Organic Reactions in Aqueous Medium Part-XI: Effect of Sonication on the Reaction of Benzoylacetone with Semicarbazide Hydrochloride in the Formation of 3-Phenyl-5-methylpyrazole and 3-Phenyl-5-methylpyrazole-1-carboxamide

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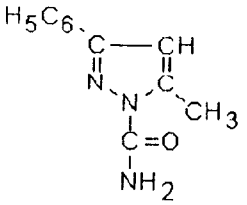
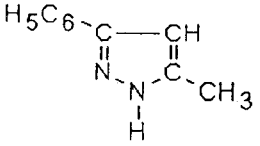
Summary: Reaction of benzoylacetone with semicarbazide hydrochloride has been studied. An intensive investigation has been carried out under varying conditions. Since benzoylacetone is not soluble in water, it does not react with semicarbazide hydrochloride in aqueous medium under ordinary conditions. The reaction has been induced to proceed under the effect of power ultrasound. As a result, methods for the synthesis of 3-phenyl-5-methylpyrazole-1-carboxamide (I) in ethanol-water mixture and 3-phenyl-5-methylpyrazle (1) in water in very high yields have been developed.

Introduction

Pyrazole derivatives belong to a very important class of heterocyclic compounds which are extensively used as pharmaceuticals, agrochemicals and chemical reagents etc. In addition, these also find utility in different industries as chemical reagents. These derivatives are hypo-glycemic metabolites, antimicrobials, bactericides, antiviral agents, potential antidotes for poisoning, and inhibitors of phosphodiesterase[1-6] These are agricultural herbicides, fungicides, insecticides and acaricides [7-12]. These derivatives are useful corrosion inhibitors, antifogging agents, and antimicrobial agents in textile and household products[13,14]. These are also useful intermediates for the synthesis of several pharmaceuticals, agrochemicals and dyes [15,16]. The methods for the preparation of these substituted pyrazoles as available in the text books and literature, covering a period of well over one hundred years, are lengthy, difficult and involve many steps.[5-11, 15-31]. In an effort to develop simple and single-step methods for the synthesis of pyrazole and pyrazolone derivatives, the reactions of hydrazine, semicarbazide hydrochloride and thiosemicrbazide with different dicarbonyl compounds were studied which led to the development of simple, economical and single-step methods for the preparation of pyrazole and pyrazolone derivatives [32,33]. The present work describes the reaction of semicarbazide hydrochloride with benzoylacetone under the effect of sonication leading to the development of convenient methods for the preparation of 3-phenyl-5-methylpyrazole-1-carboxmide (I) and 3-phenyl-5-methylpyrazole (II).



(I)



(II)

Results and Discussion:

The reaction of benzoylacetone with semicarbazide hydrochloride in water and its mixtures with ethanol affords 3-pheny-5-methylpyrazole-1-carboxamide (I) and 3-phenyl-5-methylpyrazole (1I) in high yields (60-99%) under the influence of sonication. The results are summarized in Tables 1 and 2

The results of the investigations show that equimolar quantities of benzoylacetone and semicarbazide hydrochloride in water at molar concentrations of 400 mmol/L (benzoylacetone) afforded 3-Phenyl-5-methylpyrazole (II) in fairly high yield (87.8%) after 9 hours of sonication. An almost theoretical yield (99.4%) was obtained by using benzoylacetone and semicarbazide

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Table 1: 3-Phenyl-5-methylpyrazole-1-carboxamide (I) and 3-phenyl-5-methylpyrazole (II) from benzoylacetone and semicarbazide hydrochloride in aqueous solutions (pH 2.55—1.50) at 25±2--40±2°C.

