

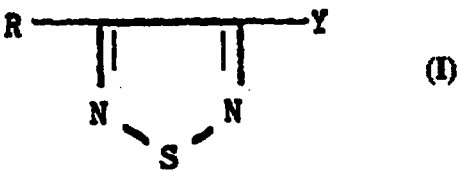
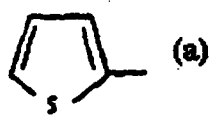
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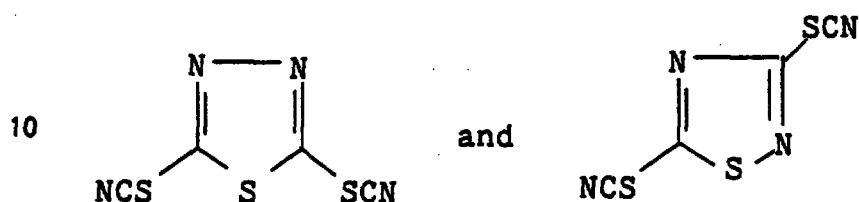
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(54) Title: SUBSTITUTED THIADIAZOLES, COMPOSITIONS CONTAINING THEM AND THEIR USE AS ANTIMICROBIAL AND MARINE ANTIFOULING AGENTS			
(57) Abstract The present invention is directed to compounds corresponding to formula (I), wherein R represents -Br, -Cl, -OCH₃, -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN, -SCH₂CH₂SCN, (a), (b) or (c); Y represents -Br, -Cl, -OCH₃, -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN or -SCH₂CH₂SCN; X represents -Br, -Cl, -F, -CH₃, -OCH₃, -COOCH₃, -NO₂, -SCH₃, -SO₂CH₃ or -CF₃ and n is an integer of from 0-5, with the proviso that at least one of R or Y represents -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN or -SCH₂CH₂SCN and with further proviso that when R is (a), (b) or (c) Y is -SCN or -SCH₂SCN. These compounds have been found to exhibit antimicrobial and marine antifouling activity in industrial and commercial applications.			
			
			
			
			

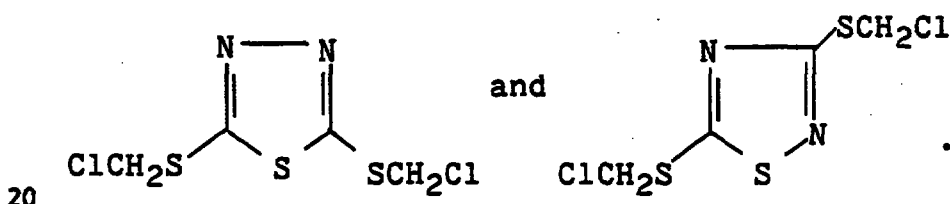
SUBSTITUTED THIADIAZOLES, COMPOSITIONS CONTAINING THEM AND THEIR USE AS ANTIMICROBIAL AND MARINE ANTIFOULING AGENTS

The present invention is directed to novel substituted thiadiazole compounds, compositions containing said compounds and the use of these compositions as antimicrobial and marine antifouling agents.

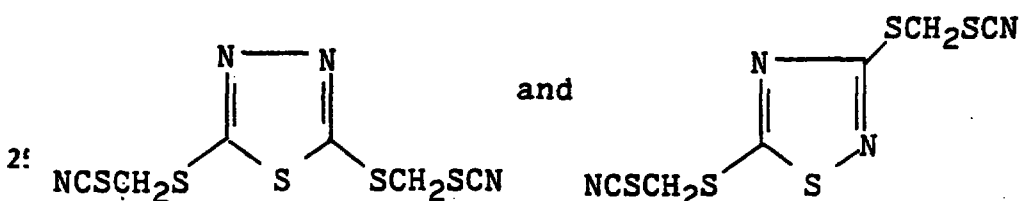
EP 0 433 616 A2 discloses antimicrobials for the control of bacteria and fungi and teaches the preparation of compounds of the formula :



U.S. Patent 4,094,880 discloses antimicrobials for the control of bacteria and fungi and the preparation and the antimicrobial use of 2,5-bis(chloromethylthio)-1,3,4-thiadiazole and its isomer 3,5-bis(chloromethylthio)-1,2,4-thiadiazole of compounds of the formula :



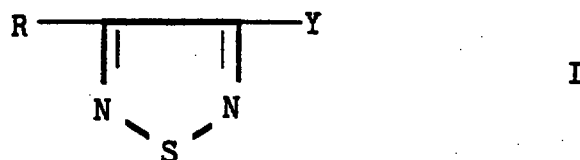
U.S. Patent 3,888,869 discloses the preparation of compounds of the formula :



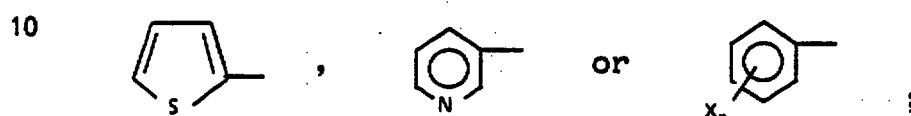
which compounds are useful as antimicrobials.

While the above compounds are somewhat active, it is still desirable to identify and/or discover new antimicrobial and/or marine antifoulant agents. Many of the known antimicrobial/marine antifoulant agents have been found to be of minimal value for several reasons; these include, but are not limited to, the problem created by microbe strains developing resistance to known agents, the occurrence of undesirable interactions of certain known agents with the medium or product in which the agent is used; and the high toxicity of certain known agents to certain non-target organisms, including mammals.

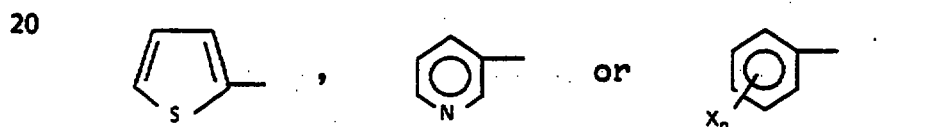
The present invention is directed to compounds corresponding to the formula :



wherein R represents -Br, -Cl, -OCH₃, -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN, -SCH₂CH₂SCN,



15 Y represents -Br, -Cl, -OCH₃, -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN or -SCH₂CH₂SCN; X represents -Br, -Cl, -F, -CH₃, -OCH₃, -COOCH₃, -NO₂, -SCH₃, -SO₂CH₃ or -CF₃ and n is an integer of from 0-5, with the proviso that at least one of R or Y represents -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN or -SCH₂CH₂SCN and with further proviso that when R is



25 Y is -SCN or -SCH₂SCN.

The present invention is also directed to antimicrobial compositions comprising an inert diluent and an antimicrobially-effective amount of a compound corresponding to Formula 1.

30 The present invention is further directed to a method for inhibiting microorganisms in a microbial habitat comprising contacting said microbial habitat with an antimicrobially-effective amount of a compound corresponding to Formula 1.

The antimicrobial compositions of the present invention can also be employed to treat surfaces exposed to a marine environment in which marine organisms grow to prevent the growth of said marine organisms on said surfaces.

35 The preferred compounds of the present invention include those wherein R represents -Cl, phenyl or -SCN when Y is -SCN; those wherein R represents -Cl, phenyl or -SCH₂SCN when Y is -SCH₂SCN and those wherein R represents -Cl or -SCH₂CH₂SCN when Y is -SCH₂CH₂SCN.

In the present specification and claims, the term "alkali metal" is employed to designate sodium, potassium, lithium or cesium.

In the present specification and claims, the term "halo" is employed to designate bromo, chloro, fluoro or iodo.

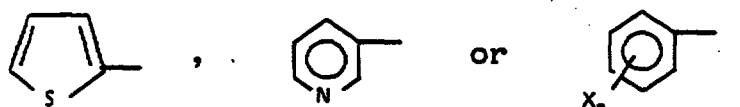
5 In the following process schematic formulas, certain specific alkali metals, that is, Na; halo groups, that is, Cl, and specific solvents are set forth within the depicted reactions. These specific representations are only presented for convenience and are not to be considered as an indication that these specific representations are the only groups or materials which can be employed. The reactions as set forth below and in the specific examples can all be carried
10 out at room temperature in the presence of conventional reaction mediums, such as for example, a 70 percent ethanol/30 percent water mixture.

In the present invention, it is to be noted that all substituent groups are sterically compatible with each other. The term "sterically compatible" is employed to designate substituent groups which are not affected by steric hindrance as this term is defined in "The
15 Condensed Chemical Dictionary", 7th edition, Reinhold Publishing Co., N.Y. page 893 (1966) which definition is as follows:

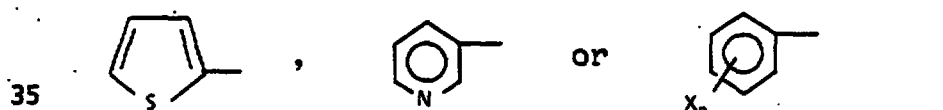
"steric hindrance. A characteristic of molecular structure in which the molecules have a spatial arrangement of their atoms such that a given reaction with another molecule is prevented or retarded in rate."

20 Sterically compatible may be further defined as reacting compounds having substituents whose physical bulk does not require confinement within volumes insufficient for the exercise of their normal behavior as discussed in Organic Chemistry by D. J. Cram and G. Hammond, 2nd edition, McGraw-Hill Book Company, N.Y., page 215 (1964).

The 1,2,5-thiadiazole compounds of the present invention, wherein R represents
25 halo and Y represents -SCN or R represents



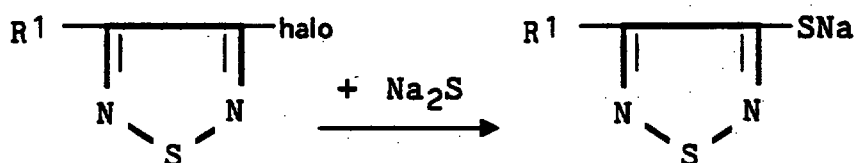
30 and Y represents -SCN or -SCH₂SCN may be prepared in a two-stage reaction procedure wherein in the first stage or step, a 4-(substituted)-3-halo-1,2,5-thiadiazole wherein the substitution set forth hereinafter as R¹ and which represents Br, -Cl,



is reacted in the presence of a solvent such as dimethylformamide, N-methylpyrrolidone, or

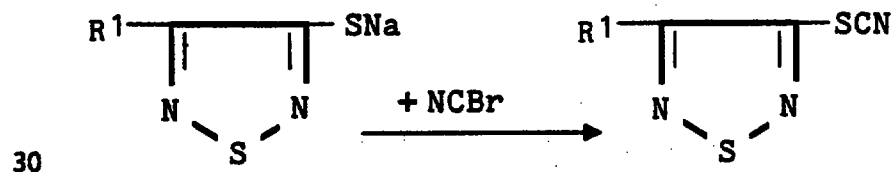
dimethylsulfoxide with an alkali metal sulfide, such as sodium sulfide to produce the corresponding 4-(substituted)-3-mercapto-1,2,5-thiadiazole: alkali metal salt.

The reactions are typically carried out at a temperature from 25 to 40°C. The reactants may be added to the reaction mixture in any order of addition; conventionally they are added as a solution in the solvent used for the reaction. The reaction is conveniently allowed to continue over a period from 1 to 24 hours. The reaction consumes the reactants in the ratio of one mole equivalent of the alkali metal sulfide per mole of the 4-(substituted)-3-halo-1,2,5-thiadiazole reactant. To assure the completion of the reaction, an excess of the alkali metal sulfide reactant is normally employed. The general scheme for this first reaction step is as follows:

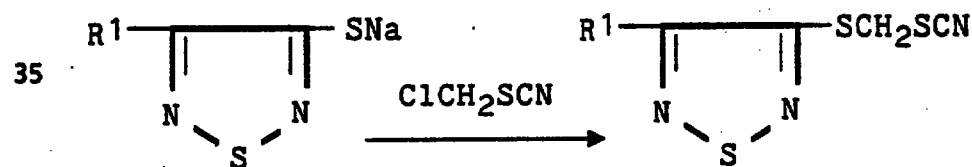


The above 4-(substituted)-3-(mercapto)-1,2,5-thiadiazole: alkali metal salt product is then reacted in situ with a cyanogen halide, such as cyanogen bromide to prepare the desired 4-(substituted)-3-thiocyanato-1,2,5-thiadiazole product or with a halomethylthiocyanate, such as chloromethylthiocyanate to prepare the desired 4-(substituted)-3-thiocyanatomethylthio-1,2,5-thiadiazole product. The reaction consumes the reactants in the ratio of one mole equivalent of the cyanogen halide or halomethylthiocyanate per mole of the 4-(substituted)-3-mercapto-1,2,5-thiadiazole: alkali metal salt reactant. To assure the completion of the reaction, a slight excess of the cyanogen halide or halomethylthiocyanate reactant is normally employed. The general reaction schemes (A and B) for this second step is as follows:

Reaction Scheme A

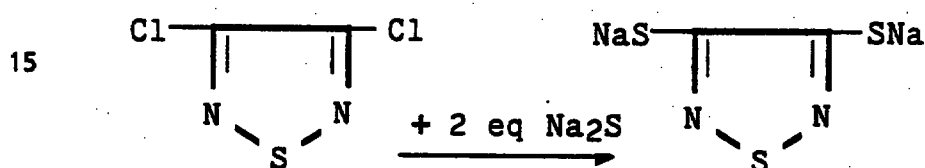


Reaction Scheme B



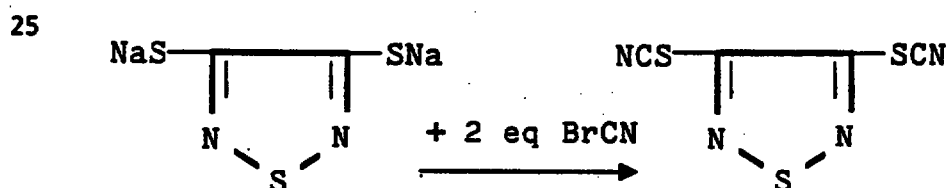
The above second stage reactions are typically carried out at a temperature from 25 to 40°C. The reactants may be added to the reaction mixture in any order of addition; conventionally they are added as a solution in the solvent used for the reaction. Subsequent to the addition of the reactants, the reaction is allowed to continue over a period of 1 to 24 hours. The reaction product may be isolated by adding a 3 to 10 volume excess of water which will precipitate the desired product. Filtration followed by washing and drying yields the desired compounds of the present invention.

