Organic Reactions in Aqueous Solution Part-VIII: Effect of Sonication on the Reaction of Thiosemicarbazide with Ethyl Acetoacetate

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Summary: The reaction of thiosemicarbazide with ethyl acetoacetate leading to the formation of thiosemicarbazone of ethyl acetoacetate (I) and 3-methylpyrazol-5-one-1-thiocarbamide (II) has been studied in the aqueous medium at room temperature. The effect of sonication on this reaction has also been investigated. Parameters for the formation of I and II have been determined. A reaction scheme for the formation of I and its subsequent cyclisation to form II has been proposed. The rate of formation of II is greatly enhanced under the influence of sonication.

Introduction

Hydrazine and hydrazine derivatives react with 1,3-dicarbonyl compounds to yield pyrazole and pyrazolone derivatives. It has been reported in the literature that these derivatives find utility in medicine as analgesics, antipyretics, germicides, fungicides and also as antimicrobial and antiinflammatory agents. They are used as dyes and colouring agents in textile and food industry. They are useful as photographic colour developers and sensitizers. They have also been used as corrosion inhibitors [1-5]. The literature methods for their preparation are lengthy and cumbersome [6-16].

In an earlier communication, the reactions of semicarbazide and hydrazine with ethyl acetoacetate and some other ß-keto compounds, leading to the development of simple methods for the synthesis of pyrazole and pyrazolone derivatives have been reported [17]. The present work describes the reaction of ethyl acetoacetate with thiosemicarbazide in the aqueous medium at room temperature. The effect of sonication on this reaction has also been studied. Parameters for the formation of ethyl acctoacetate thiosemicarbazsone (I) and 3-methylisoxazol-5-one-1-thiocarbamide (II) have been determined.

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Results and Discussion

Reaction of ethyl acetoacetate with thiosemicarbazide at room temperature (22 ± 2 °C) and in ultrasonic bath (64 ± 2 °C) in aqueous solution in equimolar quantities and at a wide range of pH (1.5 ~ 10), developed naturally or by the addition of a small quantity of acid or alkali, afforded thiosemicarbazone of ethyl acetoacetate (I) and 3-methylpyrazol-5-one-1-thiocarbamide (II). The results are summarised in Tables 1 and 2.

Table 1:Ethyl acetoacetate thiosemicarbazone (I) from ethyl acetoacetate (1.30 g; 9.01 mole) and thiosemicarbazide (0.91 g; 0.01 mole) in aqueous solution (50 mL) at room temperature (22 ± 2°C). m.p. 98-100°C

Method	pH	Duration	Yield g(%)
a)	5.3*	70-80 mins.	1.16 (57)
b)	10.0**	3-4 days	0.85 (42)
c)	1.15***	20-30 mins.	1.17 (58)

Table 2: 3-Methyl pyrazol-5-one-1-thiocarbamide (II) from ethyl acetoacetate (1.30 g; 0.01 mole) and thiosemicarbazide (0.91 g; 0.01 mole) in aqueous solution (50 mL) at room temperature (22 ± 2°C) and in ultrasonic bath (64 ± 2°C) m.p. 179-180°C.

Method	pH		At Room Temperature (24 ± 2°C)		In Ultrasonic Bath (64 ± 2°C)	
	Initial	Final	Duration (Days)	Yield g(%)	Duration	Yield g(%)
a)	5.3	3.6*	55-60	1.12(55)	15 hrs.	1.24(61)
b)	10	6.0**	15	1.16(57)	7 hrs.	1.25(62)
c)	1.5	3.2***	80-90	1.10(54)	27 hrs.	1.16(57)

* Natural
** By the addition of sodium hydroxide
*** By the addition of hydrochloric acid

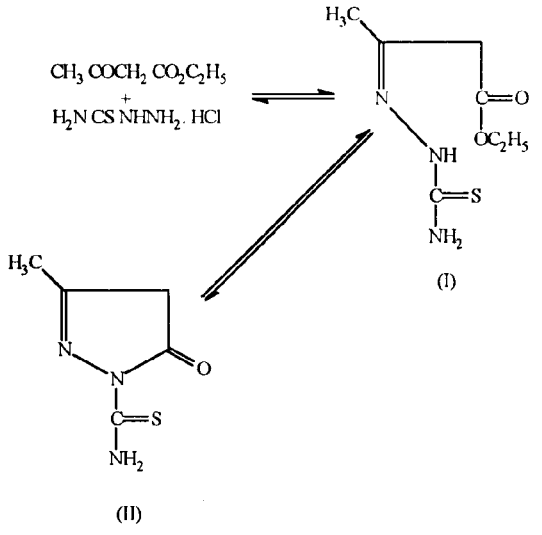
The maximum yield (58 %) of I was obtained when the reaction was carried out under highly acidic conditions (pH 1.5) in presence of a few drops of hydrochloric acid for 20-30 minutes at 22 ± 2 °C, whereas, the yield was minimum (42 %) under the basic conditions (pH 10) in presence of sodium hydroxide, even after 3-4 days. Under similar conditions the yield of I (57 %) at naturally developed pH (5.3) was close to that obtained at pH 1.5 but the reaction time was comparatively longer (70-80 minutes) as against 20-30 minutes [Table 1].

