[CONTRIBUTION FROM THE W. A. NOYES LABORATORY OF CHEMISTRY
UNIVERSITY OF ILLINOIS]

HYDRAZINE DERIVATIVES OF THE CARBONIC AND THIOCARBONIC ACIDS.[1] III. PREPARATION OF THIOSEMICARBAZIDE

EARLE S. SCOTT,[2,3] E. E. ZELLER,[4] AND L. F. AUDRIETH

Received September 24, 1953

A new method of preparing thiosemicarbazide has been developed based upon the fact that hydrazine will displace ammonia from ammonium thiocyanate in a refluxing aqueous solution and that the hydrazinium thiocyanate so formed will rearrange under the same conditions to give the desired product. Relatively pure thiosemicarbazide is crystallized directly from the reaction mixture in approximately 55% yield.

The new procedure is believed to represent a distinct improvement over other methods involving (a) the thermal rearrangement of hydrazinium thiocyanate (1–4), that is, the hydrazination of thiocyanic acid or (b) the interaction of hydrazine with dithiocarbamic acid (5), a hydrazinolysis reaction. Furthermore, no bisthiocarbamylhydrazine is formed presumably because thiosemicarbazide is too weakly basic to displace ammonia from the excess ammonium thiocyanate employed in the reaction. The procedure would not be feasible were it not for the fact that the conversion of hydrazinium thiocyanate to thiosemicarbazide occurs at a lower temperature than the rearrangement of ammonium thiocyanate to thiourea.

In general, the reaction is carried out in the following manner. Sufficient ammonium thiocyanate is dissolved in 85% hydrazine hydrate to establish a mole ratio of ammonium thiocyanate to hydrazine of approximately 3:1. Water equivalent in volume to the hydrazine hydrate used may be added if desired. The resulting solution is refluxed under a nitrogen atmosphere for a period of 2 to 3 hours, allowed to cool slightly to permit the coagulation of the small amount of sulfur formed, and filtered. Thiosemicarbazide precipitates when the filtrate is cooled to room temperature. Ammonium thiocyanate is sufficiently soluble to remain in the mother liquor at this temperature, but may crystallize with the product if the reaction mixture is cooled in an ice-bath. Washing the product with cold water removes any ammonium thiocyanate from the product without decreasing significantly the yield of thiosemicarbazide. A single re-

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[1] For the previous articles in this series see Audrieth, Scott, and Kippur; and Scott and Audrieth, *J. Org. Chem.*, **19**, May (1954) (The two preceding articles).

[2] Abstracted from the doctoral dissertation submitted to the Graduate College of the University of Illinois (1952). Present address: University of California, Berkeley 4, California.

[3] Fellowship grants from Olin Industries, Inc., East Alton, Illinois and the Atomic Energy Commission are gratefully acknowledged.

[4] Abstracted from the thesis submitted in fulfillment of requirements for the degree of Bachelor of Science in Chemical Engineering at the University of Illinois (1952). Present address: University of California, Berkeley 4, California.

crystallization from a 1:1 water-ethanol mixture is sufficient to produce pure thiosemicarbazide.

The effect of varying the mole ratio of ammonium thiocyanate to hydrazine was investigated; it was found that the yield of thiosemicarbazide is increased as this ratio increases, until it attains a value of approximately 3 (see Table I). If more ammonium thiocyanate is used, the product is contaminated with thiourea, presumably because of the higher temperature achieved in the reaction vessel due to the higher concentration of solute. It is presumed that the excess of ammonium thiocyanate buffers the reaction mixture, thereby favoring the second phase of the reaction, *i.e.*, the rearrangement of the hydrazinium thiocyanate. In all experiments, approximately the theoretical quantity of ammonia was evolved during the first 30 minutes of reaction, showing clearly that the first step of the reaction is independent of the mole ratio of the reactants.

The yield of thiosemicarbazide may be increased by cooling the reaction mixture at 30 minute intervals, removing the product which crystallizes and reheating the mother liquor. The reaction mixture must be kept under an inert atmosphere during these operations to prevent oxidation of the hydrazine. The lower yield of thiosemicarbazide obtained when the reaction is run continuously may be due either (a) to suppression of the addition (hydrazination) reaction by the build-up of the thiosemicarbazide in the reaction mixture or (b) to decomposition of the thiosemicarbazide. The first of these possibilities would best explain the increased rate and efficiency of the rearrangement of hydrazinium thiocyanate to thiosemicarbazide in the presence of acetone (6) since the concentration of free thiosemicarbazide in such a reaction mixture would be small.

The process is adaptable to the preparation of thiosemicarbazide on a semicontinuous basis. When the mother liquor from one preparation was charged with a 1:1 molar mixture of hydrazine hydrate and ammonium thiocyanate and subjected to the normal reaction conditions, the same yield of thiosemicarbazide was obtained as in the previous preparations. When this procedure was repeated several times, the amount of thiosemicarbazide produced did decrease somewhat, probably due to buildup of decomposition products in the mother liquor. A major portion of the ammonium thiocyanate can be recovered from such spent liquors and be used to start a new cycle.

