

Description

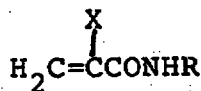
This invention is concerned with a process for preparing certain N-substituted-3-mercaptopropionamides which can be converted to biocidally active isothiazolones.

Procedures are already known for preparing N-substituted 3-mercaptopropionamides. One procedure involving two steps is disclosed by Bauer, Ludmig and Welsh, Thomas L., Addition of Thiourea to Acrylonitriles and Acrylamides, J. Org. Chem 26, p. 1443, 1444, 1445.

US-A-2448991 discloses a process for preparing N-substituted-3-mercaptopropionamides in which an alkyl alcohol is treated with acid, and then acrylonitrile added to the resulting mixture at an elevated temperature. This procedure has certain drawbacks in that the resulting reaction is very exothermic, leading to increasing side reactions and a relatively low yield.

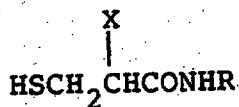
GB-A-2103216 discloses a process in which a nitrile and alcohol are fed to a heel of sulphuric acid, the ratio of acid to nitrile being from 1:1 to 2:1. This particular method results in a large number of side reactions due to the large excess of acid, causing percentage yields to decrease as the quantity of reactants is increased. Thus the method has little commercial value.

The process of the present invention, while still proceeding in two steps, is carried out in a single reaction vessel. The first step involves treating optionally substituted acrylonitrile with alcohol (or its equivalent) and strong inorganic acid; optionally a solvent may also be employed. When solvents are employed, they may be selected from inert or substantially inert organic solvents including halobenzenes, glacial acetic acid or primary alcohols. The mole ratio of nitrile to alcohol may be from about 0.8 to about 1.2 and the mole ratio of strong inorganic acid to unsaturated nitrile may be from about 1.5 to about 3.0. The reaction may be conducted at a temperature from above the freezing point of the reaction mixture to below the boiling point of the lowest boiling component for a period of time of from about 1 to about 24 hours to yield a compound of the formula:



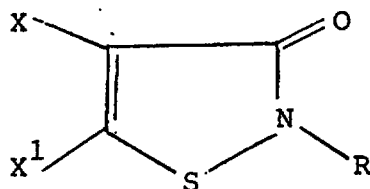
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wherein R is an unsubstituted or substituted secondary or tertiary alkyl or aralkyl and X is hydrogen, alkyl, such as C₁-C₅alkyl and the like, alkenyl such as C₂-C₆alkenyl and the like, aryl such as phenyl, phenylalkyl and the like, or chlorine. The second step of the invention comprising treating the acrylamide (I, supra) with a thiolating agent in the presence of substantially inert organic solvent and acid catalyst for from about 0.5 to about 3 hours at a temperature of from about 0° to about 70° C wherein the mole ratio of the thiolating agent to acrylamide is from about 0.9 to about 1.2 followed by treating the reaction mixture with a neutralizing amount of strong or weak base at a temperature of from about 0° to about 70° C for from about 0.5 to about 3 hours to afford N-substituted 3-mercaptopropionamide (II, infra) of the formula:



II

wherein X and R are as defined above, which may be isolated or halogenated to afford the desired biocidally active isothiazolone of the formula:



III

wherein X and R are as defined above and X¹ is hydrogen or halo.

The present invention overcomes the problem that N-cyclohexyl-3-mercaptopropionamide could not be prepared by presently employed procedures for preparing commercial biocides.

The preparation of two of the most important commercial isothiazolone biocides proceeds through appropriately substituted mercaptopropionamides. However, all attempts to use a similar procedure to prepare a cycloalkyl substituted mercaptopropionamide were unsuccessful.

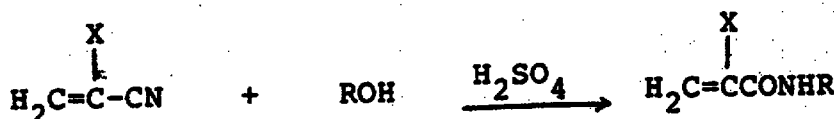
The procedure has the following advantages:

- Low raw material cost;
- Low operating cost;
- An all liquid process; and
- Nitrosamine precursor free.

