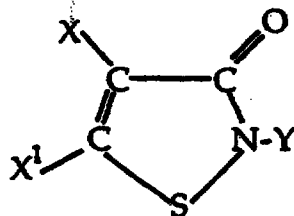


Description

This invention concerns the manufacture of 3-isothiazolones, and in particular it is concerned with a process for preparing 3-isothiazolones containing little or no salt ("salt-free"), and also little or no water ("water-free").

3-isothiazolones of the formula:



wherein Y is an alkyl or substituted alkyl of 1 to 10 carbon atoms; an unsubstituted or halogen substituted alkenyl or alkynyl of 2 to 10 carbon atoms; an aralkyl or halogen-, lower alkyl-, or lower alkoxy-substituted aralkyl of up to 10 carbon atoms; X is hydrogen or a (C₁-C₂)alkyl; and X' is hydrogen, chlorine, or a (C₁-C₂)alkyl are disclosed in U.S.-A-3,523,121 and 3,761,488.

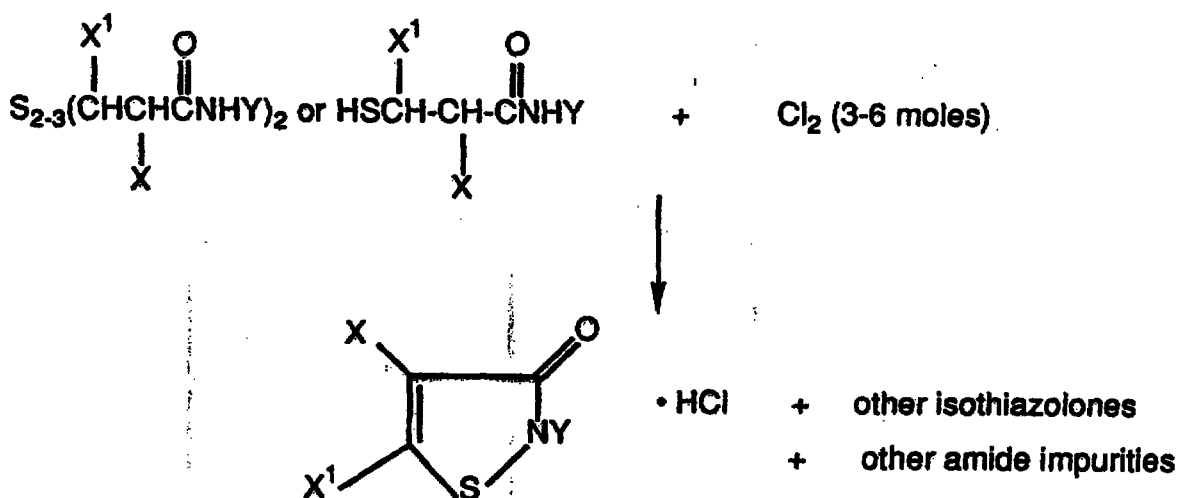
These 3-isothiazolones are well known as microbicides and are employed in many industrial and household systems. Since the 3-isothiazolones in aqueous solutions are generally unstable, stabilizing divalent metal salts as described in U.S.-A-3,870,795 and 4,087,878 are usually incorporated.

In certain applications, e.g., preservation of latex emulsion, these metal stabilization salts cause problems which can reduce the performance or value of such systems.

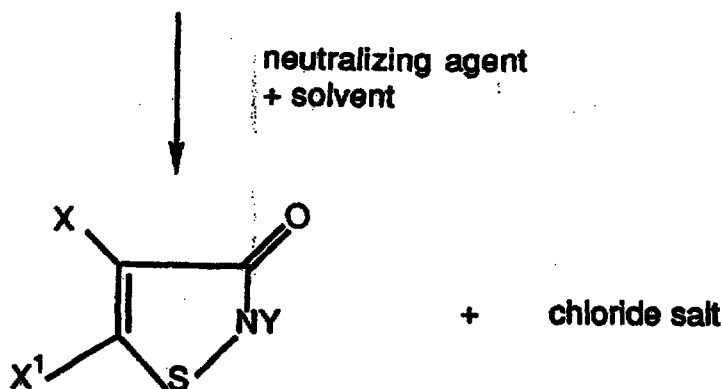
Another problem with such metal stabilization salts is that they cause corrosion in certain systems. For example, chloride salts have a corrosive effect on many metals and are to be avoided where possible. In water treatment systems where low cation and anion levels are important, it is desirable to eliminate such salts. In the stabilization of plastic articles, salts may contribute to deterioration of optical properties and/or increase water pickup and haze levels.

In some cosmetic formulations, it is also important to eliminate inorganic salt, especially nitrate.

Isothiazolone hydrochloride salts (isothiazolone·HCl) are generated in the general prior art process for manufacturing isothiazolones. Such a process for the manufacture of a mixture of 5-chloro-2-methyl-3-isothiazolone and 2-methyl-3-isothiazolone is described in U.S.-A-3,849,430 and EP-A-95907. The isothiazolone·HCl is generated in the chlorination/cyclization step of this process during which either a di- (or tri)thiodiamide or a mercaptoamide is cyclized:



The chlorination slurry is then filtered, and the isothiazolone·HCl cake is washed and reslurried or dissolved in the same or different solvent. In aqueous systems, a neutralizing agent such as magnesium oxide or calcium oxide is then added to yield the free base isothiazolone and a chloride salt:



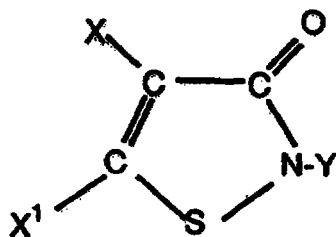
Certain organic amines have been suggested as neutralizing agents in non-aqueous organic media in U.S.-A-4,824,957. Such organic amines produce organic amine hydrohalide salts as byproduct neutralization salts. The amount of organic amine required to neutralize the isothiazolone hydrohalide salt is difficult to determine and thus the neutralization endpoint cannot be controlled precisely. Any excess organic amine remains in the organic solvent solution of the free base isothiazolone after neutralization and contaminates the final product solution, and furthermore may also chemically react with the free base isothiazolone to produce additional byproducts. In addition, these residual amines may also act as a source of nitrosamine contaminants, if such free base isothiazolone were to be formulated to aqueous solutions stabilized with nitrate salts.

