Organic Reactions in the Aqueous Medium Part-IX Effect of Sonication on the Reaction of Ethyl Acetoacetate with Hydrazine Derivatives

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Summary: The reactions of ethyl acetoacetate with semicarbazide hydrochloride and hydrazine monohydrate in the aqueous medium by stirring at room temperature and under sonication have been studied. The parameters for the formation of ethyl acetoacetate semicarbazone (I), 3-methylprazol-5-one-1-carboxamide (II), 3-methylpyrazol-5-one (III), and hydrazine-1,2-diamide have been determined. It has been observed that stirring at room temperature leads to the formation of (I) or (II), while sonication yields (III) as well, depending upon the reaction parameters. Moreover, improved yields of these products are obtained in a considerably shorter time under sonication. However, (IV) is obtained only by boiling the reactants under mild reflux. A plausible reaction scheme for the formation of different products has also been suggested.

Introduction

Hydrazine and its derivatives react with β-dicarbonyl compounds to yield substituted pyrazoles and pyrazolones. Many of such derivatives find utility in medicine, agriculture, and industry [1-8]. The reactions of ethyl acetoacetate with hydrazine and semicarbazide are known to yield ethyl acetoacetate semicarbazone (I), 3-methylpyrazol-5-one-1-carboxamide (II), 3-methylpyrazol-5-one (III), and hydrazine-1,2-diamide (IV) [9-15]. The recent literature methods for the preparation of these compounds are either lengthy and tedious, or use expensive reagents and solvents.

The reactions of ethyl acetoacetate and some other β-dicarbonyl compounds with hydrazine and its derivative were studied in the aqueous medium as well as in different organic solvents. This resulted in the development of simplified methods for the preparation of some pyrazole and pyrazolone derivatives [16]. The present work describes the results of an intensive investigation of the reactions of ethyl acetoacetate with semicarbazide hydrochloride and hydrazine monohydrate with a view to comparing the effect of sonication on such reactions.

Results and Discussion

The reaction of ethyl acetoacetate with semicarbazide hydrochloride carried out in the aqueous medium by stirring at room temperature afforded ethyl acetoacetate semicarbazone (I) and 3-methylpyrazol-5-one-1-carboxamide (II) depending upon the duration of the reaction.

The yield of (I) formed increased during the first one hour to 59% and then steadily decreased to 47% after 2 hours. The same reaction after 72 hours afforded 55% of (II) (Table-1). It appears that if (I) formed was not separated from the reaction mixture it gradually cyclized to form (II). When the reaction time exceeded 2 hours a crude mixture of (I) and (II) was obtained. Crystals of (I) and (II) could be hand-picked from this mixture to observe their melting characteristics. When ethyl acetoacetate and semicarbazide hydrochloride were allowed to react first at room temperature and then gently refluxed for 1.5 hours, a mixture of 3-methylpyrazol-5-one (III) (18%) and hydrazine-1,2-diamide (IV) (28%) was obtained. Prolonged refluxing (3 hours) resulted in the formation of (IV) alone (Table-1).

Ultrasound has a marked effect on this reaction. The reaction yielded not only (I) and (II) but also 3-methylisoxazol-5-one (III), depending upon the duration of sonication, whereas (III) was not obtained by simple stirring at room temperature. Moreover, it improved the yields of both (I) and (II) as compared with those obtained by stirring the reactants at room temperature (Table-1).

Table-1: Ethyl acetoacetate semicarbazone (I), 3-methylpyrazol-5-one-1-carboxamide (II), 3-methylpyrazol-5-one (III), and hydrazine-1,2-diamide (IV) from ethyl acetoacetate (0.025 mole) and semicarbazide hydrochloride (0.025 mole) in water (25 mL) by stirring at room temperature and in ultra sonic bath