If I was not separated from the reaction mixture, it cyclised *in situ* to form 3-methylpyrazol-5-one-1-thiocarbamide (II) after 15-90 days, depending upon the pH conditions [Table 2]. Although the yields under acidic or basic conditions were approximately the same, the ease of cyclisation was greater in alkaline medium. It took 15 days at pH 10, 55-60 days at pH 3.5, and 80-90 days at pH 1.5 to yield 57, 55, and 54 % of II respectively.,

The reaction when carried out in ultrasonic bath afforded II with improved yields and after much shorter reaction time. However, it followed the same tendency regarding the pH conditions. The yields obtained were 62 % at pH 10 after 7 hours, 61 % at pH 5.3 after 15 hours, and 57 % at pH 1.5 after 27 hours. [Table 2].

Reaction scheme

It appears that in the reaction of ethylacetoacetate with thiosemicarbazide one molecule of the ester condenses with one molecule of thiosemicarbazide with the elemination of a molecule of water to form thiosemicarbazone, which because of its low solubility in water at room temperature, precipitates out. The thiosemicarbazone (I) is in the *Z*- form (anti w.r.t. methyl) and if not separated from the reaction mixture, cyclises to form 3-methylpyrazol-5-one-1-thiocarbamide (II), giving off a molecule of ethanol. However, the formation and yields of both I and II depend upon the pH of the reaction mixture. It can be concluded that the first step of the reaction leading to the formation of I is best catalysed by acids whereas, its subsequent cyclisation to form II is facilitated in the alkaline medium. The reaction may be represented as shown in the Reaction Scheme:



Experimental

General:

Experiments were carried out in water at room temperature (22 ± 2 °C) and at elevated temperature (64 ± 2 °C) by sonication in an ultrasonic bath. The chemicals and solvents used were usually of anlytical grade. Distilled water was used in all the experiments and each experiment was repeated thrice to record the average yields of the products. The pH's were recorded by noting the natural pH of the reaction mixture or developed soon after the addition of acid or alkali. The products obtained in different reactions were isolated by filtration at mild suction by using a water-jet pump, washed several times with small portions of water, and dried in a vacuum desiccator for 2-3 days. The compounds were purified by repeated recrystallisation from ethanol and identified by carrying out combustion analysis, infrared and mass spectroscopy. Before analysis, each specimen was finely powdered and dried at room temperature in a vacuum desiccator for 5 days. Quickfit glass apparatus was used and the following instruments were employed.

Ultrasonic Bath	Jencons Ultrasonik 300.
Melting point apparatus	Kofler Microscope hot stage
pH meter	Hanna H 8417 digital
Infrared spectrometer	Hitachi 270-30
Mass spectrometer	Hitachi - Perkin Elmer

The methods of preparation at room temperature and in ultrasonic bath have been described according to the pH conditions, i.e., (a) at naturally developed pH, (b) in alkaline medium, and (c) in acidic medium. Results are recorded in Tables 1 & 2.

Ethyl acetoacetate thiosemicarbazone (I)

At room temperature

a) Ethyl acetoacetate (1.30 g; 0.01 mole) was added dropwise with stirring to a solution of thiosemicarbazide (0.91 g; 0.01 mole) in 50 mL of water. The reaction mixture (pH 5.3) was allowed to stand at room temperature (22 ± 2 °C). A white compound precipitated after about 45 minutes. The reaction mixture was allowed to stand for another 30 minutes to complete the reaction. Ethyl acetoacetate thiosemicarbazone (I) thus obtained (1.16 g; 57 %) was filtered at the pump. Recrystalisation from ethanol afforded white crystals melting at 96-100 °C, alone or mixed with an authentic specimen, literature [18] m.p. 97°C (Found: C, 41.01; H, 6.20; N, 20.41; S, 15.25 %; $C_7H_{13}N_3O_2S$ requires: C, 41.36; H, 6.44; N, 20.67; S, 15.77 %). Its molecular mass was determined by molecular ion absorption which corresponded to *m/z* 203 and agreed with its molecular formula. Its i.r. spectra was superimposable on that of authentic sample

b) Ethyl acetoacetate (1.30 g; 0.01 mole) and thiosemicarbazide (0.91 g; 0.01 mole) were dissolved in water (50 mL) and a few drops of sodium hydroxide were added to adjust pH at 10. It was stored at room temperature (22 ± 2°C) for 5 days to obtain I (0.85 g; 42 %). Recrystallisation from ethanol gave white crystals melting at 98-100°C.