	Benzoylacetone mmol(mg)	Semicarbazide Hydrochloride mmol(mg)	Molar Ratio	Water mL	Duration Hours	Product	Yield mg(%)
1	5(811)	5(558)	1:1	12.5	4.5	II	570(72.2)
2	"	"	"	12.5	9.0	"	694(87.8)
3	"	"	"	25.0	4.5	I + II	235(23.3) + 660(83.5)
4	"	10(1116)	1:2	12.5	4.5	"	785(99.4)
5	"	"	"	12.5	9.0	"	725(91.8)
6	"	"	"	25.0	4.5	I + II	460(45.7) + 66(8.35)
7	"	15(1674)	1:3	12.5	4.5	I + II	755
8	"	"	"	12.5	2.5	I+II	828
9	"	20(2232)	1:4	"	2.5	I + II	881

Table 2: 3-Phenyl-5-methylpyrazole-1-carboxamide (I) from benzoylacetone and semicarbazide hydrochloride in aqueous alcohol (pH 0.90 1.45) in ultrasonic bath at 25±2--40±2°C

	Benzoylacetone mmol(mg)	Semicarbazide Hydrochloride mmol(mg)	Molar Ratio	Ethanol:Water Ratio (mL)	Duration Hours	Yield mg(%)
1	5(811)	5(558)	1:1	1.5:1.0(25)	1.0	455(45.3)
2	"	10(1116)	1:2	"	"	595(59.2)
3	"	10(1116)	"	1.0:1.0(20)	"	605(60.2)
4	"	15(1674)	1:3	1.5:1.0(25)	"	560(55.7) (crude)
5	"	20(2232)	1:4	"	"	350(34.8) (crude)

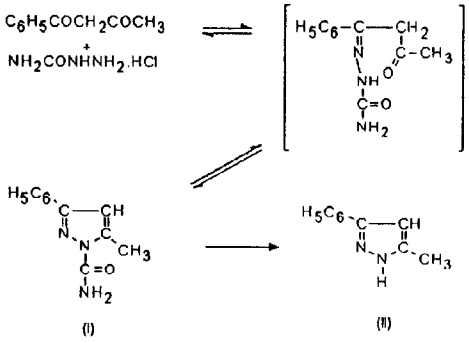
hydrochloride in the molar ratio 1:2 only after 4.5 hours [Table 1(4)]. Excess of semicarbazide hydrochloride (molar ratio1:3), however, favoured the formation of a mixture of I and II [Table 1(7,8)]. A large excess of semicarbazide hydrochloride in the molar ratio 1:4 only increased the yield of the products. Both I and II are soluble in most polar solvents like water, methanol, ethanol etc., but to a different extent. Therefore, to resolve the components, the mixture was first boiled in about 50 ml of water. The filtrate upon cooling yielded pure compound II. The remaining undissolved portion was I, and was purified by recrystallisation from methanol.

Reactions carried out by using lower concentrations of the reactants (200 mmol of benzoylacetone) in the molar ratio 1:1 yielded a small amount of I (0.235 g; 23.3%) after 4.5 hours. However, when the filtrate, after the removal of I, was stored at 10—12°C for 24 hours, an additional crop of a white crystalline precipitated. It turned out to be II, and the yield was quite high (0.006 g; 83.5%) [Table 1(3)]. Under similar conditions, when semicarbazide hydrochloride was used in excess(molar ratio 1:2), the yield of I increased to 0.460 g; 45.7% and that of II decreased to 0.006 g: 8.3% [Table 1(6)].

In order to evolve a method for the exclusive formation of I, reactions were carried out in methanol, ethanol and also in their mixtures with water under different parameters. Maximum yield (60.2%) of II was obtained when the reaction was carried out in ethanol-water mixture (1:1) after the reaction mixture was sonicated for I hour [Table 29(3)]. The reactants failed to yield any product in pure methanol or ethanol.

It appears that the reaction is proceeding in the acidic medium at a pH range of 2.57-0.9 through three different stages. Benzoylacetone reacts with semicarbazide hydrochloride to form initially Z-semicarbazone (anti w.r.t. phenyl group). This

intermediate is very labile, and being soluble remains in the solution and very likely cyclises as soon as it is formed to yield an insoluble product (I) which either precipitates out or undergoes acid hydrolysis and decarboxylation to form II which is also insoluble in the media. Therefore, depending upon the reaction conditions, either I (at the lower part of the pH range 0.90—1.45) or II or a mixture of both I and II(at pH 1.5-- 2.55) is obtained.