The bis(thiocyanato)-1,2,5-thiadiazole compound of the present invention, wherein R and Y both represent -SCN, may be prepared by first reacting in the presence of a solvent an alkali metal sulfide, such as sodium sulfide, with a 4,5-dihalo-1,2,5-thiadiazole, such as 3,4-dichloro-1,2,5-thiadiazole, to produce a bis(mercapto)-1,2,5-thiadiazole: di(alkali metal) salt, such as the bis(mercapto)-1,2,5-thiadiazole: disodium salt. The general scheme for this first reaction step is as follows:



The desired bis(thiocyanato)-1,2,5-thiadiazole is then prepared by reacting the thus prepared bis(mercapto)-1,2,5-thiadiazole: di(alkali metal) salt with a cyanogen halide, such as cyanogen bromide. Two mole equivalents of the cyanogen halide are used per mole of the bis(mercapto)-1,2,5-thiadiazole, di(alkali metal) salt to prepare the bis(thiocyanato)-1,2,5-thiadiazole.

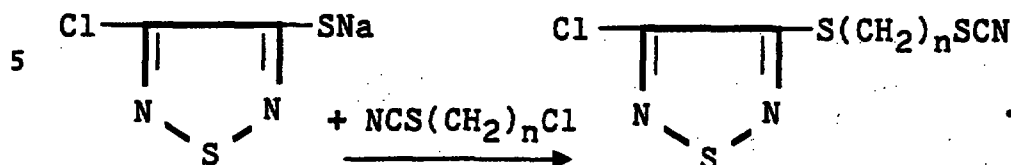
The general scheme for this second reaction step is as follows:



The halothiomethyl(or ethyl)thiocyanato-1,2,5-thiadiazole compounds of the present invention, wherein, for example, R represents -Cl or -Br and Y represents -SCH₂SCN or -SCH₂CH₂SCN, may be prepared by first preparing a (halomercapto)-1,2,5-thiadiazole, alkali metal salt, as described hereinabove. The halothiomethylthiocyanato-1,2,5-thiadiazole is then prepared by reacting the (halomercapto)-1,2,5-thiadiazole, alkali metal salt with a halomethyl(or ethyl)thiocyanate, such as chloromethylthiocyanate or chloroethylthiocyanate. One mole equivalent of the halomethyl(or ethyl)thiocyanate is used per mole of

(halomercapto)-1,2,5-thiadiazole: alkali metal salt to prepare the halothiomethyl(or ethyl)thiocyanato-1,2,5-thiadiazole.

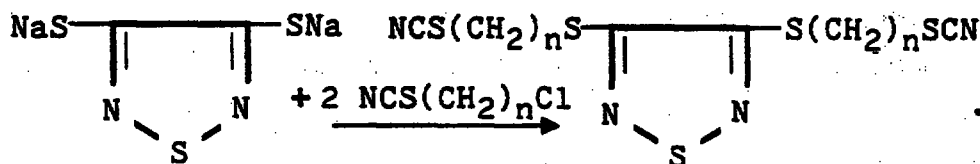
The general reaction scheme is as follows:



wherein n is 1 or 2.

10 The bis(thiomethyl(or thioethyl)thiocyanato-1,2,5-thiadiazole compounds of the present invention, wherein, for example, R and Y each represent $-SCH_2SCN$ or $-SCH_2CH_2SCN$, may be prepared by reacting a halomethyl(or ethyl)thiocyanate, such as chloromethylthiocyanate or chloroethylthiocyanate with a bis(mercapto)-1,2,5-thiadiazole: alkali metal salt (prepared as described hereinabove). Two mole equivalents of the
15 halomethyl(or ethyl)thiocyanate is used per mole of the bis(mercapto)-1,2,5-thiadiazole: alkali metal salt to prepare the desired bis(thiomethyl(or thioethyl)-thiocyanato-1,2,5-thiadiazole.

The general reaction scheme is as follows:

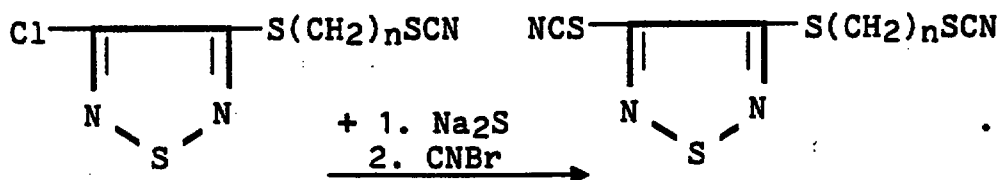


wherein n is 1 or 2.

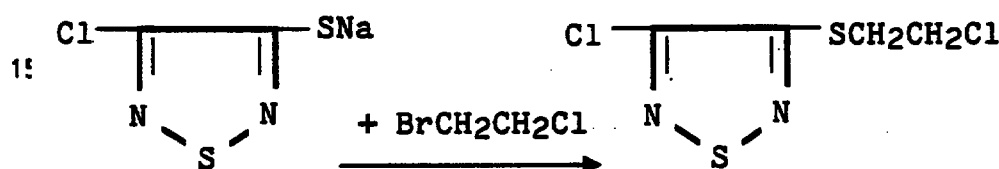
Preferably, the hereinabove depicted reactions are carried out in the presence of an inert solvent such as dimethylformamide, methanol, ethanol, acetonitrile, acetone, or pyridine. Preferably, the reactions are carried out at 0°C under an ambient pressure of inert gas. Subsequent to the addition of the appropriate reaction materials, the reaction mixture is allowed to stir at a temperature between 25°C to 60°C for a period between 2 to 24 hours in order to increase the reaction rate and promote extinction of the limiting reagent. Final work-up of the reaction mixture then provides the desired final product.

The thiadiazole compounds of the present invention, wherein R represents -SCN and Y represents -SCH₂SCN or -SCH₂CH₂SCN, may be prepared by first reacting a 4-halo-3-thiomethyl(or ethyl)thiocyanato-1,2,5-thiadiazole, as prepared hereinbefore, an alkali metal sulfide, such as sodium sulfide, followed by reacting the thus formed 4-mercapto-3-
35. -thiomethyl(or ethyl)thiocyanato-1,2,5-thiadiazole: alkali metal salt with a cyanogen halide, such as cyanogen bromide to form the desired 3-thiocyanato-4-thiomethyl(or

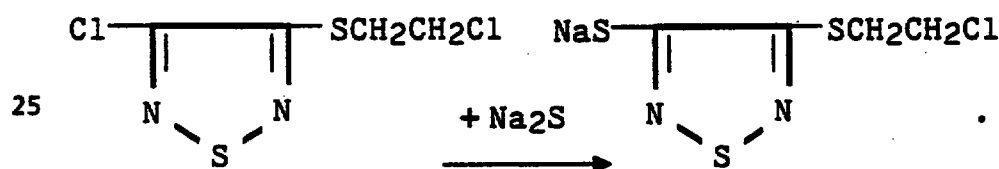
ethyl)thiocyanato-1,2,5-thiadiazole. In the above reactions, equimolar amounts of the reactants are normally employed. The general scheme for this reaction step is as follows:



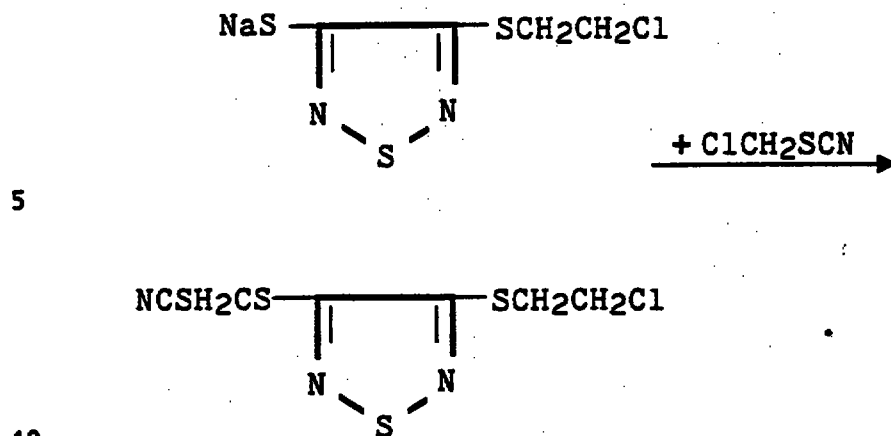
The thiadiazole compounds of the present invention, wherein R represents -SCH₂SCN and Y represents -SCH₂CH₂SCN, may be prepared by first reacting a 3-halo-4-mercapto-1,2,5-thiadiazole: alkali metal salt, as prepared hereinbefore, with a dihaloethane such as 1-bromo-2-chloroethane to produce a 4-halo-3-halothioethyl-1,2,5-thiadiazole such as 4-chloro-3-chlorothioethyl-1,2,5-thiadiazole. The general scheme for this reaction step is as follows:



The thus formed 4-halo-3-halothioethyl-1,2,5-thiadiazole is then reacted with an alkali metal sulfide, such as sodium sulfide, to produce the corresponding alkali metal salt, such as 4-mercapto-3-halothioethyl-1,2,5-thiadiazole: sodium salt. The general scheme for this reaction step is as follows:



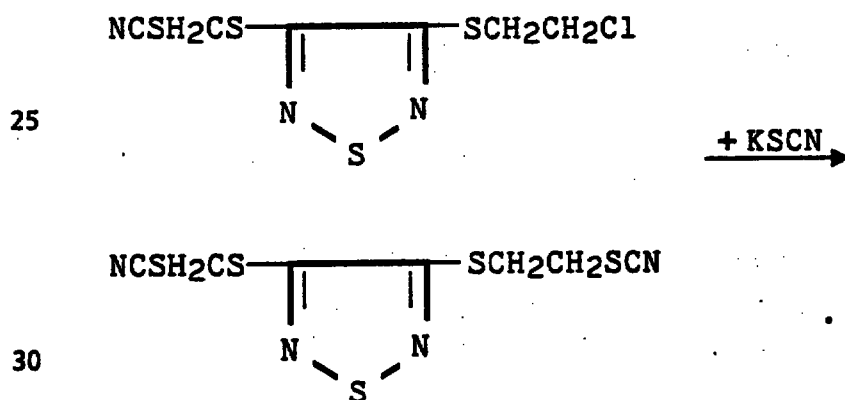
This product can, without separation and purification, be reacted with a halomethylthiocyanate, such as chloromethylthiocyanate to form a 3-halothioethyl-4-thiomethylthiocyanato-1,2,5-thiadiazole, such as 3-chlorothioethyl-4-thiomethylthiocyanato-1,2,5-thiadiazole. One mole equivalent of the halomethylthiocyanate reactant is used per mole of the 4-mercapto-3-halothioethyl-1,2,5-thiadiazole: alkali metal salt and such equimolar amounts of the reactants are normally employed. The general scheme for this reaction step is as follows:



The above 3-haloethioethyl-4-thiomethylthiocyanato-1,2,5-thiadiazole product is dissolved in a solvent such as acetone containing an alkali metal thiocyanate such as potassium thiocyanate and refluxed for a period of about 16 hours. The reaction mixture is filtered, and concentrated under reduced pressure and the residue treated by conventional procedures such as, chromatography over silica gel using hexane/ethyl acetate as eluent, to recover the desired 3-thioethylthiocyanato-4-thiomethylthiocyanatomethyl-1,2,5-thiadiazole. The reaction consumes the reactants in the ratio of one mole equivalent of the alkali metal thiocyanate per mole of the thiadiazole reactant and such equimolar amounts of the reactants are normally employed. However to ensure completion of the reaction, a slight excess, about 1.0-1.25 equivalents, of alkali metal thiocyanate is usually provided. The general scheme for this reaction step is as follows:

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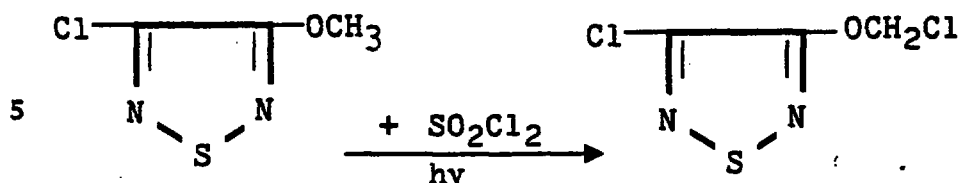
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The halothiocyanatomethyloxo-1,2,5-thiadiazole compounds of the present invention, wherein, for example, R represents -Cl or -Br and Y represents -OCH₂SCN, may be prepared by first irradiating a solution of 4-halo-3-methoxy-1,2,5-thiadiazole such as 4-chloro-3-methoxy-1,2,5-thiadiazole in carbon tetrachloride with a sunlamp while adding a solution of sulfur chloride in carbon tetrachloride. Upon completion of the reaction, the reaction mixture is washed with aqueous sodium bicarbonate and concentrated under reduced

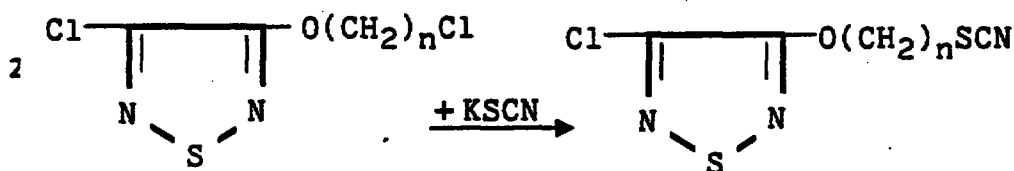
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pressure to yield 4-chloro-3-halomethoxy-1,2,5-thiadiazole. The general scheme for this first reaction step is as follows:

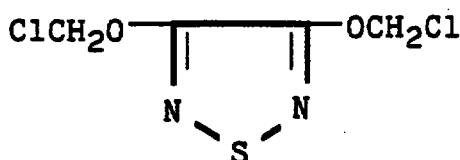
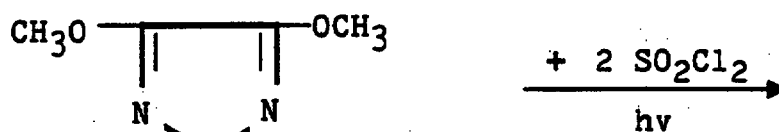


The above 4-chloro-3-halomethoxy-1,2,5-thiadiazole product is dissolved in a solvent such as acetone containing an alkali metal thiocyanate such as potassium thiocyanate and refluxed for a period of about 16 hours. The reaction mixture is filtered, and concentrated under reduced pressure and the residue treated by conventional procedures such as, chromatography over silica gel using hexane/ethyl acetate as eluent, to recover the desired halothiocyano-methoxy-1,2,5-thiadiazole. The reaction consumes the reactants in the ratio of one mole equivalent of the alkali metal thiocyanate per mole of the thiadiazole reactant and such equimolar amounts of the reactants are normally employed. However to ensure completion of the reaction, a slight excess, about 1.0-1.25 equivalents, of alkali metal thiocyanate is usually provided.

