and the 1,3,4-thiadiazole **6**.

Scheme 3



This reaction was interpreted in terms of the partial rearrangement of the starting thiosemicarbazide. In fact, while compound **9a** comes from the unchanged thiosemicarbazide, the mesoionic compound **1a** comes from the rearranged thiosemicarbazide. The rearrangement to 1-methyl-4-phenylthiosemicarbazide explains why mesoionic compound **1a** is the product of the synthetic route that could, in principle, yield either the mesoionic compound **1a** or its isomer **10**. However the isomerization of **10** to **1a** under reflux has been studied [15]. Finally the 1,3,4-thiadiazole **6** comes from the aforesaid equilibrium (Scheme 2).

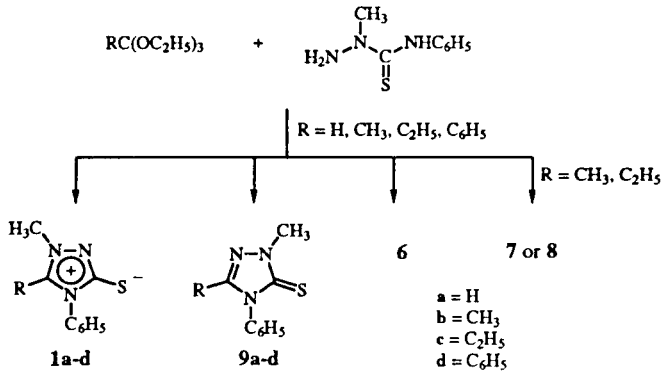
Scheme 4



Having shown the nature of the products isolated from the reaction between the 2-methyl-4-phenylthiosemicarbazide (**3**) and triethyl orthoformate under the condition adopted, in order to confirm the course of the reaction we performed this reaction using different orthoesters. In all cases we isolated the mesoionic compounds **1b-d**, 1,2,4-triazoline-5-thiones **9b-d** and the 1,3,4-thiadiazole **6**. When the 2-methyl-4-phenylthiosemicarbazide was treated with triethyl orthoacetate or triethyl orthopropionate, from the reaction mixture it was possible to isolate another product to which we assigned the structure of the 1,2,4-triazoline-5-thiones **7** or **8**. The yields of compounds **1a-d** can be improved by carrying out the reaction in the absence of a solvent (yields up to 60%).

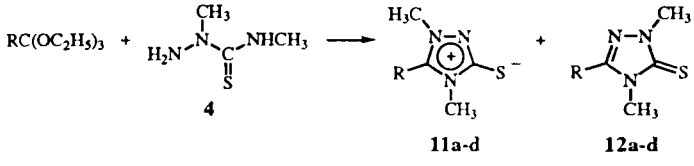
In addition to 2-methyl-4-phenylthiosemicarbazide we also used 2,4-dimethylthiosemicarbazide (**4**) in the reaction with orthoesters. By adopting the same conditions we found as products the corresponding mesoionic compounds **11a-d** and 1,2,4-triazoline-5-thiones **12a-d**. The occurrence of the mesoionic products confirmed the rearrangement of the 2,4-dimethylthiosemicarbazide, how-

Scheme 5



ever the yields of compounds **11a-d** were lower than the yields of compounds **1a-d**, indicating a minor tendency in the rearrangement of the 2,4-dimethylthiosemicarbazide compared to the 2-methyl-4-phenylthiosemicarbazide.

Scheme 6



In conclusion, it has been shown that the reaction between 2,4-disubstituted-thiosemicarbazides and orthoesters, due to rearrangement of the thiosemicarbazides, which are easily available compounds, can be used for the synthesis of mesoionic compounds, especially in the case of the 2-methyl-4-phenylthiosemicarbazide. The data collected allow us to explain the course of the above reaction.

EXPERIMENTAL

Melting point were determined with a Kofler hot stage and are uncorrected. The ^1H nmr spectra were recorded using a Bruker AC-E series 250 MHz. The ^1H and ^{13}C chemical shifts (δ) are given in ppm relative to tetramethylsilane as the internal standard. Column chromatography was performed on silica gel (Merck, 0.063-0.2 mm, deactivated with 15% water).