Sr. No.	Reaction Time (hours)	pH	Reaction conditions: Stirring at room temeprature (21 ± 22°C) Product	Yield gms.(%)	Sonication (21-35°C) Product	Yield gms (%)
01.	0.25	1.15-1.55	(I)	1.70 (36.4)	(I)	2.23 (69.2)
02.	0.50	""	""	2.30 (49.2)	""	2.60 (55.7)
03.	1.00	""	""	2.77 (59.3)	""	2.40 (51.4)
04.	1.50	""	""	2.28 (48.8)	""	2.30 (49.2)
05.	2.00	""	""	2.22 (47.5)	""	2.26 (48.4)
06.	1.00	3.90-4.00*	""	2.95 (63.2)	-	-
07.	0.50	""	""	""	(I)	4.63 (99.1)
08.	1.50	1.15-1.55	(III)+(IV) (at reflux)	0.69 (17.9) + 0.53 (28.1)	-	-
09.	3.00	""	(IV) (at reflux)	0.85 (28.8)	(II)	2.15 (61.0)
10.	4.50	""	-	-	(III)	1.40(57.1)
11.	5.00	""	-	-	""	1.20(49.0)
12.	72.00	""	(II)	1.95 (55.3)	-	-
13.	72.00	3.50-4.00*	(I)	3.70(79.2)	-	-

*By the addition of NaOH (0.025 mole)

The effect of sonication was even more pronounced when the reaction was carried out in presence of an equimolar quantity of sodium hydroxide. Stirring at room temperature for 72 hours yielded (I) in 79% yield. By sonicating the reaction mixture it was possible to obtain this in almost theoretical yield (99%) after only 0.5 hours (Table-1).

A similar effect was observed in the preparation of (II) from ethyl acetoacetate and semicarbazide hydrochloride. A yield of 61% was obtained after 3 hours of sonication, whereas, the yield by stirring at room temperature for 72 hours was only 55% (Table-1).

In case of hydrazine monohydrate, ethyl acetoacetate reacts to form 3-methylpyrazol-5-one (III). When the reaction was carried out by stirring at room temperature the yield of the product increased with the increase in reaction time. The reverse was found to be true in case of this reaction under sonication (Table-2). The maximum yield (93%) of (III) was obtained by stirring the reactants in methanol-water mixture of 1 hours (Table-2). However, by sonication it was possible to increase the rate of reaction in the aqueous medium and obtain (III) in considerable yield (79%) in a short span of time (0.3 hours) (Table-2).

It is obvious from these results that the reaction of ethyl acetoacetate with semicarbazide hydrochloride yields four different products namely ethyl acetoacetate semicarbazone (I), 3-methylpyrazol-5-one-1-carboxamide (II), 3-methylpyrazol-5-one (III), and hydrazine-1,2-diamide (IV). The reaction carried out by stirring at room temperature yields (I) and (II), while the reaction under the influence of ultrasound affords (I), (II) and also (III). The reaction under more vigorous conditions, i.e., boiling under mild reflux proceeds further to form (V). Evidently, the reaction proceeds through four different stages as shown in the Reaction Scheme.

The formation of semicarbazone (I) suggests that ethyl acetoacetate yields Z-semicarbazone (anti w.r.t. methyl group) which later on cyclizes to form (II). This (II) under the influence of ultrasound readily yields (III). Under mild reflux, however, a mixture of (III) and (IV), or (IV) alone is obtained.

