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PREPARATION OF 2-MERCAPTOIMIDAZOLE

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7 Claims. (Cl. 260—309)

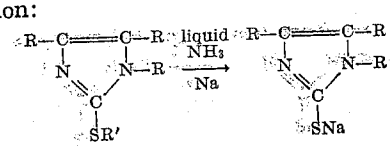
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This invention relates to a new method of preparing 2-mercaptoimidazoles and alkali metal salts thereof.

Recently it has been discovered that 2-mercaptoimidazole is more active than the thiouracils and other known compounds in the treatment of hyperthyroidism in man, even though tests made on rats did not indicate the superiority. Certain 2-mercaptoimidazoles having alkyl substituents in the imidazole ring are also active as anti-thyroid agents. It appears likely, therefore, that there will be a demand for considerable quantities of these compounds for use in medicine. Unfortunately, presently known methods of preparing the 2-mercaptoimidazoles are not satisfactory.

Marckwald described the production of 2-mercaptoimidazole as early as 1892 in Berichte, volume 25, page 2354. He used as starting materials aminoacetal and potassium thiocyanate in an involved process requiring many steps. The product of the reaction is difficult to handle, and extremely low yields of the desired 2-mercaptoimidazoles are obtained. In view of the potential demand for large quantities of 2-mercaptoimidazole and alkyl mercaptoimidazoles it is desirable, therefore, that a method of producing these substances on a commercial scale be made available. The present invention describes such a method, which uses readily available materials and gives, under favorable conditions, almost quantitative yields.

In brief, the new process of the present invention involves the cleavage of a thioether with an alkali metal as illustrated by the following equation:



In the above R represents hydrogen or an alkyl radical and R' an alkyl or aralkyl radical. The resulting product, an alkali metal salt of the 2-mercaptoimidazole, is readily converted to the desired free mercaptoimidazole by neutralization with an acid or by treatment with a salt such as ammonium chloride.

The cleavage of 2-mercaptoimidazolethioethers with alkali metals, as will be described herein with such excellent yields, is very surprising in view of the fact that numerous other known methods of cleaving thioethers were first tried with little or no success. For example; such

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diverse agents as P_2S_5, dry hydrogen chloride, sodium metal in ethanol, acetic acid, and hydrogen iodide, and still other agents which have been used before to cleave thioethers were unable to cleave the 2-mercaptoimidazolethioethers which are used herein as intermediates.

It is preferred that the reaction be conducted in liquid ammonia, which serves as a solvent and tends to reduce the hazards of the reaction. The temperature of the reaction is not critical, but care should be taken to keep the reaction mixture in liquid form to reduce the danger of an explosion from the sodamide, which may be formed under these conditions, by the addition, if necessary, of more liquid ammonia. Ordinarily, under these conditions the reaction takes place at low temperatures, but in pressure vessels it is possible to keep the ammonia in liquid form at higher temperatures. Sodium is the preferred alkali metal because of its cheapness, but other alkali metals such as potassium or lithium may be used. Theoretically, the reaction requires at least two moles of the alkali metal for each mole of the mercaptoimidazole-thioether, but it is preferred that three to seven moles of the alkali metal be used.

The reaction takes place within a very short time and is generally considered to be complete when the blue color of the alkali metal in the liquid ammonia disappears. Water is then added to decompose the alkali metal amide, and the ammonia and water removed by evaporation. The product contains the alkali metal salt of the 2-mercaptoimidazole. On neutralization with an acid or ammonium chloride or the like the free mercaptoimidazole is obtained in excellent yields. The crude product may be purified by recrystallization from solvents.

Examples showing the preparation of 2-mercaptoimidazole and alkyl substituted mercaptoimidazoles from representative 2-alkyl and 2-aralkylthioimidazoles will now be given. It will be understood, of course, that other 2-alkyl and 2-aralkylthioimidazoles may be used and that the process is not limited to the exact conditions described.

Example 1

To 11.40 g. (0.041 mole) of methyl isothiourea sulfate were added 10.00 g. (0.082 mole) of freshly distilled bromacetaldehyde, and the mixture was stirred for 4½ hours on a steam bath at 85° C. The solution was made basic with potassium carbonate solution and then ether extracted. Concentration of the ether solution gave 2-

methyl-thioimidazole. Mixed melting point with a sample prepared by another process was not depressed.

To 4.2 g. (0.037 mole) of 2-methylthioimidazole dissolved in liquid ammonia were added 2.5 g. (0.111 mole) of sodium. After stirring for 75 minutes, the blue color disappeared and 35 cc. of water were added to the solution. Then the ammonia and water were removed at reduced pressure. The residue was dissolved in a minimum of water and neutralized with dilute HCl. The solid separating melted at 221–225° C. After an acetone extraction of the solid, 3.7 g. (theoretical yield) of 2-mercaptoimidazole melting at 226–227° C. were obtained.

Example 2

To a solution of 4.4 g. (0.034 mole) of 2-ethylthioimidazole in liquid ammonia were added 2.5 g. (0.102 mole) of sodium. In 40 minutes the blue color disappeared, and water was added to the solution. The ammonia and water were removed at low pressure, and the residue was neutralized with dilute HCl. An acetone extraction of the solid obtained gave 3.3 g. (97% yield) of 2-mercaptoimidazole melting at about 226° C.