The free base isothiazolone and amine hydrochloride salt (amine·HCl) which are formed from the neutralization reaction are separated by filtering off the solid salt from the solution of free base isothiazolone. However, amine·HCl salts are sparingly to appreciably soluble in most solvents, and consequently the final isothiazolone product may not be entirely salt-free.

None of the prior art processes is able to produce an isothiazolone which is substantially pure, salt-free, and water-free.

It is an object of the present invention to provide a process which produces isothiazolones of high purity and in high yield, which are substantially salt free and substantially water free.

These objects and others which will become apparent from the following disclosure are achieved by the present invention which provides in one aspect a process for preparing a 3-isothiazolone of the formula



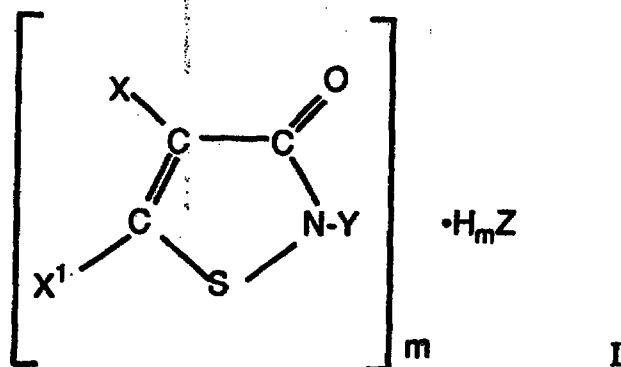
wherein

Y is alkyl of 1 to 10 carbon atoms, optionally substituted, preferably with halogen or lower alkoxy; unsubstituted or halogen-substituted alkenyl or alkynyl of 2 to 10 carbon atoms; or aralkyl or halogen-, lower alkyl-, or lower alkoxy-substituted aralkyl of up to 10 carbon atoms;

X is hydrogen or a (C₁-C₂)alkyl; and

X' is hydrogen, chlorine, or a (C₁-C₂)alkyl; comprising

(a) reacting anhydrous ammonia with an isothiazolone salt of the formula



wherein

Z is chlorine, bromine, sulfate or fluorosulfonate;

m is 1 when Z is chlorine, bromine, or fluorosulfonate and m is 2 when Z is sulfate; and

(b) separating the resultant $(\text{NH}_4)_m\text{Z}$ from the resultant free base isothiazolone.

Y is preferably methyl, ethyl, propyl, isopropyl, butyl, hexyl, octyl, hydroxymethyl, chloromethyl, chloropropyl, benzyl, 4-methoxybenzyl, 4-chlorobenzyl, phenethyl, 2-(4-chlorophenyl)ethyl, 4-phenylbutyl, and most preferably $(\text{C}_1\text{-C}_8)$ alkyl, particularly methyl or n-octyl.

X is preferably H, and X' preferably H or Cl.

Z is preferably chlorine or bromine, and most preferably chlorine.

The expressions "lower" alkyl, lower alkoxy, mean that the alkyl or alkoxy portion thereof has 1 to 2 carbon atoms.

The process of the invention comprises contacting the isothiazolone salt or a solution/suspension thereof in organic solvent with anhydrous ammonia, in an amount sufficient to neutralize the H_mZ present to form free base isothiazolone and an insoluble $(\text{NH}_4)_m\text{Z}$ salt, and then separating the $(\text{NH}_4)_m\text{Z}$ salt from the mixture. The organic solvents are selected such that the free base isothiazolone is essentially soluble and the $(\text{NH}_4)_m\text{Z}$ salt is essentially insoluble therein. By the term "essentially soluble" we mean that the free base isothiazolone is sufficiently soluble in the solvents used such that > 95% of the free base isothiazolone available is recovered after separation of the $(\text{NH}_4)_m\text{Z}$ salt. By the term "essentially insoluble" we mean that the $(\text{NH}_4)_m\text{Z}$ salt is sufficiently insoluble in the solvent or solvent mixture used such that <0.5% $(\text{NH}_4)_m\text{Z}$ salt is found in the isolated free base isothiazolone, and preferably <0.1%.

Preferably the solvent selected is also employed as the solvent in the preceding halogenation/cyclization step of making the isothiazolone salt. Suitable solvents for the neutralization include alcohols, glycols, glycol ethers, aromatic hydrocarbons, chlorinated aromatic hydrocarbons, aliphatic hydrocarbons, chlorinated aliphatic hydrocarbons, and acetate esters. Acetate esters are preferred, particularly ethyl and butyl acetate.

Preferred organic solvents for dissolving or suspending the salt are selected from the group consisting of $(\text{C}_1\text{-C}_5)$ alkyl alcohol, $(\text{C}_2\text{-C}_8)$ alkylene glycol, $(\text{C}_3\text{-C}_{10})$ alkylene glycol ether, (C_6) aromatic hydrocarbon, $(\text{C}_1\text{-C}_2)$ alkyl-substituted aromatic hydrocarbon, chloro-substituted (C_6) aromatic hydrocarbon, chloro-substituted $(\text{C}_1\text{-C}_2)$ alkyl-substituted aromatic hydrocarbon, $(\text{C}_6\text{-C}_8)$ alkane, chloro-substituted $(\text{C}_1\text{-C}_3)$ alkane, and $(\text{C}_1\text{-C}_4)$ alkyl ester of acetic acid.

A particularly preferred group of solvents is selected from the group consisting of ethylene glycol, propylene glycol, 1,3-butanediol, dipropylene glycol, ethylene glycol butyl ether, toluene, monochlorobenzene, heptane, dichloromethane, 1,2-dichloroethane, ethyl acetate, and butyl acetate.

During the neutralization, the amount of ammonia introduced to the solution or suspension of I salt should be less than or just equal to the stoichiometric amount necessary to neutralize the salt. Excess ammonia should be avoided to prevent reacting with the free base isothiazolone, resulting in lower yields, generation of byproducts giving lower purity, and high color. We have discovered that we are able to avoid excess ammonia by monitoring for ammonia in the vapor space above the neutralized I solution. We prefer to use an ammonia gas sensing probe or moist litmus paper to precisely control the amount of ammonia introduced for neutralization so that little or no excess accumulates in the free base isothiazolone solution once all of the H_mZ has been neutralized.