Experimental:

Experiments were conducted in Jencons Ultrasonik 300 ultrasonic bath at room temperature (25±2°C) which had a tendency to rise to 40±2°C towards the end the reaction. The reactants were taken in a Quickfit 100 mL conical flask fitted with a condenser to prevent possible escape of solvent. The same apparatus was used throughout the investigation to ensure similar effect of sonication. Analytical grade chemicals and solvents were used. Distilled water was used in all the experiments and each experiment was repeated thrice to record the average yields of the products obtained. pHs were recorded on Henna H8417 Digital pH Meter by noting the pH of the filtrate immediately after the product was filtered off at mild suction by using a water-jet pump. The products were purified by repeated recrystallisation from appropriate solvents and dried for 3-5 days before analysis. Melting points were taken on Griffin Melting Point Apparatus. Infrared spectra were run by using pressed-disc(KBr) on Hitachi 270-30 Infrared Spectrometer. Results are given in Tables 1 and 2.

3-Phenyl-5-methylpyrazole-1-carboxamide (I)

Benzoylacetone (0.558 g ; 5 mmol) and semicarbazide hydrochloride (1.116 g; 10 mmol), were dissolved in 20 mL of ethanol-water mixture (1:1) in a Quickfit 100 mL conical flask fitted with a condenser.The mixture was placed in the ultrasonic bath and sonicated for 1hour at room temperature (25±2°C). The temperature gradually rose to 40±2°C during this period.. At the end of the reaction the flask containing off-white crystalline compound was placed in a refrigerator and cooled to 10-12°C. 3-Pheny-5-methylpyrazole-1-carboxamide thus obtained (0.605 g;60.2%) was filtered at the pump, washed several times with small lots of cold water and dried in a vacuum desiccator for 3-5 days. Recrystallisation from methanol yielded white lustrous crystals melting at 156-157°C alone, or mixed with authentic samples prepared by literature methods [21,32]. Their i.r. spectra were also identical.

Semicarbazide hydrochloride (10 mmol; 1.116 g) was dissolved in 12.5 mL of water. To this was added 0.811 g (5 mmol) of benzoylacetone. The mixture was sonicated for 4.5 hours and then cooled to 10-12°C to afford 0.460 g; 45.7% of I. The filtrate was allowed to stand in a refrigerator at the same temperature for 24 hours to yield a small amount of 3-phenyl-5-methylpyrazole (II).

3-Phenyl-5-methylpyrazole (II)

Semicarbazide hydrochloride (1.116 g; 10 mmol) was dissolved in 12.5 mL of water in 100 mL conical flask. To this was added 0.558 g (5 mmol) of benzoylacetone and the mixture transferred to ultrasonic bath. It was sonicated for 4.5 hours till white crystalline compound was formed. The reaction mixture was cooled to 10-12°C and the compound was filtered and washed with small portions of ice-cold water. Recrystallisation from boiling water afforded 3-Phenyl-5-methylpyrazole (0.785 g; 99.4%) in the form of white fine fluffy crystals melting at 127-128°C, lit.[19-21,32] m.p.127-128°C. Its mixture melting point with authentic samples remained undepressed, and their i.r. spectra overlapped each other.

To a solution of semicarbazide hydrochloride (0.558 g; 5 mmol) in 25.0 mL of water was added benzoylacetone (0.811 g; 5 mmol). The mixture was subjected to sonication for 4.5 hours. The reaction mixture containing a small amount of precipitate (0.235 g) was cooled and filtered to obtain (I). The filtrate was allowed to stand at 10-12°C for 24 hours to yield 0.660 g; 83.5% of II. Recrystallisation from

boiling water afforded fluffy compound melting at 127-128°C alone or mixed with the sample obtained as above.

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