Experiments were carried out to determine the effect of using solvents other than water on the yield of thiosemicarbazide. No thiosemicarbazide was obtained when ethanol was used as a solvent, presumably because the temperature of the refluxing solution was too low to effect the desired rearrangement. Impure thiosemicarbazide was obtained when the reaction was carried out in ethylene glycol at 120°; total decomposition of the product occurred in the same solvent at its boiling point. The thiosemicarbazide obtained by carrying out the reaction in commercial dioxane-water mixtures was yellow and could not be purified satisfactorily by recrystallization. However, a pure product was obtained in as high as 75% yield when the reaction was carried out using dioxane purified by distillation from sodium. The necessity of purifying the dioxane makes this solvent unattractive despite the observed increase in yield.

TABLE I

EFFECT OF MOLE RATIO OF AMMONIUM THIOCYANATE TO HYDRAZINE ON THE YIELD OF THIOSEMICARBAZIDE

RUN NO.	MOLE RATIO $NH_4SCN:N_2H_4$	REFLUX TIME (hrs.)	YIELD	
			Grams	%
1	0.5	2.0	0	0
2	1.0	3.0	6.25	22.1
3	1.0	2.0	7.00	23.0
4	2.0	1.5	11.30	37.7
5	2.0	2.0	13.70	45
6	2.0	1.5	13.40	45
7	3.0	1.5	14.70	48

Acetone was added to the reaction mixture after the evolution of ammonia was essentially complete (30 minutes) and the resulting solution was refluxed. In two such preparations, crude acetone thiosemicarbazone was obtained in about 80% yield using a shorter reaction time. Since this intermediate may be used in the preparation of thiosemicarbazones of reactive carbonyl compounds (7), the synthesis giving the acetone thiosemicarbazone may be useful in some cases.

EXPERIMENTAL

Effect of mole ratio of ammonium thiocyanate to hydrazine on yield of thiosemicarbazide. Sufficient ammonium thiocyanate to establish the indicated mole ratio was dissolved in 21 ml. (0.33 mole of N_2H_4) of 85% hydrazine hydrate. The resulting solution was refluxed for the indicated period of time (1.5–3 hrs.) while oxygen-free nitrogen was bubbled through the mixture. The solution was then chilled to effect separation of solid thiosemicarbazide which was purified by recrystallization from a 1:1 water-ethanol mixture. The yields of pure thiosemicarbazide (m.p. 180–182°) are reported in Table I. In Experiments 6 and 7 the reaction mixture was diluted with 15 ml. of water to prevent precipitation of ammonium thiocyanate.

Thiosemicarbazide. Numerous preparations of thiosemicarbazide using approximately 3 moles of ammonium thiocyanate per mole of hydrazine have been carried out to give yields ranging from 45 to 60%. Typical directions for preparation on a laboratory scale follow:

Ammonium thiocyanate (200 g.) was dissolved in a solution containing 59 ml. of 85% hydrazine hydrate and 25 ml. of water. The resulting solution was refluxed for three hours under a nitrogen atmosphere, then allowed to cool slightly and filtered to remove the coagulated sulfur. The filtrate was allowed to stand overnight to crystallize the product. The thiosemicarbazide so obtained was collected and recrystallized from a 1:1 water-ethanol mixture. Thus 46 g. of thiosemicarbazide (m.p. 180–182°) was obtained directly. Evaporation of the mother liquor from the recrystallization to half volume and cooling gave an additional 5 g. of product. Total yield, 56.6%.

Acetone thiosemicarbazone. A solution containing 32 ml. of 85% hydrazine hydrate, 18 ml. of water, and 105 g. of ammonium thiocyanate was refluxed for 45 minutes. The resulting solution was cooled slightly, 30 g. of acetone was added, and the solution was refluxed for an additional two hours. The reaction mixture was then filtered and chilled to crystallize the product which was collected and recrystallized from alcohol. Acetone thiosemicarbazone (61.5 g., m.p. 179–180°) was obtained, corresponding to an 85% yield.

SUMMARY

A new method for the synthesis of thiosemicarbazide has been developed based upon reaction between ammonium thiocyanate and hydrazine in refluxing aqueous solution. Maximum yields are obtained with a mole ratio of NH_4SCN to $N_2H_4 = 3:1$. Hydrazinium thiocyanate is formed and caused to rearrange to thiosemicarbazide in aqueous solution from which it can be crystallized directly on cooling. Conversion into the acetone thiosemicarbazone can be effected by addition of acetone to the NH_4SCN-N_2H_4 reaction mixture after the initial ammonia evolution equivalent to the added hydrazine has occurred.

URBANA, ILLINOIS

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