c) Ethylacetoacetate (1.30 g; 0.10 mole) and thiosemicarbazide (0.91 g; 0.01 mole) in water (50 mL) in presence of a few drops of hydrochloric acid at pH 1.5 under the conditions as in (a) and (b) above afforded 1.17 g (58 %) of I after only 20-30 minutes. Purification by recrystallisation from ethanol afforded white crystals m.p. 98-100°C.

3-Methylpyrazol-5-one-1-thiocarbamide (II)

At room temperature

a) To a solution of thiosemicarbazide (0.91 g; 0.01 mole) in water (50 mL) was added ethyl acetoacetate (1.30 g; 0.01 mole) dropwise with stirring. The reaction mixture (pH 5.30) was allowed to stand at room temperature (22 ± 2 °C). A white precipitate formed after 45 minutes. It was allowed to remain in the reaction mixture and stand further at the same temperature for 60 days with occasional shaking. During this period the white precipitate transformed into a pink product. It was separated to yield 3-methylpyrazol-5-one-1-thiocarbamide (II) (1.12 g; 55 %). Recrystallisation afforded light pink crystals melting at 179-180° C, literature [19] m.p. 180 °C. Its mixture melting point with authentic sample remained undepressed (Found: C, 37.88; H, 4.70; N, 26.31; S, 19.95 %; $C_5H_7N_3OS$ requires: C,

38.19; H, 4.48; N, 26.73; S, 20.39 %). Its molecular mass as determined by the molecular ion absorption corresponded to *m/z* 157. Its n.m.r. spectra gave expected absorption bands and was superimposable on that of authentic sample.

b) Thiosemicarbazide (0.91 g; 0.01 mole) was dissolved in 50 mL of water, and ethyl acetoacetate (1.30 g; 0.01 mole) was gradually added to this with stirring. The reaction mixture was made alkaline (pH 10) and stored at room temperature. (22 ± 2 °C) with occasional shaking. After 15 days pink crystals of II (1.16g; 57 %) were separated. Recrystallisation from ethanol afforded light pink crystals melting at 179-180°C.

c) To thiosemicarbazide (0.91 g; 0.01 mole) dissolved in water (50 mL) were added a few drops of hydrochloric acid (to adjust pH at 1.5). It was followed by the addition of ethyl acetoacetate (1.3 g; 0.01 mole) and allowed to stand at 22 ± 2 °C. After 90 days II (1.1 g; 54 %) was obtained and recrystallised from ethanol to yield light pink crystals m.p. 179-180°C.

In ultrasonic bath

a) To a solution of thiosemicarbazide (0.91 g; 0.01 mole) in water (50 mL) was added ethyl acetoacetate (1.30 g; 0.01 mole) and mixed thoroughly. The reaction mixture was placed in ultrasonic bath. Sonication was carried out for 15 hours at 64 ± 2°C. 3-Methylpyrazol-5-one-1-thiocarbamide (II) obtained was separated. The yield was 1.24 g (61 %). Recrystallisation from ethanol afforded light pink crystals melting at 179-180°C, alone or mixed with the authentic samples prepared at room temperature by method (a), (b) and (c). Their i.r. spectra were also superimposable.

b) Thiosemicarbazide (0.91 g; 0.01 mole) and ethyl acetoacetate (1.30 g; 0.01 mole) were taken in 50 mL of water and mixed well. The pH of the mixture was adjusted at 10 by the addition of aqueous sodium hydroxide. It was placed in the ultrasonic bath for sonication at 64 ± 2 °C for 7 hours to afford II in 62 % yield (1.20 g). Recrystallisation gave pink crystals melting at 179-180 °C.

c) A mixture of ethyl acetoacetate (1.30 g; 0.01 mole) and thiosemicarbazide (0.91 g; 0.01 mole) was prepared in 50 mL of water and was acidified by adding a few drops of hydrochloric acid (pH 7.5). The reaction after sonication for 27 hours at 64 ± 2 °C afforded pink crystals of II (1.16 g; 57 %), which melted at 179-180 °C after purifi-cation by recrystallisation from ethanol.

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