United States Patent Office 3,009,955 Patented Nov. 21, 1961

3,009,955
PROCESS FOR THE PREPARATION OF THIOSEMICARBAZIDE

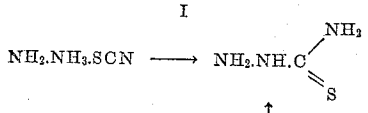
Alfred Rieche, Berlin-Wendenschloss, Günter Hilgetag, Berlin-Grunau, Anneliese Martini, Berlin-Kopenick, and Rainer Phillipson, Berlin, Germany, assignors to Deutsche Akademie der Wissenschaften zu Berlin, Berlin-Adlershof, Germany

No Drawing. Filed July 8, 1959, Ser. No. 825,634
6 Claims. (Cl. 260—552)

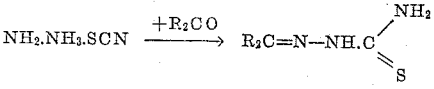
This invention relates to a single stage process for the preparation of thiosemicarbazide and, more particularly, to such a process wherein the yields obtained are at least 90% of the theoretical yield.

The prior art processes for the preparation of thiosemicarbazide are cumbersome throughout. Moreover, in these processes after many operating steps a yield is obtained which at best is only between 60% and 80% of the theoretical yield. In general, these processes begin with hydrazoniumthiocyanate which under the appropriate conditions is converted either directly to thiosemicarbazide (see Equation I below) or is converted to the thiosemicarbazide indirectly through certain thiosemicarbazones (see Equation II):

I

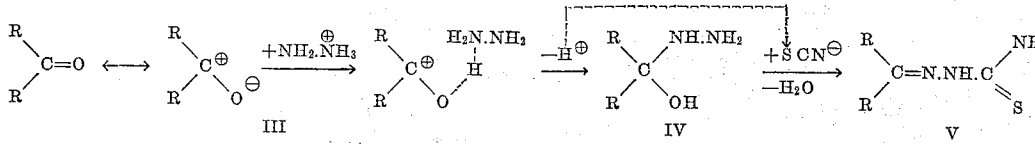


II



The possible rearrangement of hydrazoniumthiocyanate to thiosemicarbazide shown in Equation I can be effected either by heating the material in a concentrated aqueous solution or in an inert organic solvent. It must be assumed that the direct rearrangement of hydrazoniumthiocyanate to the thiosemicarbazide is always accompanied by an extensive dissociation of hydrazoniumthiocyanate into hydrazine and thiocyanic acid which only occurs at elevated temperatures.

The conversion of hydrazoniumthiocyanate according to Equation II above takes place with at least equimolar quantities of a ketone. This is a known reaction which has been used to prepare acetonethiosemicarbazone in almost quantitative yield. The process of Equation II above proceeds primarily through the formation of an intermediate product (see III below) which results from the reaction of the hydrazonium cation with the ketone. This is stabilized by the addition of a proton which can migrate to the electron deficiency of the thiocyanate ion or the resulting thiocyanic acid resulting in the formation of the thiosemicarbazone (see V below):



III IV V

With regard to another method of obtaining the thiosemicarbazide in this manner the reaction of II→I is employed. Thus, for example, acetonethiosemicarbazone is converted to the thiosemicarbazide in good yield by boiling it in water.

It has now been found that the thiosemicarbazide may be obtained in yields of at least 90% of the theory in a one-step process by heating an aqueous, aqueous-alcoholic, or alcoholic solution of the hydrazoniumthiocyanate to

boiling or to 90–120° C. in the presence of a small catalytic quantity of a ketone or ketone derivative. The quantity of the catalyst employed amounts to, at the maximum, only 5% of he equimolar amount of ketone which, for example, is used in the preparation of the acetonethiosemicarbazone described above. Instead of a ketone, a small amount of a ketone thiosemicarbazone, a ketazine, or a ketone hydrazone may be used with equally good results.

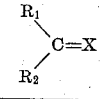
After a reaction time of e.g. 8 hours, when water is used as solvent, and up to at most 24 hours, when low boiling alcohols are used, for instance, a 60% methanol, a thiosemicarbazide is obtained in practically pure state and in a yield of at least 90% of the theory.

As stated above, one of the preferred embodiments of the process according to the invention is the preparation of thiosemicarbazide in aqueous solution. When the reaction is carried out in aqueous solution, it is a considerable advantage that the salts formed incidentally in the preparation of hydrazoniumthiocyanate, e.g., ammonium sulfate and potassium sulfate, need not be eliminated from the reaction mixture. The reaction time is short and, in general, the reaction is carried out under the simplest and least expensive conditions.

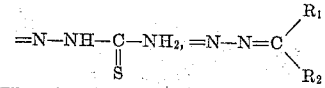
When alcohols are used as solvents, the short chain aliphatic alcohols are particularly adaptable for the present purposes which are miscible with water; these are for instance, methanol, ethanol, glycol, and the like. The preferred alcohols contain only hydroxy groups as functional groups and these may be monohydroxy, dihydroxy, trihydroxy, etc. The proportion of alcohol to water can be varied considerably, but between 65% and 90% alcoholic solutions and particularly of methanol have proved especially satisfactory.