The general scheme for this second reaction step is as follows:

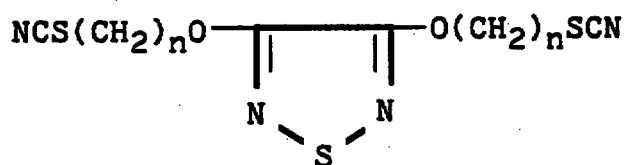
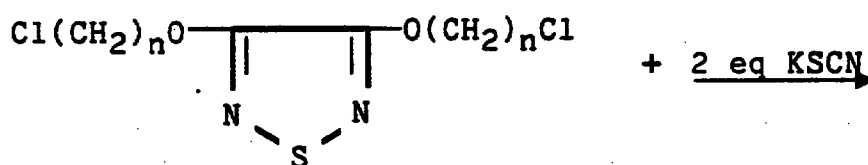


The bis(thiomethoxythiocyanato)-1,2,5-thiadiazole compounds of the present invention, wherein R and Y both represent $-\text{O}(\text{CH}_2)_n\text{SCN}$ and n is 1 or 2, may be prepared by first irradiating a solution of a bis(methoxy)-1,2,5-thiadiazole in carbon tetrachloride with a sunlamp while adding a solution of sulfur chloride in carbon tetrachloride. The reaction mixture is washed with aqueous sodium bicarbonate and concentrated under reduced pressure to yield bis(chloromethoxy)-1,2,5-thiadiazole. The general scheme for this first reaction step is as follows:



The above bis(chloromethoxy)-1,2,5-thiadiazole is dissolved in a solvent such as acetone containing an alkali metal thiocyanate such as potassium thiocyanate and refluxed for a period of about 16 hours. The reaction mixture is filtered, and concentrated under reduced pressure and the residue treated by conventional procedures such as, chromatography over silica gel using hexane/ethyl acetate as eluent, to recover the desired bis(thiomethoxythiocyanato)-1,2,5-thiadiazole compound. The reaction consumes the reactants in the ratio of two mole equivalents of the alkali metal thiocyanate per mole of the thiadiazole reactant and such amounts of the reactants are normally employed. However to ensure completion of the reaction, a slight excess, about 1.2-1.25 equivalents, of alkali metal thiocyanate is usually provided.

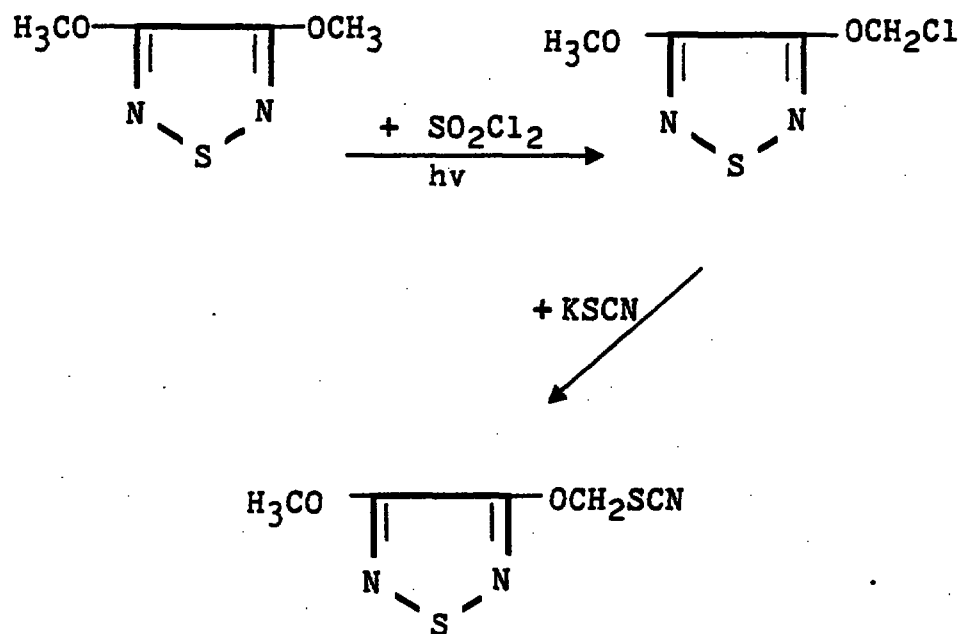
The general reaction scheme for this reaction is as follows:



The 4-methoxy-3-thiocyanatomethoxy-1,2,5-thiadiazole compound of the present invention, that is, wherein R represents -OCH₃ and Y represents -OCH₂SCN may be prepared by first irradiating a solution of a bis(methoxy)-1,2,5-thiadiazole in carbon tetrachloride with a sunlamp while adding a solution of sulfuryl chloride in carbon tetrachloride. Upon completion of the reaction, the reaction mixture is washed with aqueous sodium bicarbonate and concentrated under reduced pressure to yield 4-methoxy-3-halomethoxy-1,2,5-thiadiazole. This product is then dissolved in a solvent such as acetone containing an alkali metal thiocyanate such as potassium thiocyanate and refluxed for a period

of about 16 hours. The reaction mixture is filtered, and concentrated under reduced pressure and the residue treated by conventional procedures such as, chromatography over silica gel using hexane/ethyl acetate as eluent, to recover the desired 4-methoxy-3-

5 -thiocyanatomethyloxo-1,2,5-thiadiazole. The reaction consumes the reactants in the ratio of one mole equivalent of the alkali metal thiocyanate per mole of the thiadiazole reactant and such equimolar amounts of the reactants are normally employed. However to ensure completion of the reaction, a slight excess, about 1.0-1.25 equivalents, of alkali metal thiocyanate is usually provided. The general scheme for these reaction steps are as follows:

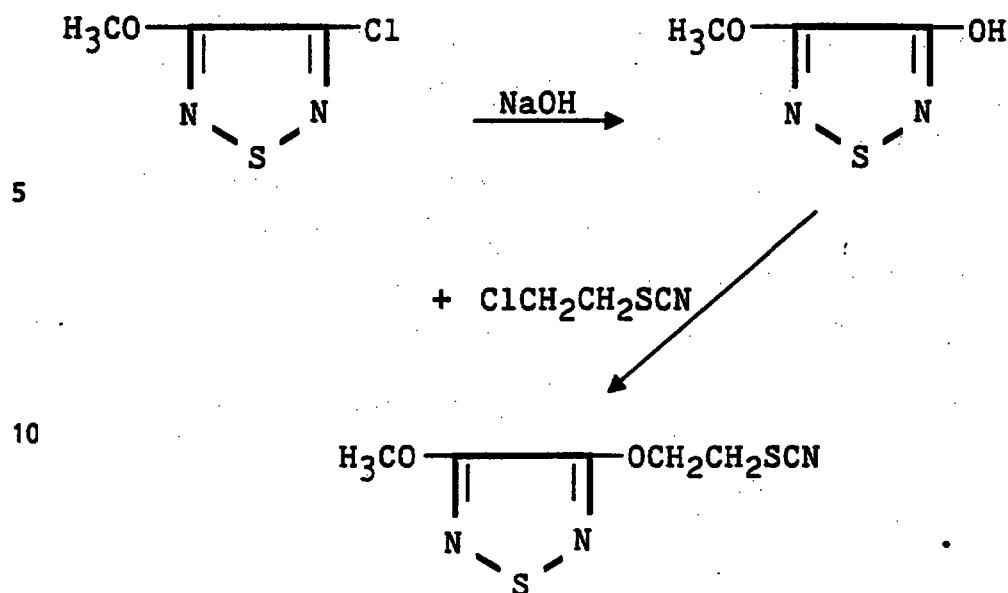


The 4-methoxy-3-thiocyanatoethyloxo-1,2,5-thiadiazole compound of the present invention, that is, wherein R represents $-\text{OCH}_3$ and Y represents $-\text{OCH}_2\text{CH}_2\text{SCN}$ may be

25 prepared by treating 4-chloro-3-methoxy-1,2,5-thiadiazole, prepared as set forth hereinbefore, with an alkali metal hydroxide, such as sodium hydroxide, to prepare the corresponding 4-hydroxy-3-methoxy-1,2,5-thiadiazole which is then reacted with a haloethylthiocyanate, such as chloroethylthiocyanate to give the desired 4-methoxy-

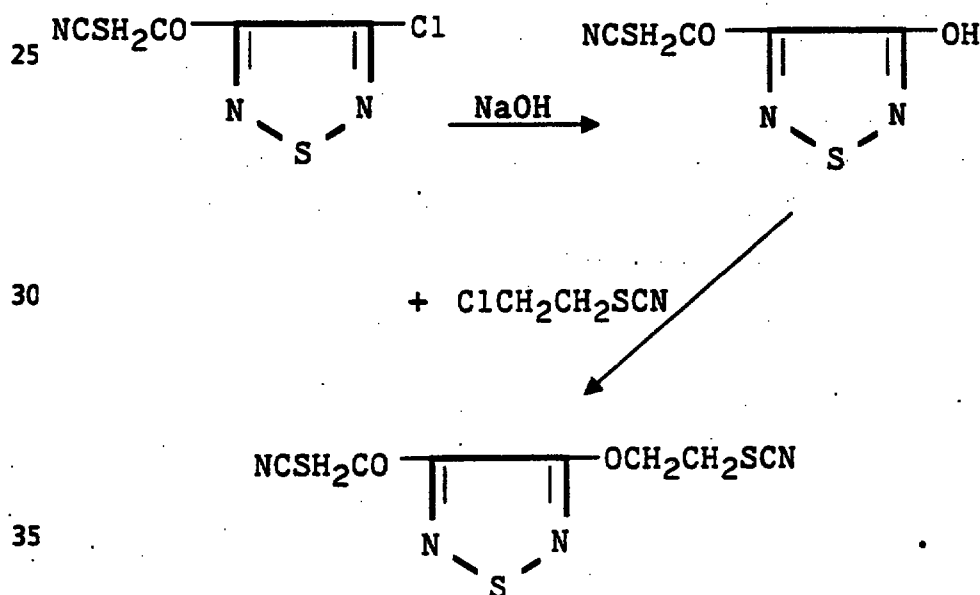
30 -3-thiocyanatoethyloxo-1,2,5-thiadiazole product. The general reaction scheme is as follows:

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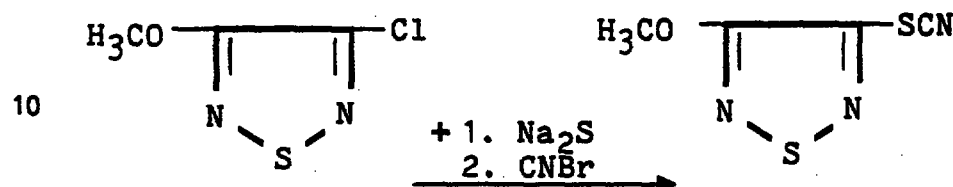


15 The 3-thiocyanatoethyloxo-4-thiocyanato-methyloxo-1,2,5-thiadiazole compound of the present invention, that is, wherein R represents $-\text{OCH}_2\text{SCN}$ and Y represents $-\text{OCH}_2\text{CH}_2\text{SCN}$ may be prepared by treating a 4-halo-3-thiocyanatomethyloxo-1,2,5-thiadiazole, such as 4-chloro-3-thiocyanatomethyloxo-1,2,5-thiadiazole, prepared as set forth hereinbefore, with an alkali metal hydroxide, such as sodium hydroxide, to prepare the

20 corresponding 4-hydroxy-3-thiocyanatomethyloxo-1,2,5-thiadiazole which is then reacted with a haloethylthiocyanate, such as chloroethylthiocyanate to give the desired 3-thiocyanatoethyloxo-4-thiocyanatomethyloxo-1,2,5-thiadiazole product. The general reaction scheme is as follows:

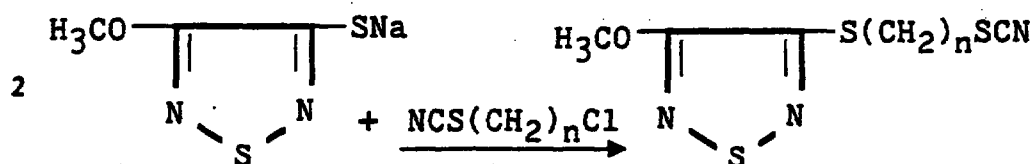


The 3-methoxy-4-thiocyanato-1,2,5-thiadiazole compound of the present invention, wherein, R represents $-OCH_3$, and Y represents $-SCN$, may be prepared by reacting a 4-halo-3-methoxy-1,2,5-thiadiazole such as 4-chloro-3-methoxy-1,2,5-thiadiazole, prepared as set forth hereinbefore, with an alkali metal sulfide, such as sodium sulfide followed by reacting the thus formed 3-methoxy-4-mercapto-1,2,5-thiadiazole; alkali metal salt with a cyanogen halide, such as cyanogen bromide to form the desired 3-methoxy-4-thiocyanato-1,2,5-thiadiazole. The general scheme for this reaction is as follows:



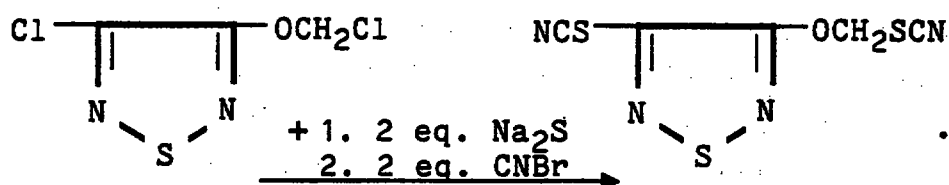
The 3-methoxy-4-thiomethyl(or ethyl)-thiocyanato-1,2,5-thiadiazole compounds of the present invention, wherein, for example, R represents $-OCH_3$, represents $-SCH_2SCN$ or $-SCH_2CH_2SCN$, may be prepared by reacting at room temperature in dimethylformamide a 3-methoxy-4-mercapto-1,2,5-thiadiazole; alkali metal salt, such as 3-methoxy-4-mercapto-1,2,5-thiadiazole; sodium salt, prepared as set forth hereinbefore, with a halomethyl(or ethyl)thiocyanate, such as chloromethylthiocyanate or chloroethylthiocyanate. One mole equivalent of the halomethyl(or ethyl)thiocyanate is used per mole of the 3-methoxy-4-mercapto-1,2,5-thiadiazole: alkali metal salt to prepare the 3-methoxy-4-thiomethyl(or ethyl)thiocyanato-1,2,5-thiadiazole.

The general reaction scheme is as follows:



wherein n is 1 or 2.