The key to the process lies in cofeeding the sulfuric acid and premixed nitrile/alcohol.

STEP 1

Amide Formation



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wherein X and R are as defined above.

Nitriles that are suitable for this preparation are those wherein X is hydrogen, alkyl (acyclic or cyclic) such as methyl, ethyl, propyl, butyl, pentyl, cyclopentyl, cyclohexyl and the like, or unsubstituted or substituted aryl for example phenyl or phenyl substituted with one or more dialkyl, halo, nitro, alkoxycarbonyl, alkoxy and the like, or chlorine, and R is secondary or tertiary alkyl such as isopropyl, cyclopentyl, cyclohexyl, tert-butyl, 2-methyl-2-butyl, or substituted or unsubstituted benzyl wherein the substituent is one or more alkyl, halo, nitro, alkoxycarbonyl, alkoxy and the like. (Any olefins corresponding to dehydration of ROH, for example the dehydration of cyclohexanol to form cyclohexene or otherwise able to form a stable carbonium ion may also be used.) Inorganic acids which may be employed include sulfuric, p-toluic, hydrochloric, phosphoric, perchloric and the like. Sulfuric acid is the preferred inorganic acid. The acid which may be used should have a concentration in the range of from 50 to 100% and, preferably in the range of from about 96 to about 99.5%. The reaction can be carried out neat or in a solvent such as inert organic solvents including halobenzene and the like, or glacial acetic acid or primary alcohols such as methanol, ethanol and the like.

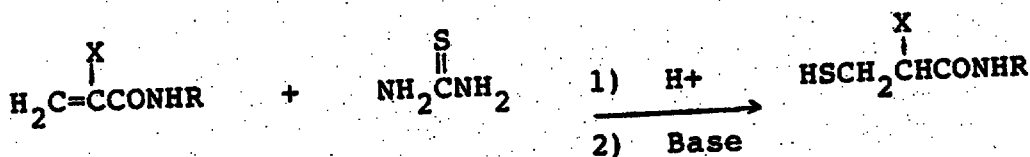
In a preferred procedure, a premixed solution of nitrile and alcohol (or olefin) and concentrated sulfuric acid are added concurrently to a heel of solvent or sulfuric acid at temperatures ranging from about 0° to about 65° C. The mole ratio of nitrile to alcohol is in the range of from about 0.8 to about 1.2 and preferably 1.0. The mole ratio of sulfuric acid to nitrile (or alcohol) is in the range of from about 1.5 to about 3.0 and, preferably, 2.0. The temperature at which the reactants are mixed is dependent on the substrate nature, and

is preferably above the freezing point of the reaction mixture and below the boiling point of the lowest boiling component. The whole mixture is then held at room temperature or some elevated temperature for from 1 to 24 hours. The organic solvent used for the entire process is then added to the above mixture followed by slow addition of water to produce the desired amide in the organic solvent. This mixture is

ready for the second step (thiolation) without any further isolation or purification.
The only by-products from this procedure we have detected are hydrolyzed forms of the nitrile such as the amide and acid in about 0.2% weight of the total product mixture. Their existence at such small levels has not interfered with the thiolation step.