2-Methyl-4-phenylthiosemicarbazide was prepared as described in the literature [16]. A sample of 2-methyl-4-phenylthiosemicarbazide was then purified by chromatography (eluent chloroform/ethyl acetate/benzene 2/1/1), mp 150-151° (lit 143° [16], 146-147° [9]).

Rearrangement of 2-Methyl-4-phenylthiosemicarbazide (**3**).

A suspension of 2-methyl-4-phenylthiosemicarbazide (10.9 g, 0.06 mole) in xylene was slowly heated until dissolution (30 minutes) in an oil bath at *ca* 123°. The solution was maintained at this temperature for further 30 minutes. After 24 hours, 0.68 g (6.2%) of the starting material was recovered by filtration then 1-methyl-4-phenylthiosemicarbazide (**5**) precipited. After an additional 24 hours 1-methyl-4-phenylthiosemicarbazide was collected and washed with xylene (6.95 g, 0.038 moles, 64%). Compound **5** was purified by column chromatography (eluent ethyl acetate/ligroin 1/1.5) to remove the 4-methyl-5-phenylimino-2-phenylamino-Δ^2-1,3,4-thiodiazoline (**6**). Compound **5** had mp 102-103° (lit 99-100° [9]); ^1H nmr (DMSO-d_6): δ 2.60 (3H, d, NHCH_3, J = 4.5 Hz), 4.12 (1H, q, N*H*CH_3, J = 4.5 Hz), 7.05-7.90 (5H, m, ArH), 8.52 and 9.38 (each 1H, br s, NH). Compound **6** had mp 177-178° (lit 175° [11], 175.5-176° [12]). ^1H nmr (deuteriochloroform): δ 3.62 (3H, s, NCH_3), 6.47 (1H, s, NH), 7.01-7.08 (4H, m, ArH), 7.20-7.36 (6H, m, ArH).

Typical Procedure for the Reaction between 2-Methyl-4-phenylthiosemicarbazide (**3**) and Orthoesters.

A mixture of 2-methyl-4-phenylthiosemicarbazide (1.81 g, 0.01 mole) and the corresponding orthoester (0.011 mole) in xylene (12 ml) was heated to reflux for 30 minutes. The alcohol which was formed was removed continuously. The residue was cooled and the precipitate (mesoionic) which separated was collected by filtration, washed with xylene and crystallized. The mother liquors were evaporated under reduced pressure and the residue chromatographed with cycloexane/ethyl acetate 2/1.

Reaction of Compound **3** with Triethyl Orthoformate.

2-Methyl-4-phenyl-1,2,4-triazolium-5-thiolate (**1a**) was obtained in a yield of 750 mg (39%), mp 262-263° (lit 262-263° [4]) and by chromatography of the residue of the mother liquors were obtained 520 mg (27%) of 1-methyl-4-phenyl-1,2,4-triazoline-5-thione (**9a**), mp 113-114° (lit 111-112° [4]) and 250 mg (17%) of 4-methyl-5-phenylimino-2-phenylamino-Δ^2-1,3,4-thiodiazoline (**6**).

When the thiosemicarbazide **3** was heated under reflux for 1 hour with triethyl orthoformate (6 ml) without solvent, the yield of compound **1a** was higher (60%).

Reaction of Compound **3** with Triethyl Orthoacetate.

2,3-Dimethyl-4-phenyl-1,2,4-triazolium-5-thiolate (**1b**) was obtained in a yield of 750 mg (36%). The product was crystallized from methanol, mp 251-252° (lit 244-246° [17]); ^1H nmr (deuteriochloroform): δ 2.42 (3H, s, CCH_3), 3.82 (3H, s, NCH_3), 7.43-7.56 (5H, m, ArH). After cooling overnight a solid was recovered by filtration, washed with ethyl acetate, methanol then crystallized from ethanol. It was identified as compound **7** or **8**, 200 mg (14%), mp 164-165°; ^1H nmr (deuteriochloroform): δ 3.83 (3H, s, NCH_3), 5.80 (1H, s, NH), 7.01-7.07 (1H, m, ArH), 7.27-7.44 (6H, m, ArH), 7.58-7.65 (3H, m, ArH); ^{13}C nmr (deuteriochloroform): δ 36.3, 117.7, 123.0, 128.4, 129.2, 130.4, 130.6, 132.2, 137.7, 146.2, 164.3.