Solvents which may be used in the isothiazolone $\cdot$ H_mZ neutralization step but not for the preceding halogenation/cyclization step are alcohols, e.g., methanol; glycols, e.g., ethylene glycol, 1,3-butanediol, dipropylene glycol, and propylene glycol; and glycol ethers, e.g., methyl and butyl ethers of ethylene glycol and diethylene glycol. The final free base isothiazolone may be formulated in these solvents, thereby eliminating the need for a solvent removal step (via vacuum stripping or distillation) after neutralization. These solvents may also be used in combination, i.e., in mixtures, with the solvents used for the halogenation/cyclization step. Depending upon the alcohol, glycol, or glycol ether selected for the neutralization, greater concentrations of (NH₄)_mZ salt than desired may be found in the intermediate free base isothiazolone solutions; these (NH₄)_mZ salt concentrations can be reduced to acceptable levels upon formulation of the final free base isothiazolone in selected solvents, e.g., dipropylene glycol, followed by filtration.

Other strong acid salts such as the (isothiazolone)₂ $\cdot$ (H₂SO₄) or (isothiazolone) $\cdot$ HFSO₃ salts may be neutralized with anhydrous ammonia to produce the free base isothiazolone and insoluble ammonium sulfate or fluorosulfonate.

In addition to using the process of this invention to obtain highly pure salt-free water-free formulations of isothiazolones and isothiazolone mixtures, the invention may be used to obtain different ratios of two or more isothiazolones initially present in an isothiazolone salt mixture. A typical free base isothiazolone is a mixture of 5-chloro-2-methyl-3-isothiazolone and 2-methyl-3-isothiazolone preferably in a ratio of from 92:8 to 3:97. But for example, a 3/1 mixture of (5-chloro-2-methyl-3-isothiazolone/2-methyl-3-isothiazolone)_m $\cdot$ H_mZ may be only partially neutralized with ammonia, followed by isolation of the free base isothiazolone (after filtering off the remaining I and (NH₄)_mZ salts). The free base isothiazolone obtained by this procedure will be enriched in 5-chloro-2-methyl-3-isothiazolone relative to 2-methyl-3-isothiazolone due to the differences in basicity of the free base isothiazolones. This enrichment procedure may be practiced with the process of this invention whenever there is difference in basicities of the isothiazolones in the initial mixture of I salts to be neutralized. Indeed, one may use the process of the invention to isolate a highly enriched 5-chloro-2-methyl-3-isothiazolone mixture from a mixture of 5-chloro-2-methyl-3-isothiazolone/2-methyl-3-isothiazolone. The remaining isothiazolone salt may then be treated with additional ammonia to liberate the free base isothiazolone and thereby isolate a highly enriched 2-methyl-3-isothiazolone mixture.

As can be seen from the preceding disclosure and following examples, the process of the invention provides a highly advantageous process of producing free base isothiazolone which is substantially free of water and salt. The preferred isothiazolones contain less than about 0.1% water and less than about 0.1% (NH₄)_mZ based on weight of isothiazolone.

The following examples illustrate the process of the present invention; they are illustrative only.

Example 1

Preparation of 3:1 Mixture of 5-Chloro-2-Methyl-3-Isothiazolone and 2-Methyl-3-Isothiazolone

This example illustrates using ethyl acetate as the organic solvent for both the chlorination/cyclization and neutralization and anhydrous ammonia as the neutralizing agent; the chlorination/cyclization is carried out following the process of U.S.-A-3,849,430 and EP-A-95907. The same solvent is used for both chlorination/cyclization and neutralization.

Step 1: Chlorination of N-Methyl-3-Mercaptopropionamide (MMPA)

A 1-liter jacketed kettle with a bottom take-off was equipped with an overhead agitator, a thermometer, a chlorine inlet, an inlet for a 28% solution of MMPA in ethyl acetate, and a condenser connected to a caustic scrubber. To this kettle was charged ethyl acetate. To the heel of ethyl acetate were co-fed chlorine and the 28% MMPA solution over a 1-3 hour period while maintaining good mixing and temperature control. The resultant chlorination slurry of isothiazolone $\cdot$ HCl salts was filtered to isolate the isothiazolone $\cdot$ HCl cake. The isothiazolone $\cdot$ HCl cake was washed thoroughly with ethyl acetate to yield a highly pure mixture of isothiazolone $\cdot$ HCl salts (99.9% by HPLC and HCl analyses, 73.5% 5-chloro-2-methyl-3-isothiazolone/26.5% 2-methyl-3-isothiazolone or 2.8:1 ratio).

Step 2: Neutralization of the Isothiazolone $\cdot$ HCl Salt

The mixture of isothiazolone $\cdot$ HCl salts was reslurried in fresh ethyl acetate (25% solids) and anhydrous ammonia was passed gradually through the slurry at a temperature of 10-22°C until free ammonia could be detected in the head space of the container by an ammonia gas sensing probe. The isothiazolone $\cdot$ HCl salt mixture absorbed 22.3 g of ammonia before the free ammonia was detected in the gas head space. The resultant slurry of ammonium chloride in a solution of free base isothiazolone was then filtered on a vacuum Buchner funnel and the filter cake was thoroughly washed with fresh ethyl

acetate.

Step 3: Solvent Strip

The filtrate and the ethyl acetate washings were combined and stripped under reduced pressure (40°C/20 mm Hg to 50°C/2 mm Hg) to yield 176.8 g of high purity, free base isothiazolone product: 76.4% 5-chloro-2-methyl-3-isothiazolone/23.4% 2-methyl-3-isothiazolone (ratio of 3.3:1), 99.8% purity (<0.1% NH₄Cl). Overall yield was 84.2 mole % based on starting MMPA.

Step 4: Formulation of 5-chloro-2-methyl-3-isothiazolone/2-methyl-3-isothiazolone in Dipropylene Glycol (DPG)

The above highly pure free base isothiazolone mixture was dissolved in an appropriate amount of DPG to give 5% isothiazolone (active ingredient) in DPG solution.

The formulation containing 5% active ingredient was then added to various latex emulsions at 30-100 ppm (active ingredient) providing excellent protection against biological fouling without causing any gel formation in the latex.

Example 2

Preparation of 3:97 Mixture of 5-Chloro-2-Methyl-3-Isothiazolone/2-Methyl-3-Isothiazolone

In a manner similar to Step 1 of Example 1, an isothiazolone•HCl salt was obtained having purity of 98.2% and a 5-chloro-2-methyl-3-isothiazolone/2-methyl-3-isothiazolone ratio of 2:98.