STEP 2

Thiolation of Amide



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II

The amide, (I) produced in the previous step is directly treated with a thiolating agent selected from thiourea, carbon disulfide/sodium sulfide, hydrogen sulfide and the like in the same pot and the mixture is allowed to react at a temperature in the range of from about 0° to about 70° C for about 30 minutes to about 3 hours. The mole ratio of thiourea to the starting alcohol or nitrile is conveniently in the range of from about 0.9 to about 1.2 and, is preferably 1.05. The thiolation is catalyzed by strong acid such as hydrochloric, sulfuric, perchloric, p-toluenesulfonic acid and the like. Hydrochloric and sulfuric acids are preferable because they are cheaper and may give better yields. The above mixture is then treated with enough base to completely neutralize the mixture at a temperature in the range of from about 0° to about 70° C for from 30 minutes to 3 hours. (Excess base should be avoided as it destroys the mercaptoamide.) Bases that can be employed includes sodium hydroxide, ammonium hydroxide, sodium carbonate, sodium bicarbonate, alkaline earth oxides, ammonia and the like. Hydrolysis with base can be done at lower temperature and brought to higher temperature for hold, or it can be effected and held at a certain chosen temperature. After hydrolysis, the mercaptoamide solution in the specified organic solvent is dried, preferably by azeotropic removal of water employing those solvents which can form azeotropes with water for example chloroform, heptane, toluene and the like. Drying of the mercaptoamide solution is necessary as a small quantity of water can substantially lower the yield of the subsequent halogenation reaction. Other thiolating agents such as sodium sulfide, sodium hydrosulfide with combination of carbon disulfide are suitable for thiolating acrylamide (I). Typically, carbon disulfide is added to a solution of sodium sulfide at a molar ratio of 1.5 to 1.0 in methanol and water at temperatures ranging from 0° C to 30° C. Acrylamide or its solution in an inert solvent as defined earlier is added to the above mixture at 20°-50° C. The resulting mixture is then hydrolyzed with mineral acid preferably hydrochloric or sulfuric acid. Upon layer separation and solvent removal, the mercaptoamide obtained is thus formulated into an appropriate solvent for the subsequent halogenation, especially chlorination. A suitable halogenation reaction has been previously described in U.S. Patent No. 4,105,431.

The following examples illustrate this invention.

Example 1 - N-Cyclohexyl-3-mercaptopropionamide

Step A - N-Cyclohexylacrylamide

Sulfuric acid (46.0 g) was placed in a 3-liter 3-neck flask and heated to 45° C. A mixture of acrylonitrile

(94.5g) and cyclohexanol (180.2g) was prepared and added to the flask simultaneously with additional sulfuric acid (95.8%, 322.3 g) keeping the temperature at 45° - 55° C. At the end of the addition, the brown solution was heated to 60° C for 3 hours. The mixture was then poured into 3 liters of ice water with constant stirring. The white precipitate formed was filtered, washed with water until filtrate is no longer acidic and dried in a vacuum oven at 55° C to yield N-cyclohexylacrylamide (242.4 g, 88%); m.p. 109° - 110° C.

Step B - N-Cyclohexyl-3-mercaptopropionamide

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A mixture of N-cyclohexylacrylamide (15.3 g), concentrated hydrochloric acid (19.4 g, 37.6%), thiourea (7.6 g) and water (10 g) was heated to 60° C for 2 hours, cooled to 20° C and sodium hydroxide (50%, 16 g) was slowly added under nitrogen keeping the temperature below 30° C. The resulting mixture was heated to 60° C for 1 hour and extracted with methylene chloride (2 x 50 ml). Removal of the solvent afforded N-cyclohexyl-3-mercaptopropionamide (16.9 g) which was purified by vacuum distillation at 0.05 mm and 130° C to yield 13.7 g of N-cyclohexyl-3-mercaptopropionamide; m.p. 73.5° - 75.5° C.

Example 2 - N-Cyclohexyl-3-mercaptopropionamide

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A pre-mix of acrylonitrile/cyclohexanol (13.3 g/ 25.1 g) and concentrated sulfuric acid (51.1 g) were added through two addition funnels into a flask containing chlorobenzene (60 g) at 45° - 55° C. The mixture was then heated to 60° - 70° C for 3 - 5 hours and cooled to 20° C when water (150 g) was added slowly. After 30 minutes stirring, thiourea (19 g) was added and the mixture brought to 60° C for 1 hour. On cooling to 20° C, caustic (50%, 80 g) was added between 20° - 60° C under nitrogen and held at 80° C for 1 hour. The organic layer was separated and washed with warm water to yield 33.9 g of N-cyclohexyl-3-mercaptopropionamide in chlorobenzene (72.4% yield).