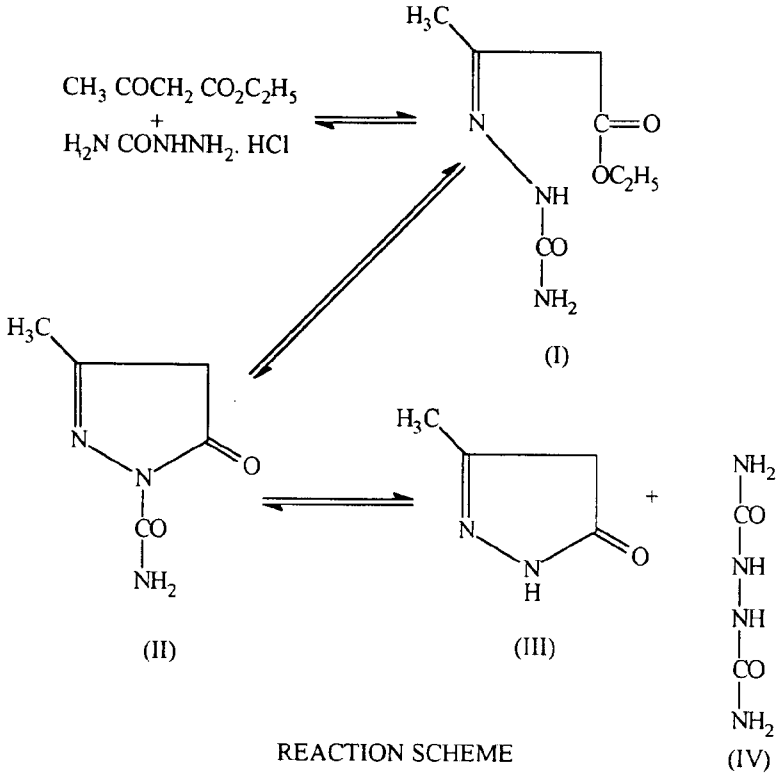
Experimental

General

Experiments recorded in Table 1 and 2 were performed in aqueous solutions by stirring at room temperature (21 ± 2°C) on a magnetic stirrer, by heating under mild reflux and also in an ultrasonic bath (21 - 35°C). Distilled water was used in all the reactions, and the chemicals used were of analytical grade. The pHs of the reaction mixtures were observed immediately after the mixing of the reactants and were taken once again at the end of the

Table-2: 3-Methylpyrazol-5-one (III) from ethyl acetoacetate (0.05 mole) and hydrazine monohydrate (0.05 mole) by stirring at room temperature and in ultrasonic bath.

S.No.	Reaction Medium	Reaction conditions			
		Stirring at room temperature (21 ± 2°C)		Sonication (21-25°C)	
		Reaction Time (hours)	Yield g. (%)	Reaction Time (Hours)	Yield g (%)
01.	Water (25 mL)	0.30	1.39 (28.4)	0.30	3.86 (78.8)
02.	"	1.00	3.33 (67.9)	1.00	2.81 (57.3)
03.	Methanol:Water 1:1 (10 mL)	0.30	3.28 (66.9)	0.30	3.30 (67.3)
04.	"	1.00	4.57 (93.3)	1.00	3.01 (61.4)



REACTION SCHEME

reaction. After the stated times, which were found after a number of trials, the products were separated by filtration at a suction pump, washed several times with small lots of cold distilled water, and dried for 1-2 days in a vacuum-desiccator. The compounds prepared were identified by taking mixture melting points with authentic specimens prepared by literature methods and confirmed by infrared and mass spectroscopy.

Before analysis each compound was purified by repeated recrystallisation and dried in a vacuum-desiccator for 2-3 days. The melting points are uncorrected. The instruments used consisted of Jencons Ultrasonic 300 ultrasonic bath, Griffin capillary tube melting point apparatus, Hanna H 8417 digital pH meter, Hitachi 270-30 infrared spectrometer and Hitachi-Perkin Elmer mass spectrometer.

Ethyl acetoacetate semicarbazone (I)

By stirring

Semicarbazide hydrochloride (2.79 g, 0.025 mole) was dissolved in 25 mL of water in a conical flat-bottomed flask and placed on a magnetic stirrer. To this was added ethyl acetoacetate (3.125 g, 0.025 mole) dropwise with stirring. The reaction mixture

was stirred for 1 hour at room temperature to obtain ethyl acetoacetate semicarbazone (I) in the form of white fluffy mass. The yield of the compound was 2.77 g (59%). Recrystallisation from ethanol gave white crystals melting at 128-129°C alone, or mixed with authentic samples prepared by literature methods [12,13]. Their infrared spectra were also superimposable.

Reaction carried out in presence of an equimolar quantity of sodium hydroxide (0.025 mole; 1.0 g) under similar conditions yielded 2.95 g (63%) of (I). A higher yield (3.70 g, 79%) was obtained after 72 hours.

By sonication

Ethyl acetoacetate (2.79 g; 0.025 mole) and semicarbazide hydrochloride (3.125 g; 0.025 mole) were dissolved in water (25 mL) in a flat-bottomed flask and placed in an ultrasonic bath. Sonication was carried out for 0.25 hours to obtain 3.23 g (69%) of ethyl acetoacetate semicarbazone (-Z) (I). Purification of this white fluffy compound by recrystallisation from ethanol afforded white crystals melting at 128-129°C. Its mixture melting point with the specimen prepared by stirring at room temperature remained undepressed.

This reaction in presence of an equimolar quantity of sodium hydroxide yielded 4.3 g (99%) of (I) after 0.5 hours.