Following the procedure of Step 2 of Example 1, the isothiazolone•HCl salt was neutralized with ammonia and the resultant free base isothiazolone was obtained in 98.2% purity (5-chloro-2-methyl-3-isothiazolone/2-methyl-3-isothiazolone ratio of 3:97, <0.1% NH₄Cl) and an overall molar yield of 86.4%.

Example 3

Preparation of 92:8 Mixture of 5-Chloro-2-Methyl-3-Isothiazolone/2-Methyl-3-Isothiazolone

Step 1: Chlorination of MMPA

Following the procedure of Step 1 of Example 1, an isothiazolone•HCl salt sample was obtained having a 99.9% purity (91% 5-chloro-2-methyl-3-isothiazolone/9% 2-methyl-3-isothiazolone or 10.1:1 ratio) based on HPLC and HCl analyses.

Step 2: Neutralization of the Isothiazolone•HCl Salt

This step was repeated as in Step 2 of Example 1 to give 181 g of the free base isothiazolone (99.5%, <0.1% NH₄Cl) in a ratio of 92% 5-chloro-2-methyl-3-isothiazolone/8% 2-methyl-3-isothiazolone (11.4:1). The overall isothiazolone yield based on starting MMPA was 82 mole %.

Example 4

Preparation of 5-Chloro-2-Methyl-3-Isothiazolone/2-Methyl-3-Isothiazolone Mixtures with Toluene Solvent

Step 1 of Example 1 was repeated except the ethyl acetate solvent was replaced with toluene. The isothiazolone•HCl obtained had a purity of only 89% (5-chloro-2-methyl-3-isothiazolone/ 2-methyl-3-isothiazolone ratio of 3.7:1).

Following the procedure of Step 2 of Example 1, the isothiazolone•HCl salt was neutralized with ammonia to produce the free base isothiazolone in 88% purity (<0.1% NH₄Cl) and 5-chloro-2-methyl-3-isothiazolone/2-methyl-3-isothiazolone ratio of 4.4:1.

Example 5

Preparation of 5-Chloro-2-Methyl-3-Isothiazolone/2-Methyl-3-Isothiazolone Mixtures Employing Butyl Acetate (BuOAc) Solvent

Step 1 of Example 1 was repeated, except the ethyl acetate solvent was replaced with BuOAc. The isothiazolone•HCl obtained had a purity of 99% (5-chloro-2-methyl-3-isothiazolone/ 2-methyl-3-isothiazolone ratio of 3.9:1).

Following the procedure of Step 2 of Example 1, the isothiazolone•HCl salt was neutralized with ammonia to produce the free base isothiazolone in > 99% purity and a 5-chloro-2-methyl-3-isothiazolone/2-

methyl-3-isothiazolone ratio of 4.7:1 (<0.5% NH_4Cl).

Example 6

5 Preparation of a 4:1 Mixture of 5-Chloro-2-Methyl-3-Isothiazolone/2-Methyl-3-Isothiazolone

This example illustrates the process of the invention using ethyl acetate as the solvent in which only the chlorination/cyclization step was carried out, and in which the neutralization step using anhydrous ammonia was carried out in a mixture of a glycol and ethyl acetate as cosolvents.

10 The isothiazolone-HCl obtained had a purity of 98.3% and the 5-chloro-2-methyl-3-isothiazolone/2-methyl-3-isothiazolone ratio was 4:1.

Step 2: Neutralization of the Isothiazolone-HCl Salt

The isothiazolone-HCl wet cake (68.4 g) was reslurried in 126.6 g of ethyl acetate and 85.8 g of dipropylene glycol (DPG). The stirred slurry was then neutralized by passing ammonia gas through the mixture until free ammonia was detected in the head space (5.5 g of ammonia were required for neutralization). The resultant slurry of free base isothiazolone and ammonium chloride was then filtered and washed thoroughly with fresh ethyl acetate.

Step 3: Solvent Strip

20 The filtrate and the ethyl acetate washings were combined and to this was added 12.1 g triethyl orthoformate stabilizer. Ethyl acetate was then stripped off from this mixture at 50 °C/20 to 5 mm Hg to give 132.3 g of a DPG liquid mixture containing 26.4% 5-chloro-2-methyl-3-isothiazolone, 6.6% 2-methyl-3-isothiazolone (4/1 ratio), <0.5% NH_4Cl .

Step 4: Formulation of 5-chloro-2-methyl-3-isothiazolone/2-methyl-3-isothiazolone in DPG

25 The above solution was further diluted by adding 150.5 g of DPG and filtered to give a final formulation of 15.2% 5-chloro-2-methyl-3-isothiazolone/2-methyl-3-isothiazolone in DPG.

Example 7

30 Preparation of 2-Octyl-3-Isothiazolone

This example illustrates the process of the invention using butyl acetate as the solvent in which both the chlorination/cyclization and neutralization are carried out, and anhydrous ammonia used as the neutralizing agent.

Step 1: Chlorination of N-Octyl-3-Mercaptopropionamide (OMPA)

35 A 1-liter jacketed kettle with a bottom take-off was equipped with an overhead agitator, a thermometer, a chlorine inlet, an inlet for a 28% solution of OMPA in butyl acetate, and a condenser connected to a caustic scrubber. To this kettle was charged butyl acetate. To the heel of butyl acetate were co-fed chlorine and the 28% OMPA solution over a 1-2 hour period while maintaining good mixing and temperature control. The resultant chlorination slurry of 2-octyl-3-isothiazolone-HCl was filtered to isolate the 2-octyl-3-isothiazolone-HCl cake. The 2-octyl-3-isothiazolone-HCl cake was washed thoroughly with butyl acetate to yield a highly pure 2-octyl-3-isothiazolone-HCl salt. An aliquot of 2-octyl-3-isothiazolone-HCl was dried and analyzed by GC (gas chromatography) for 2-octyl-3-isothiazolone and by potentiometric titration for HCl, which were 85.3% and 14.5%, respectively, bringing the total 2-octyl-3-isothiazolone-HCl purity to 99.8%.

