BIS-(2-PYRIDYL-1-OXIDE) DISULFIDE

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References Cited

UNITED STATES PATENTS

2,686,786 8/1954 Shaw et al. ................. 260/294.8 G


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ABSTRACT

An improved integrated route to bis-(2-pyridyl-1-oxide) disulfide is provided by oxidizing 2-chloropyridine with permaleic acid to form 2-chloropyridine-1-oxide followed by mercaptization with a selected alkali metal sulfide to form the alkali metal salt of 2-mercaptopyridine-1-oxide and then oxidation with hydrogen peroxide under selected pH conditions.

8 Claims, No Drawings
BIS-(2-PYRIDYL-1-OXIDE) DISULFIDE

This invention relates to an improved, integrated method for preparing bis-(2-pyridyl-1-oxide) disulfide in high purity and high yield. More particularly, this invention involves the preparation of the aforesaid disulfide compound in an integrated, in-situ method by oxidizing the alkali metal salt of 2-mercaptopypyridine, which is obtained by oxidation of 2-chloropyridine with permaleic acid followed by mercaptization with a selected sulfide, with hydrogen peroxide using selected pH conditions.

The preparation of bis-(2-pyridyl-1-oxide) disulfide (also referred to as 2,2'-dithiodipyridine-1,1'-disulfide) hereinafter referred to as the disulfide, has been previously broadly disclosed in U.S. Pat. No. 2,742,476 wherein mercaptopypyridine-1-oxide is reacted with an oxidizing agent. U.S. Pat. No. 3,759,932 also generally discloses the preparation of a disulfide compound using an in-situ preparation technique wherein mercaptopypyridine is not isolated. While these references broadly disclose the preparation of the disulfide, problems have arisen when using the alkali metal salt of 2-mercaptopypyridine-1-oxide in an in-situ technique wherein the alkali metal salt was obtained by oxidizing 2-chloropyridine with permaleic acid to form the N-oxide followed by mercaptization to form the salt. When using this system, oxidation by the known techniques as shown for example in U.S. Pat. No. 2,742,476 resulted in the formation of undesired by-products such as the alkali metal maleate and alkali metal fumarate. This contaminated the desired disulfide product and lowered the yield.

It has now been found that when using permaleic acid in the preparation of 2-chloropyridine-1-oxide during the integrated preparation of the disulfide, the above noted by-product formation can be avoided and surprisingly high yields obtained by operating the final oxidation in the presence of hydrogen peroxide at selected pH conditions. More particularly the oxidation of the alkali metal salt of 2-mercaptopypyridine-1-oxide is carried out at a pH of about 4 to about 5 and preferably from about 4.5 to about 5. The overall reaction scheme of this invention is illustrated by the following equation:

\[
\text{N}^\text{O} \quad \text{NaSH} \quad \rightarrow \quad \text{N} \quad \text{NaS} \\
\text{H}_2\text{O}_2 \quad \text{pH} 4-5
\]

In the reaction of this invention as illustrated above, 2-chloropyridine is oxidized to the N-oxide using permaleic acid in accordance with known procedures as disclosed for example in U.S. Pat. No. 2,951,844. The mercaptization of the 2-chloropyridine N-oxide is carried out using an alkali metal sulfide or alkali metal hydroxide in accordance with known procedures as disclosed in U.S. Pat. No. 2,686,786. This key step in this invention is the oxidation of the prepared alkali metal salt of 2-mercaptopypyridine-1-oxide using hydrogen peroxide and a reaction pH of about 4 to about 5. By maintaining the reaction under these conditions, the precipitation of undesired impurities, primarily derived from the salts of fumaric acid is avoided and surprisingly high yields resulted.

In carrying out the reaction of this invention, the temperature may generally be maintained from about 15° to about 35°C. with about 20° to about 30°C. being preferred. The hydrogen peroxide concentration may be varied with about 5 to about 30 percent in aqueous solution being generally used. Generally a stoichiometric ratio of the alkali metal salt of 2-mercaptopypyridine and hydrogen peroxide of about 2 moles of the mercaptopypyridine salt to about 1 mole of peroxide or a slight excess of up to about 15 percent peroxide is used.

It is also generally advisable to agitate the reaction mixture in the peroxide oxidation step to maintain an effectively dilute hydrogen peroxide solution.

The pH of the reaction mixture is generally adjusted before the peroxide oxidation step by using any suitable acidifying agent such as the non-oxidizing mineral acids such as HCl and the non-oxidizing organic acids.