Anal. Calcd. for $C_{15}H_{14}N_4S$: C, 63.81; H, 5.00; N, 19.84; S, 11.35. Found: C, 63.70; H, 5.04; N, 19.89; S, 11.40.

By chromatography of the residue from the mother liquors, there was obtained 150 mg (7%) of 1,3-dimethyl-4-phenyl-1,2,4-triazoline-5-thione (**9b**), mp 74-75° (lit 74-75° [18]), and a small amount of 4-methyl-5-phenylimino-2-phenylamino-Δ^2-1,3,4-thiodiazoline (**6**).

Reaction of Compound **3** with Triethyl Orthopropionate.

2-Methyl-3-ethyl-4-phenyl-1,2,4-triazolium-5-thiolate (**1c**) was obtained in a yield of 850 mg (39%). The product was crystallized from methanol, mp 254-255°; ^1H nmr (deuteriochloroform): δ

1.05 (3H, t, CH_2CH_3, J = 7.6 Hz), 2.76 (2H, q, CH_2CH_3, J = 7.6 Hz), 3.84 (3H, s, NCH_3), 7.20-7.60 (5H, m, ArH).

Anal. Calcd. for $C_{11}H_{13}N_3S$: C, 60.25; H, 5.97; N, 19.16; S, 14.62. Found: C, 60.34; H, 6.03; N, 19.00; S, 14.53.

By chromatography of the residue from the mother liquors, compounds **7** or **8** (300 mg, 21%) were obtained. A small amount of 4-methyl-5-phenylimino-2-phenylamino-Δ^2-1,3,4-thiodiazoline (**6**) and 280 mg (13%) of 1-methyl-3-ethyl-4-phenyl-1,2,4-triazoline-5-thione (**9c**) was also obtained as an oil; ^1H nmr (deuteriochloroform): δ 1.13 (3H, t, CH_2CH_3, J = 7.5 Hz), 2.46 (2H, q, CH_2CH_3, J = 7.5 Hz), 3.80 (3H, s, NCH_3), 7.00-7.62 (5H, m, ArH).

Anal. Calcd. for $C_{11}H_{13}N_3S$: C, 60.25; H, 5.97; N, 19.16; S, 14.62. Found: C, 60.32; H, 6.04; N, 18.96; S, 14.53.

Reaction of Compound **3** with Triethyl Orthobenzoate.

To a suspension of 2-methyl-4-phenylthiosemicarbazide (3.6 g, 0.02 mole) in xylene (16 ml) was added triethyl orthobenzoate (5 ml). The mixture was heated for 30 minutes in an oil bath (130°). After cooling overnight, 2-methyl-3,4-diphenyl-1,2,4-triazolium-5-thiolate (**1d**) was collected, washed with xylene and ethyl acetate then crystallized from methanol, 2.58 g (48%), mp 294-295° (lit 286-287° [19]); ^1H nmr (deuteriochloroform): δ 3.82 (3H, s, NCH_3), 7.32-7.50 (10H, m, ArH).

The mother liquors were evaporated under reduced pressure, allowed to stand for a few days then washed with a small amount of methanol to give 350 mg (7%) of the 1-methyl-3,4-diphenyl-1,2,4-triazoline-5-thione (**9d**) that was crystallized from ethanol, mp 185-186° (lit 185-186° [18]).

Typical Procedure for the Reaction between the 2,4-Dimethylthiosemicarbazide (**4**) and Orthoesters.