45 Step 2: Neutralization of the 2-Octyl-3-Isothiazolone-HCl Salt

The 2-octyl-3-isothiazolone-HCl salt was reslurried in fresh butyl acetate (25% solids) and anhydrous ammonia passed gradually through the slurry (maintained at 10-22 °C) until free ammonia could be detected in the head space of the container by either wet litmus indicator paper or by an ammonia gas sensing probe. The resultant slurry of free base 2-octyl-3-isothiazolone and ammonium chloride was then filtered on a vacuum Buchner funnel and the filter cake thoroughly washed with fresh butyl acetate.

Step 3: Solvent Strip

The filtrate and the butyl acetate washings were combined and stripped under reduced pressure to yield high purity (>99%) free base 2-octyl-3-isothiazolone product, <0.5% NH_4Cl .

Step 4: Formulation of 2-Octyl-3-Isothiazolone in Propylene Glycol

55 2-Octyl-3-isothiazolone (266 g) was dissolved in 1,2-propylene glycol (312 g) to give a 46% active ingredient solution. This formulation may be added to a commercial acrylic latex paint formulation, such that the paint will exhibit good storage stability in the can against bactericidal attack and will exhibit excellent resistance to mildew upon application to exterior surfaces.

Example 8Partial Neutralization of Isothiazolone-HCl Salt Mixture with Ammonia

5 This example describes the process of obtaining a mixture of the two isothiazolones in different ratios than they were present in the initial isothiazolone-HCl mixture.

10 A 95 g mixture of 5-chloro-2-methyl-3-isothiazolone-HCl and 2-methyl-3-isothiazolone-HCl (in 75.4:24.6 ratio) in 400 g ethyl acetate was partially neutralized at 10 °C, using 95% of theoretical ammonia (6.2 g) needed to fully neutralize 5-chloro-2-methyl-3-isothiazolone-HCl. The resultant slurry, containing ammonium chloride and the isothiazolone-HCl salts mixture as solids and free base isothiazolone in solution was filtered on a vacuum Buchner funnel and the cake was washed with ethyl acetate.

The combined filtrate was stripped under vacuum (50 °C/20 mm Hg) to give 55.3 g of a free base containing essentially 5-chloro-2-methyl-3-isothiazolone (96.1%) with only a small amount of 2-methyl-3-isothiazolone (1.1%).

15 The above wet cake of NH₄Cl/isothiazolone-HCl salts mixture was reslurried in 275 g ethyl acetate and was neutralized completely. It adsorbed 2.8 g NH₃ before NH₃ was detected in the head space. The resultant slurry was filtered and washed on a vacuum Buchner funnel. The filtrate on stripping in vacuum at 50 °C/20 mm Hg) provided 23.9 g of a free base mixture containing 5-chloro-2-methyl-3-isothiazolone and 2-methyl-3-isothiazolone in a 25:75 ratio.

COMPARATIVE EXAMPLESEXAMPLES 9 and 10

25 Examples 9 and 10 illustrate the use of prior art practices with triethylamine (TEA) and pyridine (PYR) as neutralizing agents. Final product purity was lower when these organic amines were used, resulting in 2% or more amine-HCl salt (TEA-HCl or PYR-HCl) impurity being present compared to <0.5% ammonium chloride impurity in Examples 1-7.

Example 9 (Comparative)Preparation of a 4/1 Mixture of 5-Chloro-2-Methyl-3-Isothiazolone/2-Methyl-3-Isothiazolone Using Triethylamine (TEA)

35 A sample of isothiazolone-HCl wet cake (83.2 g) obtained following the procedure of Step 1 of Example 6 was reslurried in 383.5 g of ethyl acetate and 43 g of TEA was added dropwise to a stirred slurry of the isothiazolone-HCl wet cake while maintaining the temperature at 8-12 °C. At the end of the neutralization, the resultant slurry was allowed to warm to 23 °C and then filtered on a Buchner funnel. The solid TEA-HCl was washed with 300 g of ethyl acetate. The filtrate and washings were combined and the solvent was stripped off at 50 °C at 20 to 5 mm Hg to give 57.0 g of free base isothiazolone, containing 78.3% 5-chloro-2-methyl-3-isothiazolone/19.8% 2-methyl-3-isothiazolone/2.0% TEA-HCl.

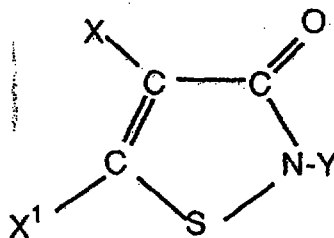
Example 10 (Comparative)Preparation of a 4/1 Mixture of 5-Chloro-2-Methyl-3-Isothiazolone/2-Methyl-3-Isothiazolone using Pyridine (PYR)

45 A sample of isothiazolone-HCl wet cake (74.4 g) obtained according to Step 1 of Example 6 was reslurried in 410 g of ethyl acetate and 29.3 g of PYR was added dropwise to a stirred slurry of the isothiazolone-HCl wet cake while maintaining the temperature at 10 °C. At the end of the neutralization, the resultant slurry was allowed to warm to 25 °C and was divided into two equal portions. One portion of the resultant slurry (246 g) was then filtered on a Buchner funnel. The solid PYR-HCl was washed with 250 g of ethyl acetate. The filtrate and washings were combined and the solvent was stripped off at 50 °C at 20 to 5 mm Hg to give 26.2 g of free base isothiazolone, containing 77.6% 5-chloro-2-methyl-3-isothiazolone/19.4% 2-methyl-3-isothiazolone/2.5% PYR-HCl. The second portion of the resultant slurry (244 g) was then treated with an additional 4.4 g of PYR and then filtered on a Buchner funnel. The solid PYR-HCl was washed with 250 g of ethyl acetate. The filtrate and washings were combined and the solvent was stripped off at 50 °C at 20 to 5 mm Hg to give 25.0 g of free base isothiazolone, containing 74.3% 5-chloro-2-methyl-3-

isothiazolone/20.0% 2-methyl-3-isothiazolone/4.4% PYR·HCl.