Example 3 - N-Cyclohexyl-3-mercaptopropionamide

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Carbon disulfide (76 g) was added to a mixture of sodium sulfide (55 g) in methanol (80 g) and water (80 g) and kept at 20° C. To this was slowly added N-cyclohexylacrylamide (110 g) maintaining the pot temperature at 20° - 30° C. The resulting solution was stirred for an additional 2 - 3 hour and neutralized with concentrated hydrochloric acid. The organic layer was separated, washed with water and evaporated to dryness to afford 122.6 g of N-cyclohexyl-3-mercaptopropionamide (90.5% yield).

Preparation of Other Amides

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Example 4 - N-Tert-butylacrylamide

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To a solution of acrylonitrile (5.3 g), tertbutyl alcohol (7.4 g) and acetic acid (50 ml), cooled in an ice-bath, was added dropwise concentrated sulfuric acid (10.1 g, 97%) at a temperature below 40° C. The mixture was held at 40° C for 1 hour and then poured into 200 g of ice water with constant stirring. The precipitate was filtered, washed with water and dried to afford N-tert-butylacrylamide (10.3 g, 82.4%); m.p. 124° - 6° C.

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Example 5 - N-(2-Methyl-2-butyl)methacrylamide

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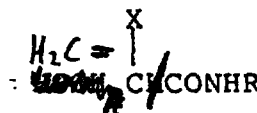
2-Methyl-2-butene (7.0 g) was added to a stirred mixture of methacrylonitrile (6.7 g) in acetic acid (50 ml) and concentrated sulfuric acid (10 g) at 10° to 20° C. The mixture was allowed to stand overnight at room temperature, and then poured into 200 g of water and extracted with methylene chloride (2 x 100 ml). The methylene chloride solution was dried over sodium sulfate, the solid filtered off and the methylene chloride evaporated to afford an oily product. Distillation of the product at 10 mm yielded N-(2-methyl-2-butyl)methacrylamide (10.1 g, 65%); bp 84° C.

Preparation of IsothiazolonesExample 6 - 4,5-Dichloro-N-cyclohexylisothiazolone

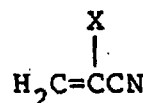
A 45% solution (100 g) of N-cyclohexyl-3-mercaptopropionamide in chlorobenzene was fed into a reactor containing a small heel of the same solvent concurrently with chlorine. (The molar feed ratio of chlorine to propionamide ranges from 3.0 to 3.6). The temperature was kept at 40° - 70° C during the chlorination. After the end of propionamide feed, the remaining chlorine to make up to 4.0 equivalents was charged at the same temperature. The mixture was held for 30 minutes, washed with water, 80 to 85% solvent of the solvent removed and the crude material was recrystallized from acetone/water to afford 36.0 g of white crystals of 4, 5-dichloro-N-cyclohexylisothiazolone (59.5% yield); m.p. 115 - 116° C.

Claims

1. A process for preparing a compound of the formula:

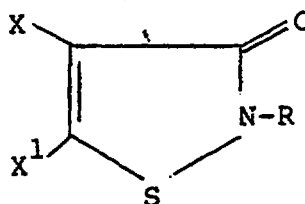


wherein X is hydrogen, alkyl, alkenyl, aryl or chlorine and R is an unsubstituted or substituted secondary alkyl, tertiary alkyl or aralkyl in which (a) a mixture of a compound of the formula:

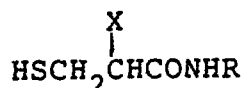


wherein X is as defined above and an alcohol (ROH) or its equivalent and (b) a strong inorganic acid are cofed optionally to an appropriate solvent.