The 2,4-dimethylthiosemicarbazide (2.4 g, 0.02 mole) in xylene (12 ml) was heated in a round bottom flask equipped with a condenser under reflux for 1 hour, then the corresponding orthoester (0.022 moles) was added and the mixture refluxed for 1 hour. The reaction mixture was allowed to stand at room temperature for 24 hours. The precipitate (mesoionic) was collected by filtration, washed with xylene and ethyl acetate and crystallized. The mother liquors were evaporated under reduced pressure and the residue chromatographed.

Reaction of Compound **4** with Triethyl Orthoformate.

2,4-Dimethyl-1,2,4-triazolium-5-thiolate (**11a**) was obtained in a yield of 480 mg (19%). The product was crystallized from methanol, mp 231-232° (lit 235° [8]); ^1H nmr (DMSO-d_6): δ 3.52 and 3.75 (each 3H, s, NCH_3), 9.30 (1H, s, CH). By chromatography (eluent cycloexane/ethyl acetate 2/1 and cycloexane/ethyl acetate/methanol 2/1/0.2) of the residue from the mother liquors 1,4-dimethyl-1,2,4-triazoline-5-thione (**12a**) was obtained 1.05 g (41%), mp 94-95° (lit 93° [20]); ^1H nmr (deuteriochloroform): δ 3.58 and 3.78 (each 3H, s, NCH_3), 7.76 (1H, s, CH).

Reaction of Compound **4** with Triethyl Orthoacetate.

2,3,4-Trimethyl-1,2,4-triazolium-5-thiolate (**11b**) was obtained in a yield of 450 mg (16%), the product was crystallized from methanol, mp 259-261° (lit 256-257° [21]); ^1H nmr (DMSO-d_6): δ 2.50 (3H, s, CCH_3), 3.42 and 3.66 (each 3H, s, NCH_3). By chromatography (eluent cycloexane/ethyl acetate 2/1 and 1/1) of the residue from the mother liquors, 1,3,4-trimethyl-1,2,4-triazoline-5-thione (**12b**) was obtained, 1.25 g (44%), mp 107° (lit 106-107° [18]).

Reaction of Compound **4** with Triethyl Orthopropionate.

2,4-Dimethyl-3-ethyl-1,2,4-triazolium-5-thiolate (**11c**) was obtained in a yield of 400 mg (13%), the product was crystallized from ethyl acetate then from methanol, mp 166-168°; ^1H nmr (deuteriochloroform): δ 1.28 (3H, t, CH_2CH_3, J = 7.0 Hz), 2.95 (2H, q, CH_2CH_3, J = 7.0 Hz), 3.55 and 3.75 (each 3H, s, NCH_3).

Anal. Calcd. for $C_6H_{11}N_3S$: C, 45.83; H, 7.05; N, 26.72; S, 20.39. Found: C, 45.79; H, 7.10; N, 26.82; S, 20.31.

By chromatography (eluent cycloexane/ethyl acetate 2/1 and 1/1) of the residue from the mother liquors, 1,4-dimethyl-3-ethyl-1,2,4-triazoline-5-thione (**12c**) was obtained, 1.40 g (45%), mp 94-95° (lit 93° [20]); ^1H nmr (deuteriochloroform): δ 1.30 (3H, t, CH_2CH_3, J = 7.0 Hz), 2.62 (2H, q, CH_2CH_3, J = 7.0 Hz), 3.45 and 3.70 (each 3H, s, NCH_3).

Reaction of Compound **4** with Triethyl Orthobenzoate.

2,4-Dimethyl-3-phenyl-1,2,4-triazolium-5-thiolate (**11d**) was obtained in a yield of 850 mg (21%). The product was crystallized from methanol, mp 277-279° (lit 270-272° [21], 280° [19]); ^1H nmr (deuteriochloroform): δ 3.55 and 3.74 (each 3H, s, NCH_3), 7.49-7.68 (5H, m, ArH). By chromatography (eluent cycloexane/ethylacetate 2/1) of the residue from the mother liquors 1,4-dimethyl-3-ethyl-1,2,4-triazoline-5-thione (**12d**) was obtained 1.45 g (35%), mp 94-95° (lit 93° [18]).

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