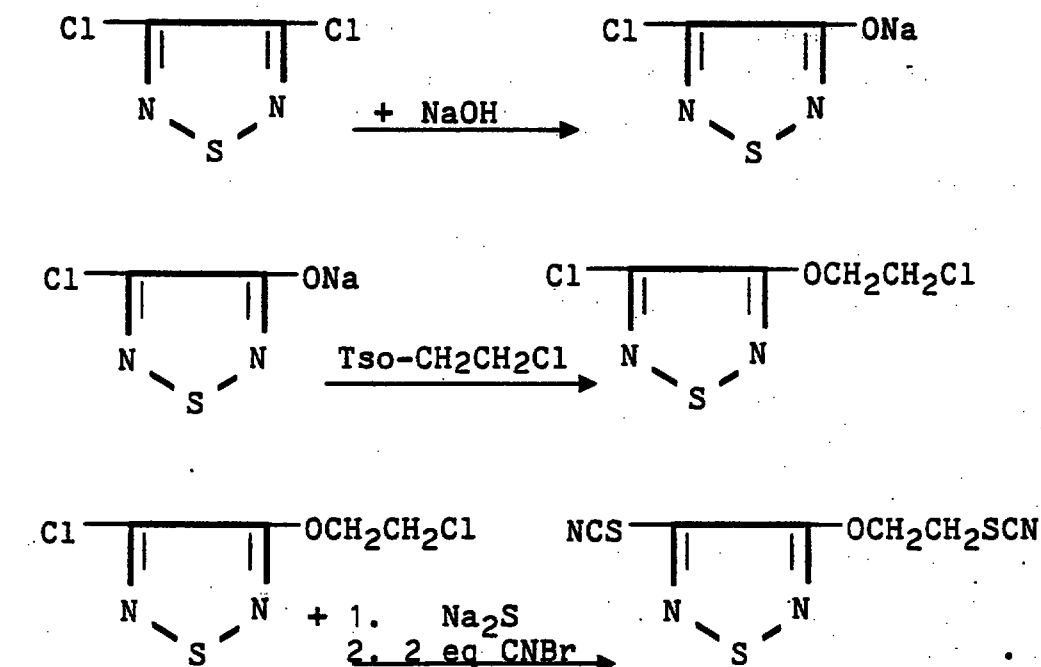
The 3-thiocyanatomethyloxo-4-thiocyanato-1,2,5-thiadiazole compound of the present invention, wherein, for example, R represents $-OCH_2SCN$ and Y represents $-SCN$, may be prepared by reacting a 4-chloro-3-halomethoxy-1,2,5-thiadiazole such as 4-chloro-3-chloromethoxy-1,2,5-thiadiazole, prepared as set forth hereinbefore, with 2 equivalents of an alkali metal sulfide, such as sodium sulfide followed by reacting the thus formed 4-mercaptomethoxy-3-mercapto-1,2,5-thiadiazole, dialkali metal salt with 2 equivalents of a cyanogen halide, such as cyanogen bromide to form the desired 3-thiocyanatomethyloxo-4-thiocyanato-1,2,5-thiadiazole. The general scheme for this reaction is as follows:



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(intermediate structure is not shown)

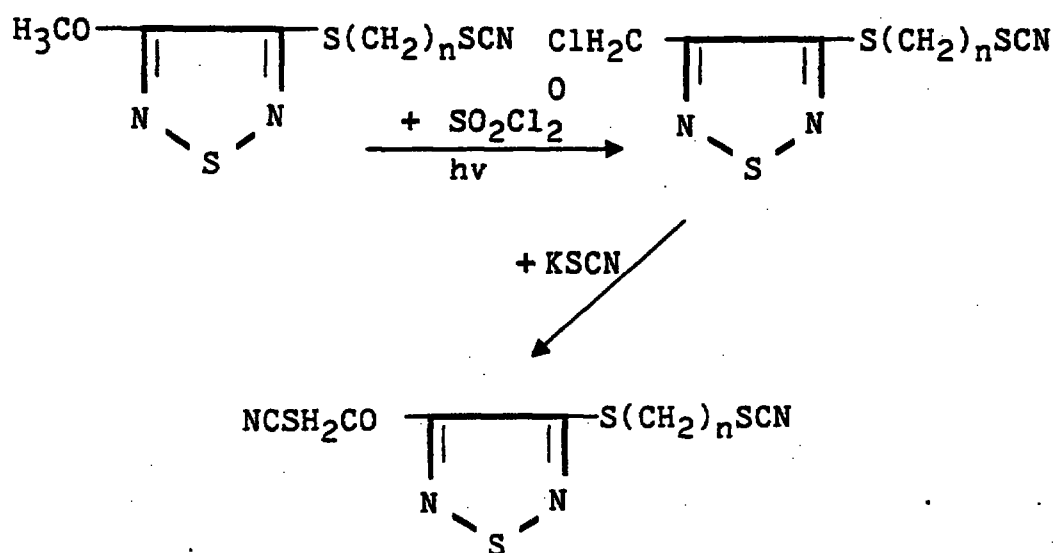
The 3-thiocyanato-4-thiocyanatoethyloxy-1,2,5-thiadiazole compound of the present invention, wherein, for example, R represents $-\text{OCH}_2\text{CH}_2\text{SCN}$ and Y represents $-\text{SCN}$, may be prepared by first reacting a 3,4-dihalo-1,2,5-thiadiazole, such as 3,4-dichloro-1,2,5-thiadiazole with an alkali metal hydroxide, such as sodium hydroxide and the resulting 3-chloro-4-hydroxy-1,2,5-thiadiazole: sodium salt is then reacted at room temperature in dimethylformamide with chloroethyltosylate ($\text{Tso}-\text{CH}_2\text{CH}_2\text{Cl}$). The thus formed 3-chloro-4-chloroethyloxy-1,2,5-thiadiazole is then reacted with an alkali metal sulfide, such as sodium sulfide followed by reacting the thus formed 3-mercapto-4-chloroethyloxy-1,2,5-thiadiazole: alkali metal salt with 2 equivalents of a cyanogen halide, such as cyanogen bromide to form the desired 3-thiocyanato-4-thiocyanatoethyloxy-1,2,5-thiadiazole. The general scheme for this reaction is as follows:



(intermediate structure is not shown)

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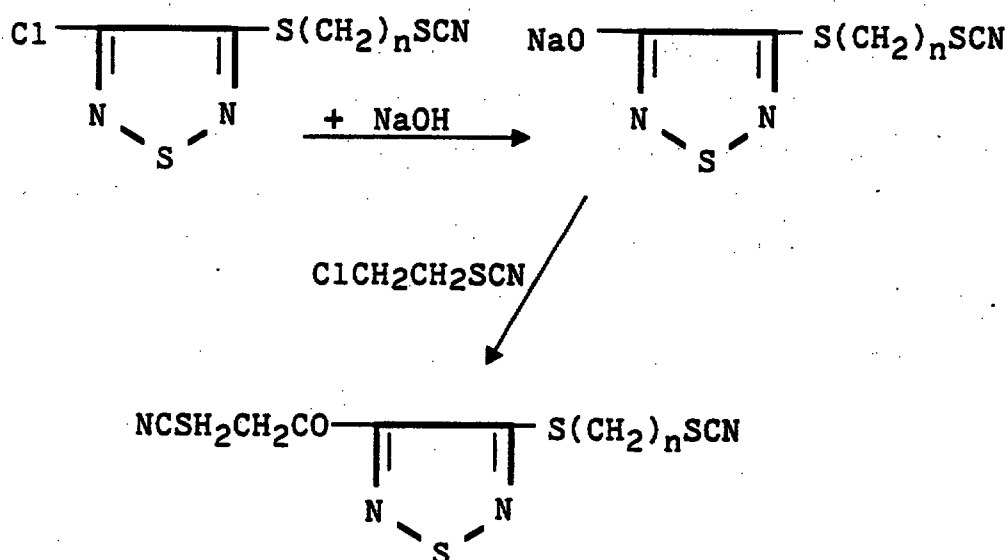
The 3-thiomethyl(or ethyl)cyanato-4-thiocyanatomethyloxo-1,2,5-thiadiazole compound of the present invention, wherein, for example, R represents $-\text{OCH}_2\text{SCN}$ and Y represents $-\text{S}(\text{CH}_2)_n\text{SCN}$ wherein n is as defined hereinbefore, may be prepared by irradiating a solution of 3-methoxy-4-thiomethyl(or ethyl)thiocyanato-1,2,5-thiadiazole, prepared as described hereinbefore, in a solvent such as carbon tetrachloride with a sunlamp while adding a solution of a sulfuryl halide such as sulfuryl chloride in a solvent such as carbon tetrachloride. The thus formed 3-halomethoxy-4-thiomethyl(or ethyl)thiocyanato-1,2,5-thiadiazole product is dissolved in a solvent such as acetone containing an alkali metal thiocyanate such as potassium thiocyanate and refluxed for a period of about 16 hours. The reaction mixture is filtered, and concentrated under reduced pressure and the residue treated by conventional procedures such as, chromatography over silica gel using hexane/ethyl acetate as eluent, to recover the desired above-indicated compound. The reaction consumes the reactants in the ratio of one mole equivalent of the alkali metal thiocyanate per mole of the thiadiazole reactant and such equimolar amounts of the reactants are normally employed. However to ensure completion of the reaction, a slight excess, about 1.0-1.25 equivalents, of alkali metal thiocyanate is usually provided. The general scheme for this reaction is as follows:



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The 3-thiomethylcyanato-4-thiocyanatoethyloxo-1,2,5-thiadiazole compound of the present invention, wherein, for example, R represents $-OCH_2CH_2SCN$ and Y represents $-SCH_2SCN$, may be prepared by first reacting a 4-halo-3-thiomethylcyanato-1,2,5-thiadiazole, such as 4-chloro-3-thiomethylcyanato-1,2,5-thiadiazole, prepared as described hereinbefore, with an alkali metal hydroxide, such as sodium hydroxide and the thus formed 4-hydroxy-3-thiomethylcyanato-1,2,5-thiadiazole: sodium salt is then reacted at room temperature in dimethylformamide with a haloethylthiocyanate, such as chloroethylthiocyanate to prepare the desired 3-thiomethylcyanato-4-thiocyanatoethyloxo-1,2,5-thiadiazole. The general scheme for this reaction is as follows:



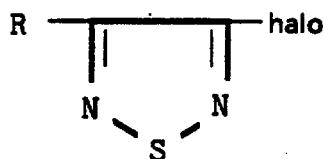
wherein n is as hereinbefore defined.

Chloromethylthiocyanate is well known and is described in JP-B-62215561 and 25 JP-B-62215562.

3,4- and 4,5-Dichloro-1,2,5-thiadiazoles are described in U.S. Patent 3,115,497.

The synthesis of cyanogen bromide is described in Organic Synthesis Collective, Vol. 2, page 150.

The 4-substituted-3-halo-1,2,5-thiadiazole reactant corresponding to the formula



35 wherein R is as hereinabove defined are known compounds. The compounds are well known in the literature. The compounds wherein R is phenyl or substituted phenyl are either specifically taught or they can be prepared as described by L. M. Weinstock et al. in the Journal

of Organic Chemistry, Vol. 32, pages 2823-29, (1967); or in U.S. Patent 4,555,521. Other references include Japanese Patents JPO 5,163,257 A2; 5,163,258 A2; and 5,163,259 A2.

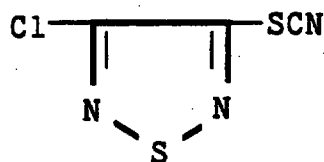
The following examples illustrate the present invention and the manner by which it can be practiced but, as such, should not be construed as limitations upon the overall scope of the same.

Since the hereinabove and hereinafter set forth compound preparation procedures employ only standard chemistry practices and it is known that slightly different reactants can require slightly different reaction parameters from those for other reactants, it is to be understood that minor modifications to the reaction parameters set forth such as the use of an excess of one reactant, the use of a catalyst, the use of high temperature and/or high pressure equipment, high speed mixing and other such conventional changes are within the scope of the present invention.

The desired product can be separated from the reaction product of the above preparative procedures employing conventional separatory procedures known to those skilled in the art including steps of solvent extraction, filtration, water washing, column chromatography, neutralization, acidification, crystallization and distillation..

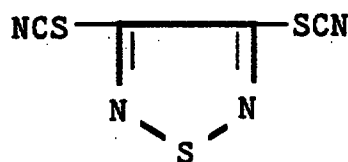
The structure identity of all compounds is confirmed by proton nuclear magnetic resonance spectroscopy (^1H NMR), recorded at 300 MHz; carbon nuclear magnetic resonance spectroscopy (^{13}C NMR) recorded at 75 MHz; infrared spectroscopy (IR) and gas chromatography/mass spectrometry (GC/MS). All of the present reactions were conducted at room temperature unless otherwise stated and under a positive pressure of nitrogen.

Example 1: Preparation of 4-Chloro-3-thiocyanato-1,2,5-thiadiazole



A solution of sodium sulfide (3.43 grams (g), 0.044 mole) in 70 percent ethanol/30 percent water (75 mL) was treated at room temperature with 4,5-dichloro-1,2,5-thiadiazole (6.20 g, 0.04 mole). After stirring for 1 hour, the solution was concentrated to dryness and extracted with ethanol (2 extractions of 30 mL each). Removal of ethanol under reduced pressure gave the sodium salt of the 4-chloro-3-mercapto-1,2,5-thiadiazole. The sodium salt was dispersed in dimethylformamide (15 mL) treated with cyanogen bromide (6.36 g, 0.06 mole) and stirred overnight. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water (3 washings of 40 mL each), dried and concentrated. The residue was chromatographed over silica gel with hexane and ethyl acetate as eluent to yield the 4-chloro-3-thiocyanato-1,2,5-thiadiazole as a yellow solid melting at 63-65°C. in a yield of 2.5 g, (35 percent of theoretical).

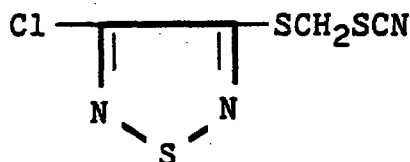
Example 2: Preparation of Bis(thiocyanato)-1,2,5-thiadiazole



A solution of sodium sulfide (3.12 g, 0.04 mole) in 70 percent ethanol/30 percent water (75 mL) was treated with 4,5-dichloro-1,2,5-thiadiazole (3.10 g, 0.02 mole). After stirring for 1 hour the solution was concentrated to dryness and extracted with ethanol (2 extractions of 30 mL each). Removal of ethanol under reduced pressure gave the disodium salt of the bis(mercapto)-1,2,5-thiadiazole. The disodium salt was dispersed in dimethylformamide (15 mL) and treated with cyanogen bromide (4.32 g, 0.04 mole) and stirred overnight. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water (3 washings of 40 mL each), dried and concentrated. The residue was chromatographed over silica gel with methylene chloride as eluent to yield the bis(thiocyanato)-1,2,5-thiadiazole as an oil (1.4 g, 35 percent of theoretical).