Claims

1. A process for preparing a 3-isothiazolone of the formula



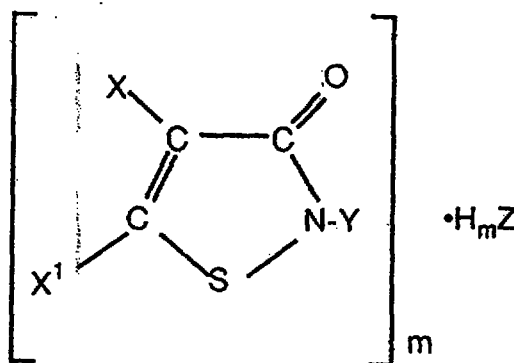
wherein

Y is alkyl of 1 to 10 carbon atoms, optionally substituted, preferably with halogen or (C₁-C₂)alkoxy; unsubstituted or halogen-substituted alkenyl or alkynyl of 2 to 10 carbon atoms; or aralkyl or halogen-, (C₁-C₂)alkyl-, or (C₁-C₂)alkoxy-substituted aralkyl of up to 10 carbon atoms;

X is hydrogen or a (C₁-C₂) alkyl; and

X' is hydrogen, chlorine, or a (C₁-C₂) alkyl; comprising

(a) reacting anhydrous ammonia with an isothiazolone salt of the formula



wherein

Z is chlorine, bromine, sulfate or fluorosulfonate, preferably chlorine or bromine;

m is 1 when Z is chlorine, bromine or fluorosulfonate, and m is 2 when Z is sulfate, which isothiazolone is dissolved or suspended in organic solvent, said solvent being selected such that the (NH₄)_mZ is essentially insoluble therein and the free base isothiazolone essentially soluble therein; and

(b) separating the resultant (NH₄)_mZ from the resultant free base isothiazolone.

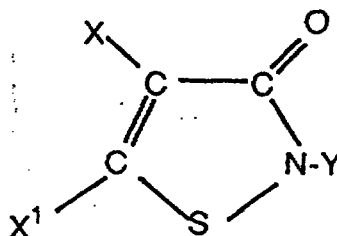
2. Process according to Claim 1 wherein said solvent is an alcohol, glycol, glycol ether, acetate ester, aliphatic hydrocarbon, chlorinated aliphatic hydrocarbon, aromatic hydrocarbon, or a chlorinated aromatic hydrocarbon solvent, preferably a (C₁-C₅)alkyl alcohol, (C₂-C₈)alkylene glycol, (C₃-C₁₀)alkylene glycol ether, (C₆)aromatic hydrocarbon, (C₁-C₂)alkyl-substituted aromatic hydrocarbon, chloro-substituted (C₆)aromatic hydrocarbon, chlorosubstituted (C₁-C₂)alkyl-substituted aromatic hydrocarbon, (C₆-C₈)alkane, chloro-substituted (C₁-C₃)alkane, and (C₁-C₄)alkyl ester of acetic acid, and more preferably ethylene glycol, propylene glycol, 1,3-butanediol, dipropylene glycol, ethylene glycol butyl ether, toluene, monochlorobenzene, heptane, dichloromethane, 1,2-dichloroethane, ethyl acetate, or butyl acetate.
3. Process according to claim 1 or 2 wherein the head space above the solution or suspension of isothiazolone salt is monitored during the reaction so as to determine when a sufficient amount of



isothiazolone/20.0% 2-methyl-3-isothiazolone/4.4% PYR•HCl.

Claims

1. A process for preparing a 3-isothiazolone of the formula



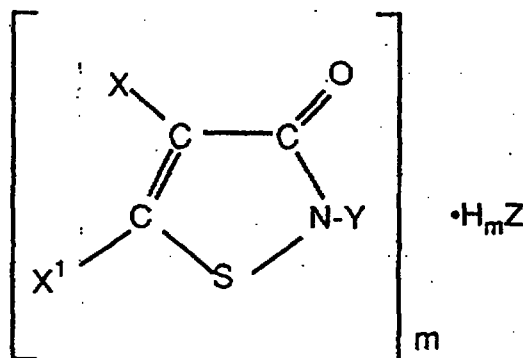
wherein

Y is alkyl of 1 to 10 carbon atoms, optionally substituted, preferably with halogen or (C₁-C₂)alkoxy; unsubstituted or halogen-substituted alkenyl or alkynyl of 2 to 10 carbon atoms; or aralkyl or halogen-, (C₁-C₂)alkyl-, or (C₁-C₂)alkoxy-substituted aralkyl of up to 10 carbon atoms;

X is hydrogen or a (C₁-C₂) alkyl; and

X' is hydrogen, chlorine, or a (C₁-C₂) alkyl; comprising

(a) reacting anhydrous ammonia with an isothiazolone salt of the formula



wherein

Z is chlorine, bromine, sulfate or fluorosulfonate, preferably chlorine or bromine;

m is 1 when Z is chlorine, bromine or fluorosulfonate, and m is 2 when Z is sulfate, which isothiazolone is dissolved or suspended in organic solvent, said solvent being selected such that the (NH₄)_mZ is essentially insoluble therein and the free base isothiazolone essentially soluble therein; and

(b) separating the resultant (NH₄)_mZ from the resultant free base isothiazolone.

2. Process according to Claim 1 wherein said solvent is an alcohol, glycol, glycol ether, acetate ester, aliphatic hydrocarbon, chlorinated aliphatic hydrocarbon, aromatic hydrocarbon, or a chlorinated aromatic hydrocarbon solvent, preferably a (C₁-C₅)alkyl alcohol, (C₂-C₈)alkylene glycol, (C₃-C₁₀)alkylene glycol ether, (C₆)aromatic hydrocarbon, (C₁-C₂)alkyl-substituted aromatic hydrocarbon, chloro-substituted (C₆)aromatic hydrocarbon, chlorosubstituted (C₁-C₂)alkyl-substituted aromatic hydrocarbon, (C₆-C₈)alkane, chloro-substituted (C₁-C₃)alkane, and (C₁-C₄)alkyl ester of acetic acid, and more preferably ethylene glycol, propylene glycol, 1,3-butanediol, dipropylene glycol, ethylene glycol butyl ether, toluene, monochlorobenzene, heptane, dichloromethane, 1,2-dichloroethane, ethyl acetate, or butyl acetate.
3. Process according to claim 1 or 2 wherein the head space above the solution or suspension of isothiazolone salt is monitored during the reaction so as to determine when a sufficient amount of

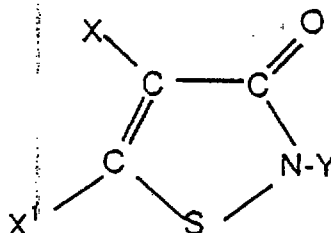


ammonia has been added.