2. A process for preparing an isothiazolone of the formula:



or an amide of the formula:



wherein X¹ is hydrogen or halo;

X is hydrogen, alkyl, alkenyl, aryl or chlorine and

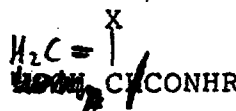
R is an unsubstituted or substituted secondary alkyl, tertiary alkyl or aralkyl, which comprises 1) performing the process of claim 1 to prepare an amide of the formula:

Preparation of IsothiazolonesExample 6 - 4,5-Dichloro-N-cyclohexylisothiazolone

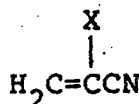
A 45% solution (100 g) of N-cyclohexyl-3-mercaptopropionamide in chlorobenzene was fed into a reactor containing a small heel of the same solvent concurrently with chlorine. (The molar feed ratio of chlorine to propionamide ranges from 3.0 to 3.6). The temperature was kept at 40° - 70° C during the chlorination. After the end of propionamide feed, the remaining chlorine to make up to 4.0 equivalents was charged at the same temperature. The mixture was held for 30 minutes, washed with water, 80 to 85% solvent of the solvent removed and the crude material was recrystallized from acetone/water to afford 36.0 g of white crystals of 4, 5-dichloro-N-cyclohexylisothiazolone (59.5% yield); m.p. 115 - 116° C.

Claims

1. A process for preparing a compound of the formula:

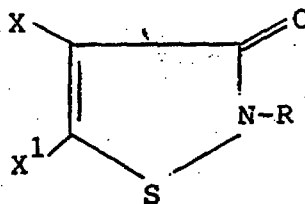


wherein X is hydrogen, alkyl, alkenyl, aryl or chlorine and R is an unsubstituted or substituted secondary alkyl, tertiary alkyl or aralkyl in which (a) a mixture of a compound of the formula:

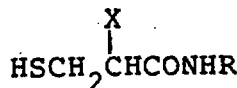


wherein X is as defined above and an alcohol (ROH) or its equivalent and (b) a strong inorganic acid are cofed optionally to an appropriate solvent.

2. A process for preparing an isothiazolone of the formula:



or an amide of the formula:

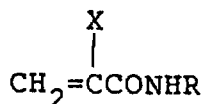


wherein X' is hydrogen or halo;

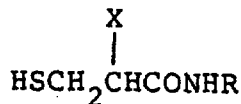
X is hydrogen, alkyl, alkenyl, aryl or chlorine and

R is an unsubstituted or substituted secondary alkyl, tertiary alkyl or aralkyl, which comprises 1) performing the process of claim 1 to prepare an amide of the formula:





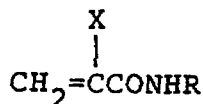
wherein X and R are as defined above, followed by (2) treatment of said amide with a thiolating agent to afford N-substituted-3-mercaptopropionamide of the formula:



wherein X and R are as defined above, optionally followed by (3) halogenation of said propionamide to afford the desired isothiazolone.

3. A process of claim 1 or 2 wherein the mole ratio of unsaturated nitrile to alcohol (or its equivalent) is from about 0.8 to about 1.2 and the mole ratio of strong inorganic acid to unsaturated nitrile is from about 1.5 to about 3.0.

4. A process of claim 2 or 3 wherein the mole ratio of thiolating agent to amide of the formula:

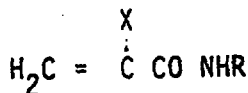


is from about 0.9 to about 1.2.

5. The process of any preceding claim wherein the inorganic acid is hydrochloric, p-toluic, perchloric or sulfuric acid having a concentration of 50 to 100%.
6. The process of claim 4 wherein the inorganic acid is sulfuric at a concentration of from about 96 to about 99.5%.
7. The process of any preceding claim wherein the alcohol is tert-butyl alcohol, iso-propyl alcohol, benzyl alcohol, and/or cyclohexanol.
8. The process of any of claims 2 to 7 wherein the thiolating agent is thiourea.
9. A process according to claim 2 for preparing 4,5-dichloro-N-cyclohexyl isothiazolone which comprises adding a mixture of acrylonitrile and cyclohexanol concurrently with concentrated sulfuric acid to either sulfuric acid or an organic solvent followed by treating the N-cyclohexylacrylamide with a thiolating agent selected from thiourea, carbon disulfide/sodium sulfide, hydrogen sulfide, followed by halogenation afford 4,5-dichloro-N-cyclohexylisothiazolone.