Example 3: Preparation of 4-chloro-3-thiomethylthiocyanato-1,2,5-thiadiazole

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A solution of sodium sulfide (3.43 g, 0.044 mole) in 70 percent ethanol/30 percent water (75 mL) was treated with 4,5-dichloro-1,2,5-thiadiazole (6.20 g, 0.04 mole). After stirring for 1 hour the solution was treated with chloromethylthiocyanate (6.48 g, 0.06 mole) and stirred overnight. The reaction mixture was concentrated and extracted with methylene chloride. The organic layer was washed with water (3 washings of 40 mL each), dried and concentrated. The residue was chromatographed over silica gel with hexane and ethyl acetate as eluent to yield the 4-chloro-3-thiomethylthiocyanato-1,2,5-thiadiazole as an oil (3.12 g, 35 percent of theoretical).

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Example 4: Preparation of Bis(thiomethylthiocyanato)-1,2,5-thiadiazole

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A solution of sodium sulfide (3.12 g, 0.04 mole) in 70 percent ethanol/30 percent water (75 mL) was treated with 4,5-dichloro-1,2,5-thiadiazole (3.10 g, 0.02 mole). After stirring for 1 hour the solution was concentrated to dryness and extracted with ethanol (2 extractions of 30 mL each). Removal of ethanol under reduced pressure gave the disodium salt of the bis(mercapto)-1,2,5-thiadiazole. The disodium salt was dispersed in dimethylformamide (15 mL) and treated with chloromethylthiocyanate (4.32 g, 0.04 mole) and stirred overnight. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water (3 washings of 40 mL each), dried and concentrated. The residue was chromatographed over silica gel with methylene chloride as eluent to yield the bis(thiomethylthiocyanato)-1,2,5-thiadiazole as an oil (1.86 g, 32 percent of theoretical).

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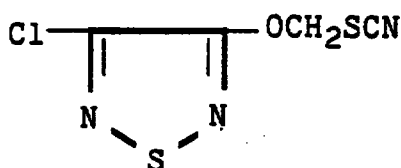
Example 5: Preparation of Bis(thioethylthiocyanato)-1,2,5-thiadiazole

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A solution of sodium sulfide (4.42 g, 0.057 mole) in 70 percent ethanol/30 percent water (125 mL) was treated with 4,5-dichloro-1,2,5-thiadiazole (4 g, 0.026 mole). After stirring for 2 hours the solution was concentrated to dryness and extracted with ethanol (2 extractions of 25 mL each). Removal of ethanol under reduced pressure gave the disodium salt of the bis(mercapto)-1,2,5-thiadiazole. The disodium salt was dispersed in dimethylformamide (30 mL) and treated with chloroethylthiocyanate (6.4 g, 0.0525 mole) and stirred overnight. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water (3 washings of 40 mL each), dried and concentrated. The residue was chromatographed over silica gel with hexane and ethyl acetate as eluent to yield 3.5 g, (42 percent of theoretical) of 3,4-bis(thioethylthiocyanato)-1,2,5-thiadiazole as a yellow solid melting at 72-74°C.

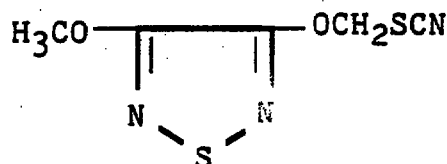
Example 6: Preparation of 4-Chloro-3-thiocyanatomethyloxo-1,2,5-thiadiazole



A solution comprised of 5 g of 60 percent pure 4-chloro-3-methoxy-1,2,5-thiadiazole in 30 mL of carbon tetrachloride was irradiated over a period of 45 minutes at 80°C. with a sunlamp while adding a solution comprised of 5 g of sulfuryl chloride in 20 mL of carbon tetrachloride. The reaction mixture was then washed with 30 mL of a saturated aqueous sodium bicarbonate solution and concentrated under reduced pressure to yield 4.87 g of 4-chloro-3-chloromethoxy-1,2,5-thiadiazole.

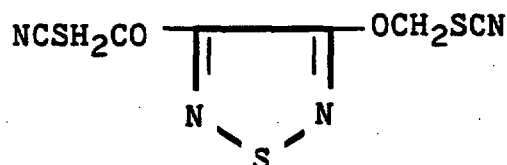
The 4-chloro-3-chloromethoxy-1,2,5-thiadiazole (4.87 g) was dissolved in 100 mL of acetone containing a 1.2 equivalent excess of potassium thiocyanate and refluxed overnight (about 16 hours). The reaction mixture was filtered, and concentrated under reduced pressure and the residue chromatographed over silica gel with hexane/ethyl acetate as eluent. The desired 4-chloro-3-thiocyanatomethyloxo-1,2,5-thiadiazole was recovered as an oil in a yield of 37 percent of theoretical. ¹H NMR (CDCl₃) δ 5.85 (s, 2H); ¹³C NMR (CDCl₃) δ 72.76, 109.78, 133.51, 156.67; MS (EI) m/e 273, 236, 209, 179, 149, 130.

Example 7: Preparation of 4-Methoxy-3-thiocyanatomethyloxo-1,2,5-thiadiazole



This compound was prepared following the preparative procedures of Example 6 employing 3,4-dimethoxy-1,2,5-thiadiazole as a starting material. The product was recovered as an oil in a yield of 29 percent of theoretical. ^1H NMR (CDCl_3) δ 4.16 (s, 3H), 5.85 (s, 2H); ^{13}C NMR (CDCl_3) δ 57.94, 72.56, 110.57, 148.43, 152.33; MS (EI) m/e 203(M^+), 145, 130, 90, 72.

5 Example 8: Preparation of 3,4-Bis(thiocyanatomethyloxo)-1,2,5-thiadiazole



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This compound was prepared following the preparative procedures of Example 6 employing 3,4-dimethoxy-1,2,5-thiadiazole as a starting material. The product was recovered in a yield of 16 percent of theoretical as a light yellow solid melting at 74-75°C. ^1H NMR (CDCl_3) δ 5.85 (s, 2H); ^{13}C NMR (CDCl_3) δ 72.38, 110.03, 148.42; MS (EI) m/e 203(M^+), 260, 202, 130, 102, 100, 72.

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Example 9: Preparation of 4-Phenyl-3-thiocyanato-1,2,5-thiadiazole



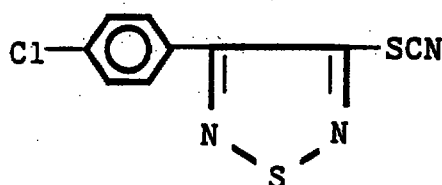
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To a stirred solution of (3.81 g, 0.05 mole) of sodium sulfide in 100 mL of dimethyl formamide was added 8 g, 0.041 mole) of 4-Phenyl-3-chloro-1,2,5-thiadiazole. The mixture was stirred overnight (~16 hours), and to the resulting dark green solution was added 6.64 g (1.5 molar equivalents) of cyanogen bromide. This mixture was stirred for about 14 hours and then diluted with 100 mL of water and extracted with 200 mL of methylene chloride. The organic layer was separated and washed with water (2x100mL), dried and concentrated under reduced pressure. The thus recovered crude material was chromatographed on silica gel with a 10 percent EtOAc:90 percent hexane mixture to yield 6.6 g (72 percent of theoretical) as an oil which turned to a white solid melting at 49°C. upon standing; ^{13}C NMR (75 MHz, CDCl_3) δ 159.10, 141.78, 130.59, 129.76, 129.06, 127.88, 105.98; MS (EI) m/e 219(M^+), 192, 160, 135, 103. By employing the above preparative procedure of Example 9 employing the appropriate starting materials, the following compounds were prepared.

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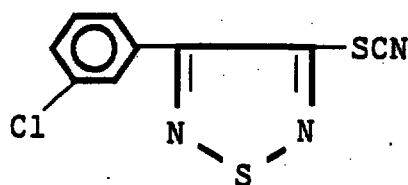
Example 10: Preparation of 4-(4-Chlorophenyl)-3-thiocyanato-1,2,5-thiadiazole



This compound was isolated as a white solid which melted at 87-88°C. in a yield of 65 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 7.67 (d, $J = 8.3$ Hz, 2H), 7.53 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.21, 141.66, 137.04, 129.45, 129.31, 128.29, 105.73; MS (EI) m/e 255, 253, 194, 171, 169, 139, 137, 116, 102.

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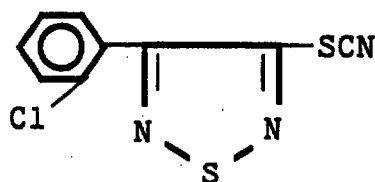
Example 11: Preparation of 4-(3-Chlorophenyl)-3-thiocyanato-1,2,5-thiadiazole



This compound was isolated as a white solid which melted at 82-83°C. in a yield of 53 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 7.72 (s, 1H), 7.08 (d, $J = 6.9$ Hz, 1H), 7.54 (m, 1H), 7.48 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.76, 141.83, 135.22, 131.40, 130.73, 130.34, 128.24, 125.87, 105.59; MS (EI) m/e 255, 253, 228, 226, 218, 196, 194, 171, 169, 139, 137, 102.

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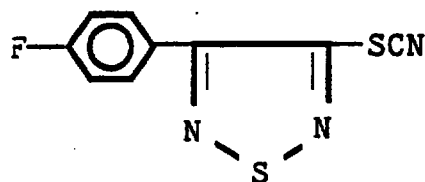
Example 12: Preparation of 4-(2-Chlorophenyl)-3-thiocyanato-1,2,5-thiadiazole



This compound was isolated as an oil in a yield of 55 percent of theoretical; ^{13}C NMR (75 MHz, CDCl_3) δ 158.12, 143.88, 131.92, 131.22, 131.12, 130.03, 129.90, 127.75, 106.33; MS (EI) m/e 255, 253, 218, 171, 169, 139, 137, 116, 102.

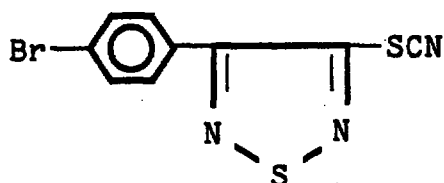
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Example 13: Preparation of 4-(4-Fluorophenyl)-3-thiocyanato-1,2,5-thiadiazole



This compound was isolated as a white solid which melted at 67-68°C. in a yield of 60 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 7.70-7.74 (dd, $J = 8.3, 5.2$ Hz, 2H), 7.24 (t, $J = 8.5$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 165.46, 162.12, 158.31, 142.00, 130.21, 130.10, 126.05, 116.54, 116.25, 105.80; MS (EI) m/e 237(M^+), 210, 178, 153, 121, 116.

5 Example 14: Preparation of 4-(4-Bromophenyl)-3-thiocyanato-1,2,5-thiadiazole

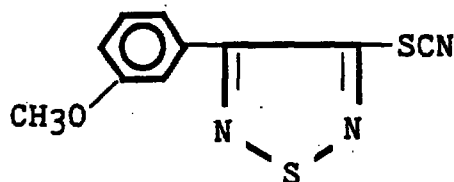


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This compound was isolated as a yellow solid which melted at 105°C. in a yield of 70 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 7.68 (d, $J = 8.5$ Hz, 2H), 7.59 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.20, 141.60, 132.35, 129.43, 128.69, 125.36, 105.69; MS (EI) m/e 299, 297, 272, 270, 218, 215, 213, 183, 181, 160, 116.

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Example 15: Preparation of 4-(3-Methoxyphenyl)-3-thiocyanato-1,2,5-thiadiazole

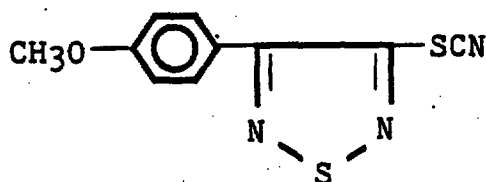


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This compound was isolated as a yellow solid which melted at 64-65°C. in a yield of 50 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 7.45 (d, $J = 8.3$ Hz, 2H), 7.22 (s, 1H), 7.07 (dd, $J = 8.3, 2.2$ Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.83, 158.85, 141.98, 130.18, 119.90, 116.53, 113.42, 105.96, 55.47; MS (EI) m/e 249(M^+), 222, 190, 175, 159, 147.

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Example 16: Preparation of 4-(4-Methoxyphenyl)-3-thiocyanato-1,2,5-thiadiazole

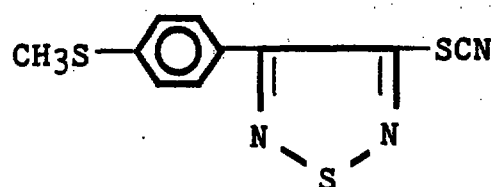


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This compound was isolated as a white solid which melted at 121°C. in a yield of 60 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 7.64 (d, $J = 8.7$ Hz, 2H), 7.32 (d, $J = 8.6$ Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 161.22, 158.93, 141.50, 129.46, 122.27, 111.50, 106.43, 55.45; MS (EI) m/e 249(M^+), 226, 165, 133, 103, 90.

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Example 17: Preparation of 4-(4-Methylthiophenyl)-3-thiocyanato-1,2,5-thiadiazole

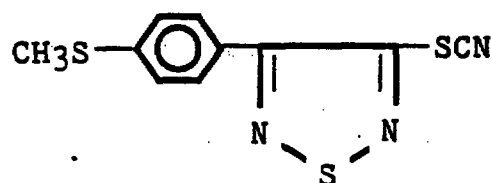


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This compound was isolated as a yellow solid which melted at 80-82°C. in a yield of 46 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 7.62 (d, $J = 8.7$ Hz, 2H), 7.35 (d, $J = 8.7$ Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.86, 142.76, 141.63, 128.62, 128.13, 125.88, 125.56, 105.98, 15.13; MS (EI) m/e 265(M^+), 205, 192, 181, 149, 116.

Example 18: Preparation of 4-(4-Trifluoromethylphenyl)-3-thiocyanato-1,2,5-thiadiazole

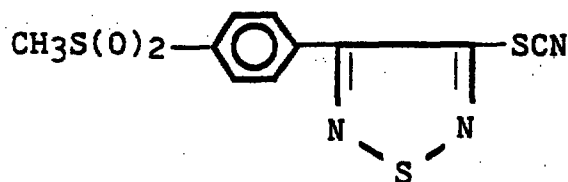


15

20

This compound was isolated as a white solid which melted at 76°C. in a yield of 65 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 7.87 (d, $J = 8.4$ Hz, 2H), 7.81 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.94, 142.06, 133.33, 132.85, 132.42, 128.65, 128.38, 126.26, 121.72, 105.69; MS (EI) m/e 287(M^+), 260, 203, 116.