While 2-chloropyridine has been shown to be a desired starting material in the method of this invention, other 2-halopyridines and substituted halopyridines containing groups such as lower alkyl and lower alkoxy which do not adversely affect the reaction may also be used.

Isolation of the final product after oxidation is obtained by a standard filtration procedure.

The disulfided compounds prepared in accordance with the method of this invention have a variety of known uses, particularly as antibacterial and antifungal agents in a variety of applications such as to combat agricultural plant diseases and in plastics and fabrics to resist mildew or other fungus attack as disclosed in U.S. Pat. No. 2,742,476.

The following examples are further illustrative of this invention.

**EXAMPLE I**

A 2-liter, 3-neck flask fitted with a stirrer, thermometer and addition funnel was charged with 1,866 g of a reaction mixture containing the sodium salt of 2-mercaptopypyridine-1-oxide. This reaction mixture had...
an assay of 7.2 percent (135 g) of the sodium salt of 2-mercaptopyridine-1-oxide, 7 percent sodium chloride and 13–14 percent total of sodium maleate and sodium fumarate. This mixture was obtained by oxidizing 2-chloropyridine with permaleic acid and then mercaptizing with NaN₃. The pH was then adjusted to 4.5 with concentrated hydrochloric acid and the resulting warm solution was cooled to 25°C, and 52 ml of 30 percent hydrogen peroxide (12 percent excess over stoichiometry) in 160 ml of water added dropwise over a 30 minute period with stirring. The reaction was slightly exothermic with the temperature rising to approximately 30°C. At the end of the peroxide addition. Stirring of the now precipitated bis-(2-pyridyl-1-oxide) disulfide product was continued for 2 more hours to assure completeness of the reaction. The disulfide product formed was collected by filtration and the filter cake washed with 50 ml of water followed by 50 ml of methanol. After air drying, a total of 112 g (98 percent yield based on starting sodium salt of 2-mercaptopyridine-1-oxide) of bis-(2-pyridyl-1-oxide) disulfide was obtained with a melting point of 200°–201°C and an assay of 98 percent.

EXAMPLE II
Using the same procedure as Example I with a reaction mixture containing 25.6 g of the sodium salt of 2-mercaptopyridine-1-oxide, 14 g of 10 percent hydrogen peroxide, a pH of 4.0 and a reaction time of 18 hours, 17.0 g of the disulfide product was obtained (79.8 percent yield based on sodium salt) having as assay of 97.8 percent.

EXAMPLE III
Using the same procedure as Example I with a reaction mixture containing 25.6 g of the sodium salt of 2-mercaptopyridine-1-oxide, 14 g of 10 percent hydrogen peroxide, a pH of 5.0, a reaction temperature of 20°C to 23°C and a reaction time of 18 hours, 19.0 g of the disulfide product was obtained (89.3 percent yield based on sodium salt) and an assay of 97.7 percent.

EXAMPLE IV
For comparative purposes, the same procedure as Example II was followed with a pH of 3.0. A product of 23.5 g was obtained, however, it was contaminated with significant quantities of furmaric acid impurities.

EXAMPLE V
For comparative purposes, the same procedure as Example III was followed with a pH of 5.5 and a reaction time of 72 hours. A product of 10.5 g (49.3 percent yield) was obtained.

What is claimed is:
1. The method of preparing bis-(2-pyridyl-1-oxide) disulfide wherein 2-chloropyridine is oxidized with permaleic acid to form a reaction mixture containing 2-chloropyridine-1-oxide which is mercaptized using an alkali metal sulfide or alkali metal hydrosulfide to form the alkali metal salt of 2-mercaptopyridine-1-oxide in solution, the improvement comprising adjusting the pH of the resulting solution to a pH of about 4 to about 5 and then oxidizing with hydrogen peroxide to form the bis-(2-pyridyl-1-oxide) disulfide compound.
2. The method of claim 1 wherein said alkali metal is sodium.
3. The method of claim 2 wherein a pH of about 4.5 to about 5 is used.
4. The method of claim 2 wherein said hydrogen peroxide oxidation is carried out at a temperature of from about 15°C to about 35°C.
5. The method of claim 4 wherein a hydrogen peroxide concentration of from about 5 to about 30 percent in aqueous solution is used.
6. The method of claim 5 wherein said resulting solution contains sodium fumarate and sodium maleate in addition to the sodium salt of 2-mercaptopyridine-1-oxide.
7. The method of claim 5 wherein a pH of about 4.5 to about 5 is used.
8. The method of claim 7 wherein a temperature of from about 20°C to about 30°C, is used.

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