Revendications

1. Procédé de préparation d'un composé de formule:



(dans laquelle X représente un atome d'hydrogène, un groupe alkyle, alcényle, aryle ou un atome de chlore; et R représente un groupe alkyle secondaire, alkyle tertiaire ou aralkyle, non substitués ou

substitués), procédé dans lequel on introduit simultanément, éventuellement dans un solvant approprié (a) un mélange d'un composé de formule :



10 (dans laquelle X est tel que défini ci-dessus) et d'un alcool ROH, ou de son équivalent, et (b) un acide minéral fort.

2. Procédé de préparation d'une isothiazolone de formule:



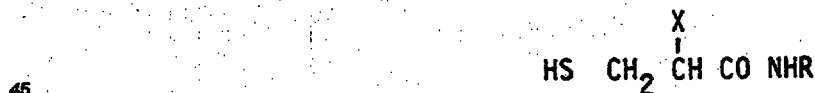
ou un amide de formule:



30 (formules dans lesquelles X' représente un atome d'hydrogène ou d'halogène ;
X représente un atome d'hydrogène, un groupe alkyle, alcényle ou aryle ou un atome de chlore; et
R représente un groupe alkyle secondaire, alkyle tertiaire ou aralkyle, substitués ou non substitués),
qui comprend (1) la mise en oeuvre du procédé de la revendication 1 pour préparer un amide de
formule



40 (dans laquelle X et R sont tels que définis ci-dessus), ce qui est suivi (2) du traitement dudit amide par
un agent de thiolation pour obtenir un 3-mercaptopropionamide substitué sur l'azote et de formule:

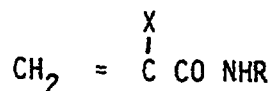


dans laquelle X et R sont tels que définis ci-dessus, ce qui est éventuellement suivi par (3) une
halogénéation dudit propionamide pour obtenir l'isothiazoline voulue.

50 3. Procédé selon la revendication 1 ou 2 , dans lequel le rapport molaire entre le nitrile insaturé et l'alcool
(ou son équivalent) est égal à environ 0,8 à environ 1,2 , et le rapport molaire entre l'acide minéral fort
et le nitrile insaturé est d'environ 1,5 à environ 3,0.

55 4. Procédé selon la revendication 2 ou 3 , dans lequel le rapport molaire entre l'agent de thiolation et
l'amide de formule:





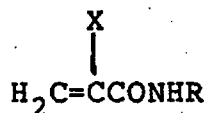
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est d'environ 0,9 à environ 1,2.

5. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'acide minéral est l'acide chlorhydrique, p-to -lrique, perchlorique ou sulfurique ayant une concentration de 50 à 100%.
- 10 6. Procédé selon la revendication 4, dans lequel l'acide minéral est l'acide sulfurique à une concentration d'environ 96 à environ 99,5 %.
7. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'alcool est l'alcool tert.-butylique, l'alcool isopropylique, l'alcool benzylique et/ou le cyclohexanol.
- 15 8. Procédé selon l'une quelconque des revendications 2 à 7, dans lequel l'agent de thiolation est la thiourée.
9. Procédé selon la revendication 2 pour préparer la 4,5-dichloro-N-cyclohexyl isothiazolone, qui comprend l'addition d'un mélange d'acrylonitrile et de cyclohexanol en même temps que de l'acide sulfurique concentré à de l'acide sulfurique ou à un solvant organique, puis le traitement du N-cyclohexylacrylamide par un agent de thiolation choisi parmi la thiourée, le sulfure de carbone/ sulfure de sodium, et l'hydrogène sulfuré, ce qui est suivi d'une halogénéation, pour obtenir la 4,5 - dichloro-N - cyclohexylisothiazolone.
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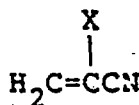
Ansprüche