Example 19: Preparation of 4-(4-Methylsulfonylphenyl)-3-thiocyanato-1,2,5-thiadiazole



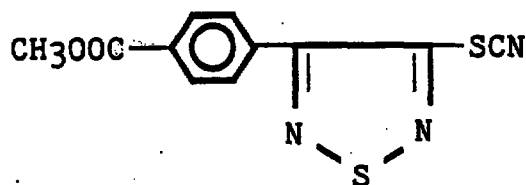
25

30

This compound was isolated as a tan solid which melted at 158-160°C. in a yield of 66 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 8.13 (d, $J = 8.1$ Hz, 2H), 7.96 (d, $J = 8.2$ Hz, 2H), 3.13 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.43, 142.24, 134.80, 129.35, 129.05, 128.18, 105.39, 44.45.

35

Example 20: Preparation of 4-(4-Carboxymethylphenyl)-3-thiocyanato-1,2,5-thiadiazole

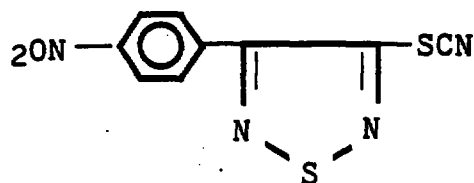


5

This compound was isolated as a yellow solid which melted at 135°C. in a yield of 48 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 8.21 (d, $J = 8.2$ Hz, 2H), 7.81 (d, $J = 8.2$ Hz, 2H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 165.64, 158.17, 141.97, 133.73, 131.90, 130.19, 127.99, 105.58, 52.54; MS (EI) m/e 278(M^+), 246, 130, 102.

10

Example 21: Preparation of 4-(4-Nitrophenyl)-thiocyanato-1,2,5-thiadiazole

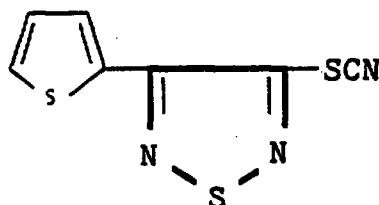


15

This compound was isolated as a yellow solid which melted at 117°C. in a yield of 48 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 8.42 (d, $J = 8.8$ Hz, 2H), 7.97 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.06, 148.56, 141.93, 135.47, 129.10, 124.19, 105.27; MS (EI) m/e 264(M^+), 218.

20

Example 22: Preparation of 4-(2-Thiophene)-3-thiocyanato-1,2,5-thiadiazole



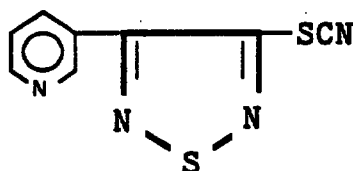
25

This compound was isolated as a white solid which melted at 70-71°C. in a yield of 48 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 7.62 (d, $J = 3.5$ Hz, 1H), 7.57 (d, $J = 5$ Hz, 1H), 7.19 (dd, $J = 3.5, 5.0$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.33, 140.01, 132.10, 130.04, 128.20, 128.12, 105.63; MS (EI) m/e 225(M^+), 198, 180, 141, 116.

30

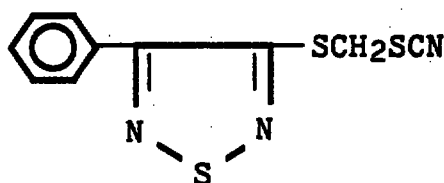
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Example 23: Preparation of 4-(3-Pyridyl)-3-thiocyanato-1,2,5-thiadiazole



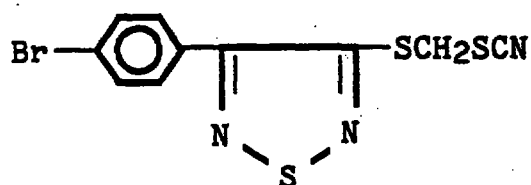
This compound was isolated as a yellow solid which melted at 120°C. in a yield of 45 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 8.97 (s, 1H), 7.58 (d, J = 3.8 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.48 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 156.74, 151.34, 148.48, 141.77, 135.33, 126.16, 123.64, 105.48; MS (EI) m/e 220(M⁺), 194, 156, 136, 130, 116.

Example 24: Preparation of 4-Phenyl-3-thiocyanatomethylthio-1,2,5-thiadiazole



To a stirred solution of (3.81 g, 0.05 mole) of sodium sulfide in 100 mL of dimethylformamide was added 8 g (0.041 mole) of 4-Phenyl-3-chloro-1,2,5-thiadiazole. The mixture was stirred ~18 hours and to this mixture was added 6.68 g (1.5 molar equivalents) of chloromethylthiocyanate. This mixture was stirred for ~14 hours and then diluted with 100 mL of water and extracted with 200 mL of methylene chloride. The organic layer was separated and washed with water (2x100mL), dried and concentrated under reduced pressure. The thus recovered crude material was chromatographed on silica gel with a 10 percent EtOAc:90 percent hexane mixture to yield 8.99 g (83 percent of theoretical) as an oil. Upon crystallization, a light yellow solid melting at 58-60°C. was recovered in a yield of 69 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 4.77 (s, 2H), 7.49 (m, 3H), 7.82 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 38.28, 111.46, 127.97, 128.78, 130.06, 151.77, 157.93; MS (EI) m/e 265(M⁺), 207, 148, 116.

By employing the above preparative procedures of Example 24 employing the appropriate starting materials, the following compounds were prepared.

Example 25: Preparation of 4-(4-Bromophenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole

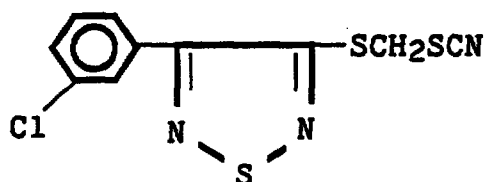
This compound was isolated as a tan solid which melted at 67-68°C. in a yield of 65 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 4.79 (s, 2H), 7.63 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 38.31, 111.32, 129.48, 129.78, 132.01, 151.62, 156.75; MS (EI) m/e 345, 343, 287, 285, 206.

10

Example 26: Preparation of 4-(4-Chlorophenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole

This compound was isolated as a white solid which melted at 62-63°C. in a yield of 60 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 4.80 (s, 2H), 7.48 (d, $J = 8.2$ Hz, 2H), 7.79 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 38.33, 111.32, 129.09, 129.32, 136.28, 151.66, 156.75; MS (EI) m/e 301($M + + 1$), 299, 243, 241, 182, 150.

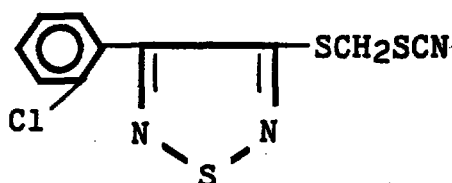
20

Example 27: Preparation of 4-(3-Chlorophenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole

This compound was isolated as a white solid which melted at 67°C. in a yield of 52 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 4.80 (s, 2H), 7.72 (m, 1H), 7.83 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 38.30, 111.23, 125.90, 128.18, 129.99, 130.09, 132.44, 134.83, 151.75, 156.35; MS (EI) m/e 301($M + + 1$), 299, 243, 241, 202, 182.

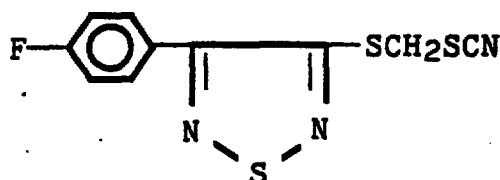
30

Example 28: Preparation of 4-(2-Chlorophenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole



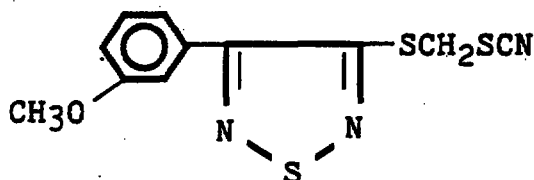
This compound was isolated as an oil in a yield of 52 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 4.74 (s, 2H), 7.41-7.52 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 38.08, 111.15, 126.90, 129.81, 130.15, 130.86, 131.32, 133.32, 153.64, 156.34; MS (EI) m/e 301($M + + 1$), 299, 205, 184, 182, 150.

Example 29: Preparation of 4-(4-Fluorophenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole



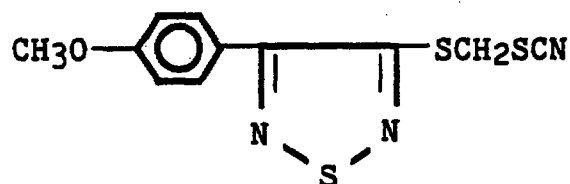
This compound was isolated as a clear oil in a yield of 65 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 4.80 (s, 2H), 7.20 (t, $J = 8.5$ Hz, 2H), 7.84 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 38.32, 11.36, 115.85, 116.44, 127.15, 130.04, 130.16, 151.51, 156.51, 161.79, 165.12.

Example 30: Preparation of 4-(3-Methoxyphenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole



This compound was isolated as a yellow oil with a yield of 70 percent of theoretical; ^1H NMR (300 MHz, CDCl_3) δ 3.87 (s, 3H), 4.79 (s, 2H), 7.05 (m, 1H), 7.42 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 38.36, 55.47, 111.39, 113.23, 116.20, 120.17, 129.84, 132.03, 151.81, 157.73, 159.60; MS (EI) m/e 295($M +$), 237, 178, 146.

Example 31: Preparation of 4-(4-Methoxyphenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole

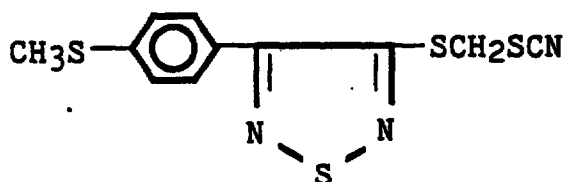


5

This compound was isolated as a white solid which melted at 79-80°C. in a yield of 69 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 3.87 (s, 3H), 4.78 (s, 2H), 7.02 (d, J = 8.52 Hz, 2H), 7.79 (d, J = 8.52 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 38.41, 55.41, 11.52, 114.17, 123.54, 129.18, 151.23, 157.68, 160.79; MS (EI) m/e 295, 237, 178, 146.

10

Example 32: Preparation of 4-(4-Methylthiophenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole

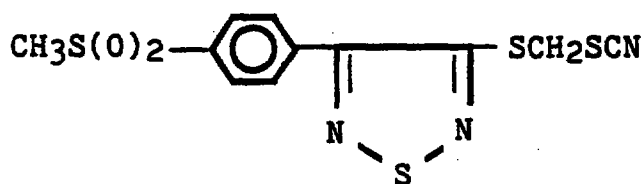


15

This compound was isolated as a white solid which melted at 79-80°C. in a yield of 64 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 2.53 (s, 3H), 4.78 (s, 2H), 7.34 (d, J = 8.71 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 15.26, 38.38, 111.36, 125.73, 127.22, 128.17, 141.72, 151.44, 157.36; MS (EI) m/e 311(M⁺), 253, 206.

20

Example 33: Preparation of 4-(4-Methylsulfonylphenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole



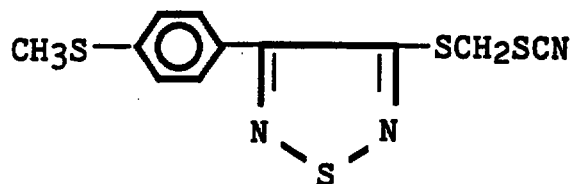
25

This compound was isolated as a white solid which melted at 120-121°C. in a yield of 54 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 3.13 (s, 3H), 4.84 (s, 2H), 8.09 (q, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 38.21, 44.48, 111.12, 127.86, 128.95, 135.81, 141.48, 152.08, 155.80.

30

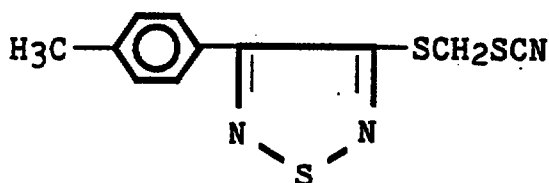
35

Example 34: Preparation of 4-(4-Trifluoromethylphenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole



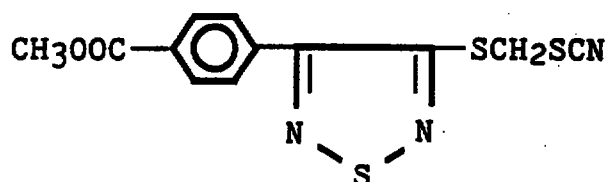
This compound was isolated as a white solid which melted at 79-80°C. in a yield of 74 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 4.81 (s, 2H), 7.78 (d, J = 8.2 Hz, 2H), 7.98 (d, J = 8.2 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 138.26, 111.19, 121.73, 125.33, 125.78, 125.82, 128.43, 131.61, 132.04, 134.18, 151.96, 156.42; MS (EI) m/e 333(M⁺), 275, 216, 184.

Example 35: Preparation of 4-(4-Methylphenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole



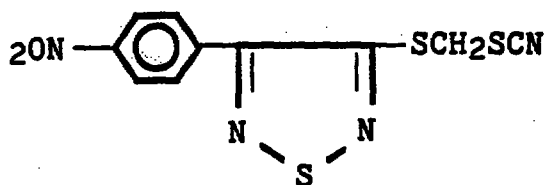
This compound was isolated as a yellow oil in a yield of 42 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 2.42 (s, 3H), 4.76 (s, 2H), 7.29 (d, J = 7.7 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.60 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 21.40, 38.26, 111.49, 125.03, 128.70, 130.92, 138.73, 151.92, 158.25.

Example 36: Preparation of 4-(4-Carboxymethylphenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole



This compound was isolated as a white solid which melted at 119-120°C. in a yield of 65 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 3.96 (s, 3H), 4.81 (s, 2H), 7.93 (d, J = 8.3 Hz, 2H), 8.17 (d, J = 8.3 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 38.31, 52.44, 111.21, 127.97, 129.93, 131.28, 134.82, 152.01, 156.76, 165.90; MS (EI) m/e 323(M⁺), 265, 221, 205, 162, 130.

Example 37: Preparation of 4-(4-Nitrophenyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole

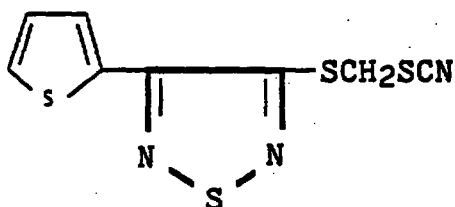


5

This compound was isolated as a yellow solid which melted at 78°C. in a yield of 56 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 4.86 (s, 2H), 8.06 (d, J = 8.8 Hz, 2H), 8.36 (d, J = 8.8 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 38.32, 111.13, 123.98, 129.02, 136.60, 148.19, 152.22, 155.43; MS (EI) m/e 310(M⁺), 252, 206.