4. Process according to any preceding claim wherein said ammonia is added in an amount sufficient to neutralize said salt, and preferably addition of excess ammonia beyond that which is necessary to neutralize said salt is avoided.
5. Process according to any one of claims 1 to 3 wherein less than a stoichiometric amount of ammonia is reacted with said salt so as to incompletely neutralize said salt, and the free base isothiazolone resulting therefrom removed before the addition of further ammonia to neutralize the remaining salt.
6. Process according to any preceding claim wherein the Y substituent is (C₁-C₈)alkyl, preferably methyl or n-octyl; X is H; and X' is H or Cl.
7. Process according to Claim 6 wherein said resultant free base isothiazolone is a mixture of 5-chloro-2-methyl-3-isothiazolone and 2-methyl-3-isothiazolone preferably in a ratio of from 92:8 to 3:97.
8. Process according to any preceding Claim wherein said free base isothiazolone contains less than 0.5%, preferably less than 0.1% (NH₄)_mZ based on weight of isothiazolone.
9. Process according to any preceding Claim wherein said resultant free base isothiazolone contains less than 0.1% water.

Patentansprüche

1. Verfahren zum Herstellen eines 3-Isothiazolons der Formel



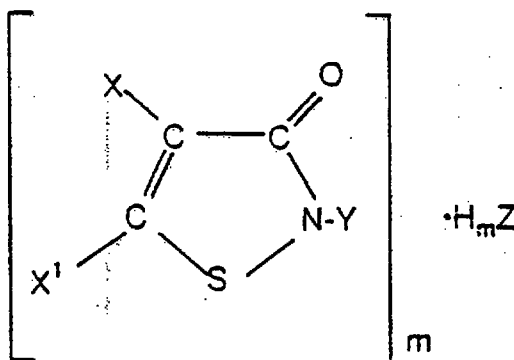
In der

Y Alkyl mit 1-10 Kohlenstoffatomen, gegebenenfalls substituiert, vorzugsweise mit Halogen oder (C₁-C₂)-Alkoxy; nicht substituiertes oder mit Halogen substituiertes Alkenyl oder Alkynyl mit 2-10 Kohlenstoffatomen oder Aralkyl oder mit Halogen, (C₁-C₂)-Alkyl oder (C₁-C₂)-Alkoxy substituiertes Aralkyl mit bis zu 10 Kohlenstoffatomen ist,

X Wasserstoff oder eine (C₁-C₂)-Alkylgruppe ist, und

X' Wasserstoff, Chlor oder (C₁-C₂)-Alkyl ist, durch

(a) Umsetzen von wasserfreiem Ammoniak mit einem Isothiazolonsalz der Formel





in der

Z Chlor, Brom, Sulfat oder Fluorsulfonat, vorzugsweise Chlor oder Brom, ist, m ist 1, wenn Z Chlor, Brom oder Fluorsulfonat ist, und m ist 2, wenn Z Sulfat ist, wobei das Isothiazolon in einem organischen Lösemittel gelöst oder suspendiert ist und das Lösemittel so ausgewählt ist, daß das $(\text{NH}_4)_m\text{Z}$ im wesentlichen darin unlöslich und die freie Isothiazolonbase im wesentlichen darin löslich ist, und

(b) Abtrennen des erhaltenen $(\text{NH}_4)_m\text{Z}$ von der erhaltenen freien Isothiazolonbase.

2. Verfahren nach Anspruch 1,
dadurch gekennzeichnet,

daß das Lösemittel ein Alkohol, Glycol, Glycolether, Acetatester, aliphatischer Kohlenwasserstoff, chlorierter aliphatischer Kohlenwasserstoff, aromatischer Kohlenwasserstoff oder ein chloriertes aromatisches Kohlenwasserstofflösemittel ist, vorzugsweise ein $(\text{C}_1 - \text{C}_5)$ -Alkylalkohol, $(\text{C}_2 - \text{C}_8)$ -Alkylenglycol, $(\text{C}_3 - \text{C}_{10})$ -Alkylenglycolether, (C_6) -aromatischer Kohlenwasserstoff, $(\text{C}_1 - \text{C}_2)$ -alkylsubstituierter aromatischer Kohlenwasserstoff, chloresubstituierter (C_6) -aromatischer Kohlenwasserstoff, chloresubstituierter $(\text{C}_1 - \text{C}_2)$ -alkylsubstituierter aromatischer Kohlenwasserstoff, $(\text{C}_6 - \text{C}_8)$ -Alkan, chloresubstituiertes $(\text{C}_1 - \text{C}_3)$ -Alkan und $(\text{C}_1 - \text{C}_4)$ -Alkylester von Essigsäure und, ganz besonders bevorzugt, Ethylenglycol, Propylenglycol, 1,3-Butandiol, Dipropylenglycol, Ethylenglycolbutylether, Toluol, Monochlorbenzol, Heptan, Dichlormethan, 1-2-Dichlorethan, Ethylacetat oder Butylacetat ist.

3. Verfahren nach Anspruch 1 oder 2,
dadurch gekennzeichnet,

daß der Kopfraum über der Lösung oder Suspension des Isothiazolonsalzes während der Reaktion überwacht wird, um festzustellen, wann eine ausreichende Menge Ammoniak zugesetzt wurde.

4. Verfahren nach einem der vorstehenden Ansprüche,
dadurch gekennzeichnet,

daß das Ammoniak in einer zum Neutralisieren des Salzes ausreichenden Menge zugesetzt wird und vorzugsweise Zusatz von Überschuß Ammoniak über die zur Neutralisation des Salzes erforderliche Menge vermieden wird.

5. Verfahren nach einem der Ansprüche 1-3,
dadurch gekennzeichnet,

daß weniger als eine stöchiometrische Menge Ammoniak mit dem Salz umgesetzt wird, um das Salz unvollständig zu neutralisieren, und die erhaltene freie Isothiazolonbase vor der Zugabe weiteren Ammoniaks zum Neutralisieren des verbleibenden Salzes entfernt wird.

6. Verfahren nach einem der vorstehenden Ansprüche,
dadurch gekennzeichnet,

daß Y $(\text{C}_1 - \text{C}_8)$ -Alkyl, vorzugsweise Methyl oder n-Octyl ist, X Wasserstoff ist und X' Wasserstoff oder Chlor ist.