- 30 1. Verfahren zur Herstellung einer Verbindung der Formel:



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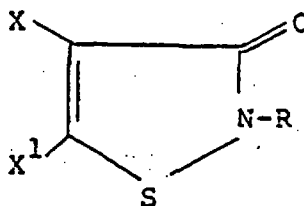
worin X Wasserstoff, Alkyl, Alkenyl, Aryl oder Chlor bedeutet und R unsubstituiertes oder substituiertes sekundäres Alkyl, tertiäres Alkyl oder Aralkyl ist, wobei (a) ein Gemisch einer Verbindung der Formel:



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- 45 worin x die oben angegebene Bedeutung hat und eines Alkohols (ROH) oder seines Äquivalentes und (b) einer starken anorganischen Säure zusammengebracht werden, gegebenenfalls mit einem geeigneten Lösungsmittel.

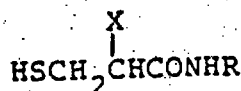
- 50 2. Verfahren zur Herstellung eines Isothiazolons der Formel:



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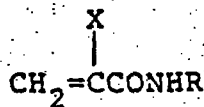
oder eines Amids der Formel:



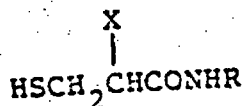
worin X¹ Wasserstoff oder Halogen bedeutet;

X Wasserstoff, Alkyl, Alkenyl, Aryl oder Chlor bedeutet, und

R ein unsubstituiertes oder substituiertes sekundäres Alkyl, tertiäres Alkyl oder Aralkyl ist, dadurch gekennzeichnet, daß man (1) das Verfahren nach Anspruch 1 durchführt, um ein Amid der Formel:



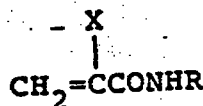
herzustellen, worin X und R die oben angegebenen Bedeutungen haben, und dann (2) dieses Amid mit einem Thiolierungsmittel behandelt um N-substituiertes-3-Mercaptopropionamid der Formel:



zu bilden, worin X und R die oben angegebenen Bedeutungen haben, gegebenenfalls gefolgt von (3) Halogenierung dieses Propionamids zur Bildung des gewünschten Isothiazolons.

3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das Molverhältnis von ungesättigtem Nitril zu Alkohol (oder seinem Äquivalent) etwa 0,8 bis etwa 1,2 und das Molverhältnis von starker anorganischer Säure zu ungesättigtem Nitril etwa 1,5 bis etwa 3,0 beträgt.

4. Verfahren nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß das Molverhältnis von Thiolierungsmittel zum Amid der Formel:



etwa 0,9 bis etwa 1,2 beträgt.

5. Verfahren nach irgendeinem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die anorganische Säure Salzsäure, p-Toluylsäure, Perchlorsäure oder Schwefelsäure mit einer Konzentration von 50 bis 100% ist.

6. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß die anorganische Säure Schwefelsäure mit einer Konzentration von etwa 96 bis etwa 99,5% ist.

7. Verfahren nach irgendeinem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Alkohol tert-Butylalkohol, Isopropylalkohol, Benzylalkohol und/oder Cyclohexanol ist.

8. Verfahren nach irgendeinem der Ansprüche 2 bis 7, dadurch gekennzeichnet, daß das Thiolierungsmittel Thiohamstoff ist.



9. Verfahren nach Anspruch 2 zur Herstellung von 4,5-Dichlor-N-cyclohexylisothiazolon, dadurch gekennzeichnet, daß man ein Gemisch von Acrylnitril und Cyclohexanol gleichzeitig mit konzentrierter Schwefelsäure zu entweder Schwefelsäure oder einem organischen Lösungsmittel zufügt und dann das N-Cyclohexylacrylamid mit einem Thiolierungsmittel aus der Gruppe Thioharnstoff, Schwefelkohlenstoff/Natriumsulfid, Schwefelwasserstoff, behandelt und dann zur Bildung von 4,5-Dichlor-N-cyclohexylisothiazolon halogeniert.

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