10

Example 38: Preparation of 4-(2-Thiophene)-3-thiocyanatomethylthio-1,2,5-thiadiazole

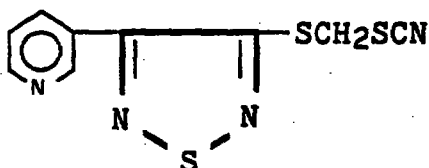


15

This compound was isolated as a tan solid which melted at 120-122°C. in a yield of 67 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 7.16 (dd, J = 4.8, 3.6 Hz, 1H), 7.71 (d, J = 3.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 38.23, 111.30, 127.56, 126.63, 129.14, 133.53, 150.44, 151.93; MS (EI) m/e 271(M⁺), 213, 180, 154, 122.

20

Example 39: Preparation of 4-(3-Pyridyl)-3-thiocyanatomethylthio-1,2,5-thiadiazole



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This compound was isolated as a yellow solid which melted at 88-90°C. in a yield of 77 percent of theoretical; ¹H NMR (300 MHz, CDCl₃) δ 4.84 (s, 2H), 7.46 (dd, J = 4.7, 7.9 Hz, 1H), 8.17 (d, J = 7.9 Hz, 1H), 8.73 (d, J = 7.9 Hz, 1H), 9.10 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 38.24, 111.08, 123.39, 127.11, 135.11, 148.75, 150.73, 151.93, 155.08; MS (EI) m/e 266(M⁺), 208, 149, 118.

30

35

The compounds of this invention are useful as antimicrobial additives, and they can be added to industrial products such as paints, inks, adhesives, soaps, cutting oils, textiles, paper pigment slurries and styrene-butadiene latexes used for paper coatings to provide needed antimicrobial properties. The compounds are also used as antimicrobial additives in
5 such personal care products as hand creams, lotions, shampoos and hand soaps. A further advantage in the use of the compounds of this invention is their cost-effectiveness for applications which need to have an antimicrobial continuously replenished, such as in cooling towers and pulp and paper mills.

As appreciated by those skilled in the art, each of the compounds disclosed herein
10 are not necessarily active at the same concentrations or against the same microbial species. There may be some compound-to-compound variation in antimicrobial potency and spectrum of antimicrobial activity.

The antimicrobial compounds of the present invention may be added to formulations susceptible to microbial growth. They may be added either undiluted or
15 dissolved in inert diluents such as organic solvents such as glycols, alcohols or acetone. They may also be added alone or in combination with other preservatives.

As used herein, the term "microorganism" is meant to refer to bacteria, fungi, viruses, algae, subviral agents and protozoa.

As used herein, the term "antimicrobially-effective amount" refers to that
20 amount of one or a mixture of the compounds, or of a composition comprising such compound or compounds, of this invention needed to exhibit inhibition of selected microorganisms. Typically, this amount varies from providing 1 part per million (ppm) to 5,000 ppm by weight of the compound to a microbial habitat being contacted with the compound. Such amounts typically vary depending upon the particular compound tested and microorganism treated.
25 Additionally, the exact concentration of the compounds to be added in the treatment of industrial and consumer formulations may vary within a product type depending upon the components of the formulation. A preferred effective amount of the compound is from 1 ppm to 500 ppm, more preferably from 1 ppm to 50 ppm by weight, of a microbial habitat.

The term "habitat" refers to a place or site where a microorganism naturally or
30 normally lives or grows. Typically, such a habitat will be an area that provides a moisture source, nutrient source, and/or an oxygen source such as, for example, a cooling water tower or an air washing system.

The terms "inhibition", "inhibit" or "inhibiting" refer to the suppression, stasis, kill, or any other interference with the normal life processes of microorganisms that is adverse
35 to such microorganisms, so as to destroy or irreversibly inactivate existing microorganisms and/or prevent or control their future growth and reproduction.

The antimicrobial activity of the compounds of the present invention is set forth as the minimum inhibitory concentration (MIC) for the active compounds and is determined

for nine (9) bacteria, using nutrient agar, and seven (7) yeast and fungi, using malt yeast agar. This determination is conducted using a one percent solution of the test compound prepared in a mixture of acetone and water.

5 Nutrient agar is prepared at pH 6.8, representing a neutral medium, and at pH 8.2, representing an alkaline medium. The nutrient agars are prepared by adding 23 g of nutrient agar to one-liter of deionized water. In addition, the alkaline medium is prepared by adjusting a 0.04 M solution of N-(tris-(hydroxymethyl)methyl)glycine buffered deionized water with concentrated sodium hydroxide to a pH of 8.5.

10 Malt yeast agar is prepared by adding 3 g yeast extract and 45 g malt agar per liter of deionized water. The specific agar is dispensed in 30 mL aliquots into 25 x 200 mm test tubes, capped and autoclaved for 15 minutes at 115°C.

The test tubes containing the agar are cooled in a water bath until the temperature of the agar is 48°C. Then, an appropriate amount of the one percent solution of the test compound is added (except in the controls where no compound is added) to the
15 respective test tubes so that the final concentrations are 500, 250, 100, 50, 25, 10, 5, 2.5, 1.0 and zero parts per million of the test compound in the agar, thus having a known concentration of test compound dispersed therein. The contents of the test tubes are then transferred to respective petri plates. After drying for 24 hours, the petri plates containing nutrient agar are inoculated with bacteria and those containing malt yeast agar are inoculated with yeast and
20 fungi.

The inoculation with bacteria is accomplished by using the following procedure. Twenty-four hour-cultures of each of the bacteria are prepared by incubating the respective bacteria in tubes containing nutrient broth for 24 hours at 30°C in a shaker. Dilutions of each of the 24 hour-cultures are made so that nine separate suspensions (one for each of the nine
25 test bacteria) are made, each containing 10^8 colony forming units (CFU) per mL of suspension of a particular bacteria. Aliquots of 0.3 mL of each of the bacterial suspensions are used to fill the individual wells of Steer's Replicator. For each microbial suspension, 0.3 mL was used to fill three wells (that is, three wells of 0.3 mL each) so that for the nine different bacteria, 27 wells are filled. The Steer's Replicator is then used to inoculate both the neutral and alkaline pH
30 nutrient agar petri plates.

The inoculated petri plates are incubated at 30°C for 48 hours and then read to determine if the test compound which is incorporated into the agar prevented growth of the respective bacteria.

The inoculation with the yeast and fungi is accomplished as follows. Cultures of
35 yeast and fungi are incubated for seven days on malt yeast agar at 30°C. These cultures are used to prepare suspensions by the following procedure. A suspension of each organism is prepared by adding 10 mL of sterile saline and 10 microliters of octylphenoxy polyethoxy ethanol to the agar slant of yeast or fungi. The sterile saline/octylphenoxy polyethoxy ethanol

solution is then agitated with a sterile swab to suspend the microorganism grown on the slant. Each resulting suspension is diluted into sterile saline (1 part suspension: 9 parts sterile saline). Aliquots of these dilutions are placed in individual wells of Steer's Replicator and petri plates inoculated as previously described. The petri plates are incubated at 30°C and read after
5 48 hours for yeast and 72 hours for fungi.

Table I lists the bacteria, yeast and fungi used in the MIC test described above along with their respective American Type Culture Collection (ATCC) identification numbers.

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TABLE I

Organisms Used in the Minimum Inhibitory Concentration Test

5	Organism	ATCC No.
	Bacteria	
	Bacillus subtilis (Bs)	8473
	Enterobacter aerogenes (Ea)	13048
10	Escherichia coli (Ec)	11229
	Klebsiella pneumoniae (Kp)	8308
	Proteus vulgaris (Pv)	881
	Pseudomonas aeruginosa (Pa)	10145
	Pseudomonas aeruginosa (PRD-10)	15442
15	Salmonella choleraesuis (Sc)	10708
	Staphylococcus aureus (Sa)	6538
	Yeast/Fungi	
	Aspergillus niger (An)	16404
20	Candida albicans (Ca)	10231
	Penicillium chrysogenum (Pc)	9480
	Saccharomyces cerevisiae (Sc)	4105
	Trichoderma viride (Tv)	8678
	Aureobasidium pullulan (Ap)	16622
25	Fusarium oxysporum (Fo)	48112

In Tables II and III, the MIC values of the compounds of the present invention as compared to the MIC of a standard commercial preservative (with 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride as the active agent and referred to in Tables III and IV as "STANDARD I") are set forth for the bacteria organisms and yeast/fungi organisms which are listed in Table I.

TABLE II
Minimum Inhibitory Concentrations for Test Compounds
in Bacteria Species (in ppm)

Compound Example No.	ORGANISMS								
	Bs	Ea	Ec	Kp	Pv	PRD	Pa	Sc	Sa
STANDARD I									
pH 6.8	50	100	100	50	50	100	100	50	100
pH 8.2	250	250	250	250	250	500	>500	100	250
(1) pH 6.8	25	50	25	25	25	50	25	25	25
pH 8.2	500	>500	>500	>500	>500	>500	>500	>500	>500
(2) pH 6.8	25	25	25	25	25	25	50	25	25
pH 8.2	100	100	50	250	100	250	250	100	100
(3) pH 6.8	<10	25	25	25	<10	<10	25	25	25
pH 8.2	25	100	50	50	25	25	100	50	50
(4) pH 6.8	<10	25	25	<10	<10	25	<10	25	<10
pH 8.2	<10	<10	<10	<10	<10	25	<10	25	<10
(5) pH 6.8	>500	>500	>500	>500	>500	>500	>500	>500	>500
pH 8.2	>500	>500	>500	>500	>500	>500	>500	>500	>500
(6) pH 6.8	<10	50	25	25	<10	100	50	<10	25
pH 8.2	25	50	25	25	25	100	50	25	25

TABLE II CONTINUATION

Compound	ORGANISMS								
	Bs	Ea	Ec	Kp	Pv	PRD	Pa	Sc	Sa
(7) pH 6.8	<10	25	25	<10	<10	25	<10	25	<10
pH 8.2	-	-	-	-	-	-	-	-	-
(8) pH 6.8	<10	250	50	100	25	500	250	25	25
pH 8.2	25	250	100	50	25	250	100	50	25
(9) pH 6.8	<10	100	50	25	50	>500	>500	50	25
pH 8.2	250	500	>500	500	500	>500	>500	>500	500
(10) pH 6.8	250	>500	50	50	>500	>500	>500	>500	250
pH 8.2	500	>500	>500	250	>500	>500	500	500	500
(11) pH 6.8	25	>500	50	50	>500	>500	>500	50	25
pH 8.2	100	>500	500	500	500	500	500	500	250
(12) pH 6.8	<10	>500	250	>500	>500	>500	>500	100	25
pH 8.2	250	500	500	500	500	500	500	500	500
(13) pH 6.8	<10	250	50	100	25	250	100	100	25
pH 8.2	50	500	250	100	100	250	100	250	50
(14) pH 6.8	25	500	500	500	500	500	500	500	50
pH 8.2	500	500	500	500	500	500	500	500	500

TABLE II CONTINUATION

Compound (Example No.)	ORGANISMS								
	Bs	Ea	Ec	Kp	Pv	PRD	Pa	Sc	Sa
(15) pH 6.8	25	>500	>500	>500	>500	>500	>500	>500	250
pH 8.2	250	500	500	500	500	500	500	500	500
(16) pH 6.8	100	>500	>500	>500	>500	>500	>500	>500	>500
pH 8.2	>500	>500	>500	>500	>500	>500	>500	>500	>500
(17) pH 6.8	<10	>500	>500	>500	>500	>500	>500	>500	50
pH 8.2	250	500	500	500	500	500	500	500	250
(18) pH 6.8	25	>500	>500	>500	>500	>500	>500	>500	>500
pH 8.2	500	500	500	500	500	500	500	500	500
(19) pH 6.8	25	500	500	250	500	500	500	500	100
pH 8.2	500	500	500	500	500	500	500	500	500
(20) pH 6.8	25	500	500	500	500	500	500	500	500
pH 8.2	500	500	500	500	500	500	500	500	500
(21) pH 6.8	25	500	500	100	500	500	500	500	50
pH 8.2	>100	>100	>100	>100	>100	>100	>100	>100	>100
(22) pH 6.8	25	100	50	25	50	500	500	50	25
pH 8.2	100	500	500	500	500	500	500	500	500

TABLE II CONTINUATION

Compound (Example No.)	ORGANISMS								
	Bs	Ea	Ec	Kp	Pv	PRD	Pa	Sc	Sa
(23) pH 6.8	25	250	250	100	100	500	500	250	50
pH 8.2	100	500	500	500	500	500	500	500	500
(24) pH 6.8	<10	50	25	25	50	25	25	25	25
pH 8.2	250	500	250	100	250	50	250	250	50
(25) pH 6.8	9	>500	>500	>500	>500	>500	>500	>500	>500
pH 8.2	25	>500	>500	>500	>500	>500	>500	>500	>500
(26) pH 6.8	500	500	500	500	500	500	500	500	500
pH 8.2	500	>500	250	>500	>500	>500	>500	>500	>500
(27) pH 6.8	9	500	500	500	500	500	500	500	9
pH 8.2	9	>500	500	>500	>500	>500	>500	>500	9
(28) pH 6.8	9	500	500	500	500	500	500	500	9
pH 8.2	9	>500	250	>500	>500	>500	>500	>500	9
(29) pH 6.8	9	500	500	500	500	250	250	500	500
pH 8.2	100	>500	250	>500	>500	>500	>500	>500	>500
(30) pH 6.8	9	500	500	500	500	500	500	500	500
pH 8.2	25	>500	500	>500	>500	>500	>500	>500	500

TABLE II CONTINUATION

Compound (Example No.)	ORGANISMS								
	Bs	Ea	Ec	Kp	Pv	PRD	Pa	Sc	Sa
(31) pH 6.8	500	>500	>500	>500	>500	>500	>500	>500	>500
pH 8.2	250	500	>500	>500	>500	>500	>500	>500	>500
(32) pH 6.8	500	500	500	500	500	500	500	500	500
pH 8.2	500	>500	250	>500	>500	>500	>500	>500	>500
(33) pH 6.8	500	500	500	500	500	500	500	500	500
pH 8.2	500	>500	500	>500	>500	>500	>500	>500	500
(34) pH 6.8	9	500	500	500	500	500	500	500	25
pH 8.2	9	>500	250	>500	>500	>500	>500	>500	25
(35) pH 6.8	25	500	500	500	500	250	500	500	250
pH 8.2	25	500	500	500	500	500	250	500	25
(36) pH 6.8	500	500	500	500	500	500	500	500	500
pH 8.2	500	>500	500	>500	>500	>500	>500	>500	500
(37) pH 6.8	50	500	500	500	500	500	500	500	500
pH 8.2	500	>500	500	>500	>500	>500	>500	>500	500
(38) pH 6.8	500	500	500	500	500	500	500	500	500
pH 8.2	500	>500	250	>500	>500	>500	>500	>500	>500
(39) pH 6.8	50	500	500	500	500	500	500	500	100
pH 8.2	25	>500	250	>500	>500	>500	>500	>500	50