If the reaction is carried out without the small quantity of catalyst employed in the present process but under the same reaction conditions and reaction time the thiosemicarbazide is obtained in a yield which is only 20% of the theoretical yield.

As noted above, the catalysts which may be used in accordance with the present invention are ketones and ketone derivatives. The ketone derivatives that are useful for the present process are those of the type wherein the keto oxygen is replaced by a nitrogen-containing radical resulting in the bond >C=N—. Thus, in addition to the ketones, such ketone derivatives as ketothiosemicarbazones, ketazines and ketohydrazones may be employed. More particularly, the aliphatic hydrocarbon ketones and cyclo-aliphatic hydrocarbon ketones and the corresponding ketazines, ketohydrazones and ketothiosemicarbazones are useful for the present purposes. These catalysts may be described by the general formula:



wherein =X is a radical selected from the class consisting of =O,



and =N·NH$_2$. In this formula R$_1$ and R$_2$ may be either the same or different radicals falling within the definition and are preferably monovalent or divalent aliphatic hy-

drocarbon radicals or cycloaliphatic hydrocarbon radicals. When R_1 and R_2 are divalent aliphatic hydrocarbon radicals, the free bonds of these radicals are joined to form a cycloaliphatic hydrocarbon radical. Thus, R_1 and R_2 may be long chain or short chain alkyl radicals. More particularly R_1 and R_2 may be alkyl radicals having up to 24 carbon atoms in their alkyl chain. However, alkyl radicals having up to about 12 and preferably 8 carbon atoms in the chain are particularly suitable. When R_1 and R_2 are divalent aliphatic hydrocarbon radicals, they are preferably those which when joined together will form a cycloaliphatic hydrocarbon ring having up to about 10 carbon atoms in the cycle. However, in the preferred form of this invention the cycloaliphatic radical has up to 6 carbon atoms in the ring. Among the ketone catalysts which may be used for the present invention may be mentioned: acetone, methyl ethyl ketone, methyl n-propyl ketone, methyl isobutyl ketone, methyl n-amyl ketone, 3-methyl-2-hexanone, methyl neopentyl ketone, n-propyl isopropyl ketone, diisopropyl ketone, methyl isohexyl ketone, 5-methyl-3-heptanone, isopropyl t-butyl ketone, methyl n-heptyl ketone, methyl n-octyl ketone, methyl n-heptadecyl ketone, di-n-undecyl ketone, di-n-heptadecyl ketone. Among the cycloaliphatic ketones which may be used in accordance with the present invention may be mentioned: cyclobutanone, methyl cyclopropyl ketone, methyl cyclobutyl ketone, methyl cyclopentyl ketone, 3-methylcyclohexanone, cycloheptanone, 2-ethyl cyclohexanone, 3-ethylcyclohexanone, 2-n-propylcyclohexanone, 2,2,6,6-tetramethylcyclohexanone, 2-decalone. Furthermore the ketothiosemicarbazones, the ketohydrazone derivatives of the above-mentioned ketones as well as the corresponding ketazines are useful as catalysts in the present invention.

In accordance with the present invention only a very small catalytic amount of ketone or ketone derivative is required to effect the desired reaction. More particularly the quantity of catalyst employed is in the range of 0.1% to 20% by weight of the hydrazoniumthiocyanate. The preferred quantity of catalyst is in the range of 1 to 5% by weight of the hydrazoniumthiocyanate.

The reaction conditions will vary somewhat with the particular catalyst used. In general, the rearrangement is effected in a temperature range of about 60° C. to 110° C. Furthermore, it is preferred that the reaction be carried out in an acid medium and more particularly in an acid medium having a pH range between 3 and 4.

The following examples are further illustrative of the present invention. However, it is to be understood that this invention is not restricted thereto.

Example 1

To a solution of 224 ml. 25% hydrazine hydrate and 100 ml. water, 144 g. hydrazine sulfate were added at 40° C. while stirring; the pH was adjusted between 3 and 4. To this solution at a temperature of 40° C., were added 240 g. ammonium thiocyanate whereby a solution of hydrazonium thiocyanate resulted with simultaneous formation of ammonium sulfate. We then added 6 ml. acetone, and the mixture was heated to 95–110° C. for 8 hours. After the reaction was completed, the reaction mixture was cooled down to 8° C. and the crystallized thiosemicarbazide was drawn off, washed with water, and dried. Obtained were 178 g. thiosemicarbazide corresponding to 89% of the theoretical yield.

Example 2

To a hydrazonium thiocyanate solution prepared in accordance with Example 1, 6 g. acetone thiosemicarbazone were added and the solution then heated to 105–115° C. for 10 hours. After cooling to 5–10° C., 181 g. thiosemicarbazide were obtained corresponding to 90.5% of the theoretical yield.

Example 3

To a hydrazonium thiocyanate solution prepared in accordance with Example 1, 6 ml. dimethylketazine were added and heated to 95–100° C. for 8 hours. Obtained were 167 g. thiosemicarbazide corresponding to 83% of the theoretical yield.