Example 3

To 5 g. (0.026 mole) of 2-benzylthioimidazole dissolved in liquid ammonia were added 1.79 g. (0.078 mole) of sodium. The blue solution was stirred for about one hour and then water was added. The ammonia and water were removed using reduced pressure, and the residue was neutralized with dilute HCl. Recrystallization of 2.8 g. of crude material from water gave 1 g. (38% yield) of pure 2-mercaptoimidazole.

Example 4

Two grams of 2-methylthio-4(5)-n propylimidazole was dissolved in liquid ammonia and .88 g. (0.0384 gram atom) sodium was added. After stirring for one hour, some blue color remained. About 5 cc. of alcohol were added and then the excess ammonia and the alcohol were removed. To the residue was added about 10 cc. of water and then the solution was neutralized with HCl. Two grams of crude material separated. This was recrystallized once from water using activated charcoal. One gram of 4(5) n-propyl-2-mercaptoimidazole melting at 182–183° C. was obtained, filtered and dried.

Example 5

Five grams of 1-methyl-2-mercaptoimidazole was dissolved as much as possible in chloroform and 15 grams of methyl iodide was added. The solution was refluxed for two hours and then cooled. A small amount of solid was filtered. The solution was concentrated and the residue treated with ether. Five grams of solid were obtained, melting at around 145° C. The hydroiodide salt of the desired compound is reported to melt at 148° C. (Marckwald, Ber. 22, 1356). The solid was dissolved in water and treated with potassium carbonate. It was finally found that the free base was not obtained in any quantity until the pH was brought up to 11 with potassium hydroxide solution. At this pH a sharp mercaptan-like odor was noticed. The solution was concentrated and the residue was treated with ether. The ether solution was dried briefly over potassium hydroxide and then was concentrated. This oily residue was dried in a desiccator. One gram o.

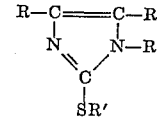
1-methyl-2-methylthioimidazole, possibly still wet, was obtained.

The gram of oily material obtained above was dissolved in liquid ammonia and 0.53 g. (0.0231 gram atom) of sodium was added. After one-half hour the blue color had disappeared, and 5 cc. of alcohol were added. Then the excess ammonia and alcohol were removed. To the residue were added 10 cc. of water. This solution was neutralized with hydrochloric acid and then concentrated to dryness. The residue was treated with alcohol, filtered and the alcohol concentrated. The product, 1-methyl-2-mercaptoimidazole was recrystallized from water.

This is a continuation-in-part of my application, Serial No. 5,200, filed January 29, 1948, now abandoned.

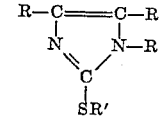
I claim:

1. The process of preparing alkali metal salts of 2-mercaptoimidazoles which comprises the step of treating a 2-mercaptoimidazolethioether having the general formula



in which R is a radical of the group consisting of hydrogen and alkyl radicals and R′ is a member of the group consisting of alkyl and aralkyl radicals, with an alkali metal whereby cleavage of the thioether occurs and an akali metal salt of a 2-mercaptoimidazole is obtained.

2. The process of preparing sodium salts of 2-mercaptoimidazoles which comprises the step of treating a 2-mercaptoimidazolethioether having the general formula



in which R is a radical of the group consisting of hydrogen and alkyl radicals and R′ is a member of the group consisting of alkyl and aralkyl radicals, with metallic sodium in liquid ammonia whereby the thioether is cleaved and a sodium 2-mercaptoimidazole is obtained.

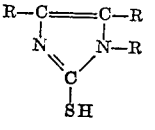
3. A method of preparing sodium 2-mercaptoimidazole which comprises treating a 2-alkylmercaptoimidazole with sodium in liquid ammonia whereby sodium 2-mercaptoimidazole is formed.

4. A method of preparing sodium 2-mercaptoimidazole which comprises treating 2-methylmercaptoimidazole with sodium in liquid ammonia whereby sodium 2-mercaptoimidazole is formed.

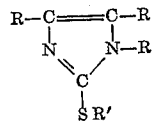
5. A method of preparing sodium 4(5)-n propyl-2-mercaptoimidazole which comprises treating 2-methylthio-4(5)-n propylimidazole with sodium in liquid ammonia whereby sodium 4(5)-n propyl-2-mercaptoimidazole is formed.

6. A method of preparing sodium 1-methyl-2-mercaptoimidazole which comprises treating 1-methyl-2-methylthioimidazole with sodium in liquid ammonia whereby sodium 1-methyl-2-mercaptoimidazole is formed.

7. A method of preparing 2-mercaptoimidazoles having the general formula



which comprises treating a compound having the formula



in which R is a member of the group consisting of hydrogen and alkyl radicals and R' is a member of the group consisting of alkyl and aralkyl radicals with an alkali metal in liquid ammonia and after reaction thereof whereby the thioether linkage is cleaved, neutralizing the reaction product with an acid to obtain 2-mercaptoimidazoles having the first illustrated formula above.

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No references cited.