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

By stirring

Ethyl acetoacetate (3.25 g; 0.025 mole) and semicarbazide hydrochloride (2.79 g; 0.025 mole) in 25 mL of water were stirred at room temperature for 72 hours to yield 3-methylpyrazol-5-one-1-carboxamide (II) (1.95 g; 55%). Recrystallisation from boiling water afforded white crystals melting with decomposition at 194-196°C, lit. [11]m.p. 192-195°C, alone or mixed with authentic specimen prepared by literature method. Their infrared spectra over-lapped each other.

By sonication

Ethyl acetoacetate (3.25 g; 0.025 mole) and semicarbazide hydrochloride (2.79 g; 0.025 mole) were dissolved in water (25 mL) in a flat-bottomed conical flask and subjected to sonication for 3 hours. The work-up resulted in the formation of 2.15 g (61%) of 3-methylpyrazol-5-one-1-carboxamide (II). The product upon recrystallisation from boiling water afforded white crystals m.p. 194-196°C. Its mixture melting point with the specimen prepared by stirring at room temperature showed no depression.

3-Methylpyrazol-5-one (III)

By stirring

Ethyl acetoacetate (3.25 g; 0.025 mole) and semicarbazide hydrochloride (2.79 g; 0.025 mole) dissolved in 25 mL water, were taken in a round-bottomed flask fitted with a reflux condenser. The contents of the flask were heated under mild reflux for 1.5 hours and then cooled to room temperature. A white compound settled at the bottom of the flask was filtered off. The filtrate was concentrated to about one third its volume by heating gently on a hot plate. The concentrate, on cooling in a refrigerator over-night yielded 0.69 g (29%) of 3-methylpyrazol-5-one (III). It was recrystallized from ethanol to afford white short needles m.p. 220-222°C, lit. [11,14] m.p. 222°C. Its mixture melting point with authentic sample remained undepressed. Their i.r. spectra were also identical.

A solution of hydrazine monohydrate (80%, 3.125 g, 0.05 mole) was prepared in 25 mL of water. Ethyl acetoacetate (6.50 g; 0.05 mole) were added to this solution and stirred magnetically at room temperature for 1 hour to yield 3-methylpyrazol-5-one (III). The yield of sufficiently pure (III) was 3.33 g (68%). Recrystallisation from ethanol gave white short needles m.p. 220-222°C, undepressed when mixed with authentic sample [11,14].

Reaction in 10 mL of methanol-water mixture (1:1) under similar conditions afforded higher yield (4.57, 93%) of (III).

By sonication

Semicarbazide hydrochloride (3.79 g; 0.025 mole) was dissolved in 25 mL of water in a flat-bottomed conical flask. The flask, after the addition of ethyl acetoacetate (3.25 g; 0.025 mole) was placed in an ultrasonic bath for sonication. After 4.5 hours

it was taken out and allowed to stand over-night in a refrigerator to yield 3-methylpyrazol-5-one (III) (1.50 g; 57%). Recrystallisation from ethanol gave white short needles, m.p. 220-222°C. Its i.r. spectra indicated expected absorptions and its mixture melting point with the specimen prepared by stirring at room temperature showed no depression.

Hydrazine monohydrate (80%, 3.125 g; 0.05 mole) was dissolved in 25 mL of water in a flat-bottomed conical flask. Ethyl acetoacetate (6.5 g, 0.05 mole) was added to this and the reaction mixture was sonicated for 0.3 hours to obtain 3-methylpyrazol-5-one (III) (3.86 g; 79%). Its mixture melting point (220-222°C) with samples prepared by the methods described earlier, remained undepressed.

Another experiment performed by using the same quantities of the reactants in 10 mL of methanol-water mixture (1:1) under similar conditions afforded 3.30 g (79%) of (III).

Hydrazine-1,2-diamide

By stirring

Semicarbazide hydrochloride (2.79 g; 0.025 mole) was dissolved in water (25 mL) in a round-bottomed flask. Ethyl acetoacetate (3.25 g; 0.025 mole) was added to this with good shaking. The flask was equipped with a reflux condenser, transferred to a heating mantle and refluxed gently for 3 hours. At the end of this period the reaction mixture was cooled in an ice bath to yield hydrazine-1,2-diamide (II). The yield of the product was 0.85% (29%). Recrystallisation was carried out from boiling water to obtain white shining crystals melting to a clear liquid at 248°C, lit [15] m.p. 248°C. Its melting point remained undepressed when mixed with an authentic sample and their i.r. spectra were identical.

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