7. Verfahren nach Anspruch 6,
dadurch gekennzeichnet,

daß die erhaltene freie Isothiazolonbase eine Mischung von 5-Chlor-2-methyl-3-isothiazolon und 2-Methyl-3-isothiazolon, vorzugsweise in einem Verhältnis von 92:8 bis 3:97, ist.

8. Verfahren nach einem der vorstehenden Ansprüche,
dadurch gekennzeichnet,

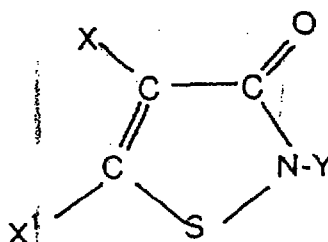
daß die freie Isothiazolonbase weniger als 0,5 %, vorzugsweise weniger als 0,1 %, $(\text{NH}_4)_m\text{Z}$, bezogen auf Gewicht des Isothiazolons, enthält.

9. Verfahren nach einem der vorstehenden Ansprüche,
dadurch gekennzeichnet,

daß die erhaltene freie Isothiazolonbase weniger als 0,1 % Wasser enthält.



1. Procédé de préparation d'une 3-isothiazolone de formule

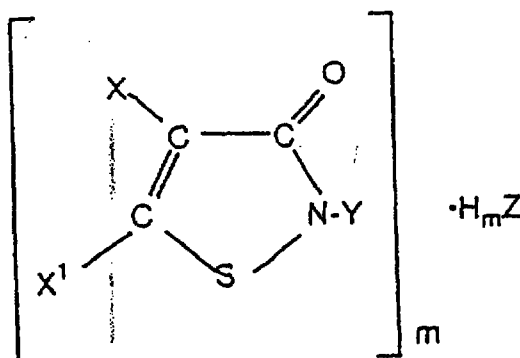


dans laquelle Y est un groupe alkyle de 1 à 10 atomes de carbone, éventuellement substitué, de préférence avec un atome d'halogène ou un groupe alcoxy(en C₁-C₂); un groupe alcényle ou alkynyle floh substitué ou substitué par un halogène de 2 à 10 atomes de carbone; ou un groupe aralkyle ou un groupe aralkyle substitué par un atome d'halogène, un groupe alkyle(en C₁-C₂), ou alcoxy(en C₁-C₂) ayant jusqu'à 10 atomes de carbone;

X est un atome d'hydrogène ou un groupe alkyle(en C₁-C₂);

et X₁ est un atome d'hydrogène, de chlore, ou un groupe alkyle(en C₁-C₂); comprenant les étapes consistant

(a) à faire réagir de l'ammoniac anhydre avec un sel d'isothiazolone de formule



dans laquelle Z est un atome de chlore, de brome, un sulfate ou un groupe fluorosulfonate, de préférence un atome de chlore ou de brome;

m vaut 1 lorsque Z est un atome de chlore, de brome ou un groupe fluorosulfonate, et m vaut 2 lorsque Z est un sulfate, isothiazolone qui est dissous ou mis en suspension dans un solvant organique, ledit solvant étant choisi de façon que (NH₄)_mZ y soit essentiellement insoluble et que l'isothiazolone sous forme de base libre y soit essentiellement soluble; et

(b) à séparer (NH₄)_mZ résultant de l'isothiazolone résultante sous forme de base libre.

2. Procédé selon la revendication 1, dans lequel ledit solvant est un alcool, un glycol, un glycoléther, un ester d'acétate, un hydrocarbure aliphatique, un hydrocarbure aliphatique chloré, un hydrocarbure aromatique, ou un solvant hydrocarboné aromatique chloré, de préférence un alcanol (en C₁-C₅), un alkylène(en C₂-C₈)glycol, un alkylène(en C₃-C₁₀)glycoléther, un hydrocarbure aromatique (en C₆), un hydrocarbure aromatique substitué par un alkyle (en C₁-C₂), un hydrocarbure aromatique (en C₆) substitué par un chlore, un hydrocarbure aromatique substitué par un alkyle (en C₁-C₂) substitué par un chlore, un alcane (en C₆-C₈), un alcane (en C₁-C₃) substitué par un chlore, et un ester alkylque (en C₁-C₄) d'acide acétique, et de façon plus particulièrement préférée l'éthylèneglycol, le propylène-glycol, le 1,3-butanediol, le dipropylèneglycol, l'éther butylique d'éthylèneglycol, le toluène, le monochlorobenzène, l'heptane, le dichlorométhane, le 1,2-dichloroéthane, l'acétate d'éthyle ou l'acétate de butyle.

3. Procédé selon la revendication 1 au 2, dans lequel l'espace libre de réservoir au-dessus de la solution ou de la suspension du sel d'isothiazolone est surveillé au cours de la réaction de façon à déterminer le moment où l'on a ajouté une quantité suffisante d'ammoniac.



4. Procédé selon l'une quelconque des revendications précédentes, dans lequel on ajoute l'ammoniac en une quantité suffisante pour neutraliser ledit sel, et de préférence l'addition d'un excès d'ammoniac au delà de ce qui est nécessaire pour neutraliser ledit sel est à éviter.
5. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel on fait réagir moins d'une quantité stoechiométrique d'aminoniac avec ledit sel de façon à neutraliser incomplètement ledit sel, et on élimine l'isothiazolone sous forme de base libre résultante avant l'addition d'ammoniac supplémentaire pour neutraliser le sel restant.
6. Procédé selon l'une quelconque des revendications précédentes dans lequel le substituant Y est un groupe alkyle (en C₁-C₈), de préférence un groupe méthyle ou n-octyle; X est un atome d'hydrogène; et X' est un atome d'hydrogène ou de chlore.
7. Procédé selon la revendication 6, dans lequel ladite isothiazolone résultante sous forme de base libre est un mélange de 5-chloro-2-méthyl-3-isothiazolone et de 2-méthyl-3-isothiazolone de préférence selon un rapport de 92:8 à 3:97.
8. Procédé selon l'une quelconque des revendications précédentes dans lequel ladite isothiazolone sous forme de base libre contient moins de 0,5%, de préférence moins de 0,1% de (NH₄)_mZ par rapport au poids d'isothiazolone.
9. Procédé selon l'une quelconque des revendications précédentes, dans lequel ladite isothiazolone résultante sous forme de base libre contient moins de 0,1% d'eau.