Example 4

To a hydrazonium thiocyanate solution prepared in accordance with Example 1, 6 g. cyclohexanonehydrazone were added and heated to boiling temperature for 8 hours. Obtained were 166 g. thiosemicarbazide corresponding to 83% of the theoretical yield.

Example 5

To a solution of 112 ml. 25% hydrazine hydrate, 72 g. hydrazinesulfate were added under stirring, and the solution was then adjusted to a pH of 3–4. To this solution, 120 g. ammonium thiocyanate were added at 40° C. Stirring was continued for another 10 minutes, whereafter 105 ml. methanol were added. After stirring for a short while, the precipitated ammonium sulfate was drawn off. After addition of 3 ml. acetone, the filtrate was boiled for 16 hours under reflux. After cooling down to 7° C., the crystallized thiosemicarbazide was drawn off, washed and dried. Obtained were 87 g., corresponding to 87% of the theoretical yield.

Example 6

To a solution of 80 ml. of water containing 28 ml. of hydrazine hydrate, 72 g. of hydrazine sulfate were added while stirring and the pH was adjusted between 3 and 4. To this solution at a temperature of 40° C. 120 g. of ammonium thiocyanate were added. The mixture was stirred for 10 minutes and then 210 ml. of methanol were added. After stirring for another 30 minutes, the precipitated ammonium sulfate was drawn off. After the addition of 2 ml. of acetone, the filtrate was boiled under reflux for 24 hours. The crystals began to separate out with the boiling. After cooling to room temperature, the crystallized thiosemicarbazide was drawn off. The yield was 90–95 g. which was equal to 89% to 94% of the theory based on the hydrazine added.

Example 7

To an aqueous methanol solution containing 102 g. of hydrazoniumthiocyanate prepared in accordance with the procedure shown in Example 6, 2 g. of acetone thiosemicarbazone were added. After 20 hours of boiling 94 g. of thiosemicarbazide were obtained.

Example 8

To a solution of 102 g. of hydrazoniumthiocyanate in aqueous ethanol solution prepared in the manner shown in Example 6, 2 g. of cyclohexanone hydrazone were added. After boiling for 24 hours under reflux conditions, on cooling 90 g. of thiosemicarbazide were obtained.

Exemple 9

To an aqueous methanol solution containing 102 g. of hydrazoniumthiocyanate prepared in accordance with the procedure of Example 6, 3 ml. of dimethyl ketazine were added. After boiling for 24 hours under reflux conditions 93 g. of thiosemicarbazide were obtained.

Example 10

To an aqueous isopropanol solution containing 102 g. of hydrazoniumthiocyanate prepared in accordance with Example 6, 2 g. methyl ethyl ketone were added. After 20 hours boiling under reflux conditions, 92 g. of thiosemicarbazide were obtained.

While the invention has been described with particular reference to specific embodiments, it is to be understood that it is not limited thereto, but is to be construed broadly and restricted solely by the scope of the appended claims.

Thiosemicarbazide is a well-known compound having wide use. It is used in organic chemistry as an analytical reagent for testing for aldehydes and ketones, and is in-

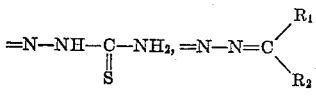
dustrially of importance as an intermediate in the preparation of several drugs.

What is claimed is:

1. A process for the preparation of thiosemicarbazide which comprises heating hydrazine thiocyanate in an aqueous solution adjusted to a pH of 3–4 to a temperature in the range of 75 to 105° C. in the presence of a catalyst in an amount from 0.1 to 20% by weight calculated on the hydrazine thiocyanate, said catalyst having the formula



wherein X stands for a member of the class consisting of =O,



and =N—NH_2, and in which R_1 and R_2 taken singularly are selected from the class consisting of lower alkyl radicals and cycloalkyl radicals, and taken together are cycloalkyl radicals of up to 6 C-atoms.

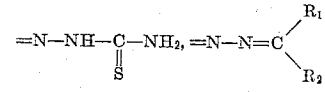
2. The process according to claim 1, wherein R_1 and R_2 are identical radicals.

3. The process according to claim 1, wherein R_1 and R_2 are different radicals.

4. A process for the preparation of thiosemicarbazide which comprises heating hydrazine thiocyanate in an aqueous-alcoholic solution containing from 1% to 99% of an alkanol having 1 to 5 C-atoms and being adjusted to a pH of 3–4, to a temperature in the range of 75 to 105° C. in the presence of a catalyst in an amount from 0.1 to 20% by weight calculated on the hydrazine thiocyanate, said catalyst having the formula



wherein X stands for a member of the class consisting of =O,



and =N—NH_2, and in which R_1 and R_2, taken singularly are selected from the class consisting of lower alkyl radicals and cycloalkyl radicals, and taken together are cycloalkyl radicals of up to 6 C-atoms.

5. The process according to claim 4, wherein R_1 and R_2 are identical radicals.

6. The process according to claim 4, wherein R_1 and R_2 are different radicals.

References Cited in the file of this patent

UNITED STATES PATENTS

2,450,406	Bambas	Oct. 5, 1948
2,731,496	Taylor	Jan. 17, 1956