TABLE III
Minimum Inhibitory Concentrations for Test Compounds
in Yeast/Fungi Species (in ppm) at pH 5.5

COMPOUND (EXAMPLE NO.)	ORGANISMS						
	An	Ca	Pc	Sc	Tv	Ap	Fo
STANDARD I	>500	>500	>500	500	>500	>500	>500
1	<10	<10	<10	<10	<10	<10	<10
2	<1	<1	<1	5	5	<1	2.5
3	<10	<10	<10	<10	<10	<10	<10
4	<2.5	<2.5	<2.5	<2.5	10	<2.5	<2.5
5	<10	100	<10	<10	>500	<10	250
6	<10	<10	<10	<10	25	<10	<10
7	<10	25	<10	<10	25	<10	<10
8	<10	50	<10	25	50	<10	25
9	2.5	2.5	2.5	<1	2.5	<1	2.5
10	<10	<10	<10	<10	<10	<10	<10
11	5	5	2.5	2.5	2.5	2.5	2.5
12	25	<10	10	2.5	10	5	5
13	5	25	2.5	5	25	2.5	10
14	5	5	10	5	<1	2.5	5
15	10	50	25	5	5	5	5
16	100	25	>500	9	9	9	50
17	<10	50	<10	<10	<10	<10	<10
18	5	5	5	2.5	2.5	2.5	5
19	500	500	500	250	250	50	100
20	25	10	100	10	10	10	10
21	<10	<10	<10	<10	<10	<10	<10
22	<10	25	<10	<10	<10	<10	<10
23	100	100	100	50	100	50	50
24	2.5	5	2.5	2.5	10	2.5	5
25	25	500	9	9	500	9	250

Table III CONTINUATION

COMPOUND (EXAMPLE NO.)	ORGANISMS						
	An	Ca	Pc	Sc	Tv	Ap	Fo
26	9	250	9	9	250	9	100
27	5	25	2.5	1	>500	2.5	500
28	9	250	9	9	>500	9	25
29	9	9	9	9	25	9	9
30	50	250	25	9	250	9	50
31	25	250	50	9	250	9	100
32	500	500	500	500	500	500	500
33	250	500	9	500	>500	250	>500
34	25	>500	2.5	2.5	>500	5	>500
35	9	50	9	9	100	9	25
36	100	500	100	250	>500	50	250
38	9	9	9	9	9	>500	9
38	50	100	9	9	250	25	100
39	25	25	9	9	50	9	25

20

The present invention is also directed to a method for inhibiting marine organisms. The term "marine organisms" is meant to include marine animals, such as barnacles, serpulid, bryozoa, oysters and hydroids, and marine plants, such as green algae and brown algae. The method for inhibiting marine organisms comprises contacting a surface exposed to a marine environment in which marine organisms grow with a marine antifouling effective amount of the compound of this invention.

As appreciated by those skilled in the art, not all of the compounds disclosed herein are active at the same concentrations or against the same marine organism species. That is, there may be some compound-to-compound variation in marine antifouling potency and spectrum of marine antifouling activity. Furthermore, a compound's marine antifouling activity may be dependent on the specific materials with which the compound is formulated to form a marine antifouling composition.

As used herein, the term "marine antifouling effective amount" refers to that amount of one or a mixture of two or more of the compounds of this invention needed to exhibit inhibition of selected marine organisms. Typically, this amount varies from providing 1 weight percent to 30 weight percent of the compound to a marine antifouling composition which is used to treat a surface exposed to a marine environment in which marine organisms live or grow. Such amounts vary depending upon the particular compound tested and marine

organism to be treated. Also, the exact concentration of the compounds to be added in the preparation of industrial and consumer formulations may vary within a product type depending upon the components of the formulation.

5 A composition comprising a marine antifouling effective amount of the compound will also comprise an inert diluent which may be, for example, in the form of a paint. Particularly preferred are those paints having a vinyl resin binder such as, for example, a plasticized polyvinyl chloride or a polyvinyl chloride-polyvinyl acetate type. Preferably, the binders are formulated as latexes or emulsions. In a paint composition, the compound of the present invention is preferably used in an amount from 1 to 30 weight percent and, most
10 preferably, from 10 to 25 weight percent. In addition to vinyl resin binder paints, epoxy and polyurethane binder paints containing the compound may also be useful. Coatings and films prepared from paints comprising the compound of the present invention typically remain substantially free from build-up of marine organisms for periods ranging from 3 to 12 months, depending upon the concentration of the compound and the thickness of the applied
15 coating or film.

The term "a surface exposed to a marine environment" refers to a surface where a marine organism naturally or normally lives or grows. Typically, such a surface will be an area that is in continual or periodic contact with a marine environment such as an ocean or other body of water. Typical surfaces include, for example, a ship hull.

20 The marine antifouling activity of the compounds of the present invention is demonstrated by the following techniques.

Test panels are prepared from clear, rigid polyvinyl chloride film that is 0.381×10^{-3} m thick and has one textured surface. The test panels are 0.1524 m by 0.1524 m squares that have 0.00635 m holes punched at corners on 0.127 m centers. A 0.102 square
25 template, with a 0.067 m diameter hole at the center, is attached to the center of the textured surface of the test panels.

A candidate marine antifoulant compound (1.0 g) is stirred into a resinous latex binder (9.0 g). A portion of the compound/binder mixture (1.5 g) is added to the center of the test panel and uniformly spread over the circular area inside the template.

30 Water is added dropwise as needed to properly spread the compound/binder mixture. The template prevents the compound/binder mixture from spreading beyond the uncovered area. The test panel is allowed to sit for between 10 to 30 minutes until the edge of the spread compound/binder mixture has dried. The template is then removed. The test panel is then allowed to dry for 8 to 12 hours at room temperature.

35 Two test panels are prepared for each candidate marine antifoulant compound. Two control test panels are also prepared by only treating with the resinous latex binder. One test panel of each candidate marine surfactant compound is attached over a white background to the topside of an exposure support apparatus. The second test panel is attached over a

black background to the underside of the exposure support apparatus. The exposure support apparatus is placed horizontally 0.0254 m under a marine surface with the white background topside facing up. The exposure support apparatus is exposed to the marine environment for both 3 and 6 weeks during which time the control test panels become substantially covered with mature marine organism growth on both the topside and underside exposures.

After being removed from the exposure support apparatus, each test panel is inspected and rated for marine organism growth on both the treated and untreated areas of the test panel. The marine organisms present on the treated and untreated areas are noted. The presence of algae spores and bacterial slime are noted but not included in rating each test panel. The test panels are rated on a scale from 10 (representing completely free of marine organism growth) to 0 (representing completely covered with marine organism growth).

In Table IV, the marine antifouling rating values for some of the compounds listed in Table I are set forth, as well as the ratings for control panels (with no marine antifouling compound and referred to in Table IV as "Control").

In addition, test panels were prepared using tributyl tin oxide, a known marine antifouling compound. One set of such panels used the tributyl tin oxide in a commercially available ship-hull paint (referred to in Table IV as "STANDARD II") which was employed in the same manner as the resinous latex binder used on the other test panels. A second set of such panels used the tributyl tin oxide at a 10 percent concentration in the resinous latex binder (referred to in Table IV as "STANDARD III").

TABLE IV

Marine Antifouling Rating for Test Compounds

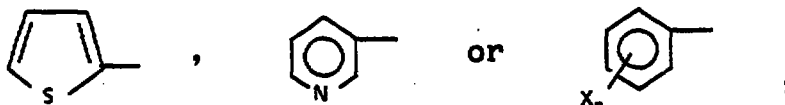
Compound Example No.	Marine Antifouling Ratings			
	10 Week Test		20 Week Test	
	Top Panel	Bottom Panel	Top Panel	Bottom Panel
2	9	9	2	7
4	9	9	7	5
9	7	7	4	3
24	9	9	4	9
Control	7	1	1	1
STANDARD II	10	7	9	7
STANDARD III	9	8	9	7

Claims :

1. A compound corresponding to the formula:



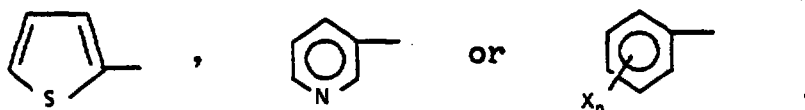
wherein R represents -Br, -Cl, -OCH₃, -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN, -SCH₂CH₂SCN



15

Y represents -Br, -Cl, -OCH₃, -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN or -SCH₂CH₂SCN; X represents -Br, -Cl, -F, -CH₃, -OCH₃, -COOCH₃, -NO₂, -SCH₃, -SO₂CH₃ or -CF₃ and n is an integer of from 0-5, with the proviso that at least one of R or Y represents -SCN, OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN or -SCH₂CH₂SCN and with further proviso that when R is

20



25

Y is -SCN or -SCH₂SCN.

2. The compound as defined in Claim 1 which is 4-phenyl-3-thiocyanatomethylthio-1,2,5-thiadiazole.

3. The compound of Claim 1 which is 4-chloro-3-thiocyanato-1,2,5-thiadiazole.

30

4. The compound of Claim 1 which is bis(thiocyanato)-1,2,5-thiadiazole.

5. The compound of Claim 1 which is 4-chloro-3-thiomethylthiocyanato-1,2,5-thiadiazole.

6. The compound of Claim 1 which is bis(thiomethylthiocyanato)-1,2,5-thiadiazole.

35

7. The compound of Claim 1 which is bis(thioethylthiocyanato)-1,2,5-thiadiazole.

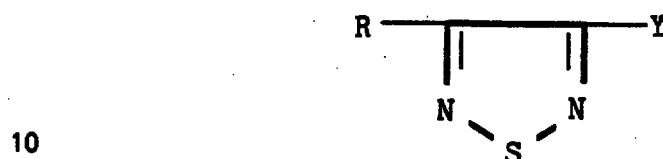
8. The compound of Claim 1 which is 4-chloro-3-thiocyanatomethyloxo-1,2,5-thiadiazole.



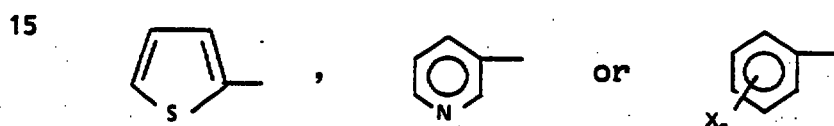
9. The compound of Claim 1 which is 4-methoxy-3-thiocyanatomethyloxo-1,2,5-thiadiazole.

10. The compound of Claim 1 which is bis(thiocyanatomethyloxo)-1,2,5-thiadiazole.

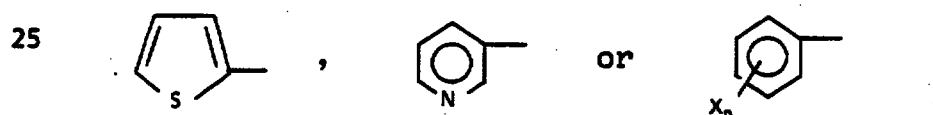
5 11. An antimicrobial composition comprising an inert diluent and an antimicrobially-effective amount of a compound corresponding to the formula:



wherein R represents -Br, -Cl, -OCH₃, -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN, -SCH₂CH₂SCN



Y represents -Br, -Cl, -OCH₃, -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN or -SCH₂CH₂SCN; X
20 represents -Br, -Cl, -F, -CH₃, -OCH₃, -COOCH₃, -NO₂, -SCH₃, -SO₂CH₃ or -CF₃ and n is an integer of from 0-5, with the proviso that at least one of R or Y represents -SCN, OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN or -SCH₂CH₂SCN and with further proviso that when R is



Y is -SCN or -SCH₂SCN.

30 12. The composition as defined in Claim 11 wherein the compound is 4-phenyl-3-thiocyanatomethylthio-1,2,5-thiadiazole.

13. The composition of Claim 11 wherein the compound is 4-chloro-3-thiocyanato-1,2,5-thiadiazole.

35 14. The composition of Claim 11 wherein the compound is bis(thiocyanato)-1,2,5-thiadiazole.

15. The composition of Claim 11 wherein the compound is 4-chloro-3-thiomethylthiocyanato-1,2,5-thiadiazole.



16. The composition of Claim 11 wherein the compound is bis(thiomethylthiocyanato)-1,2,5-thiadiazole.

17. The composition of Claim 11 wherein the compound is bis(thioethylthiocyanato)-1,2,5-thiadiazole.

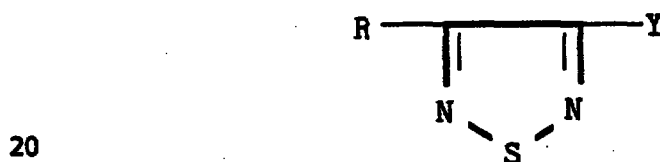
5 18. The composition of Claim 11 wherein the compound is 4-chloro-3-
-thiocyanatomethyloxo-1,2,5-thiadiazole.

19. The composition of Claim 11 wherein the compound is 4-methoxy-3-thiocyanatomethyloxo-1,2,5-thiadiazole.

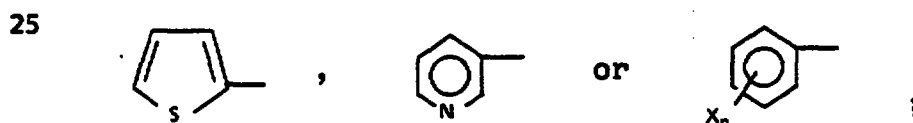
20. The composition of Claim 11 wherein the compound is
10 bis(thiocyanatomethyloxy)-1,2,5-thiadiazole.

21. The composition of Claim 11 wherein the compound is present in an amount to provide from 1 part per million to 5,000 parts per million by weight of the compound to a microbial habitat that is contacted with the composition.

22. A method for inhibiting microorganisms in a microbial habitat comprising
15 contacting said microbial habitat with an antimicrobially-effective amount of a compound
corresponding to the formula:

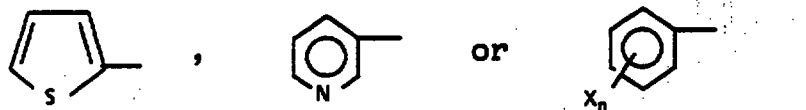


wherein R represents -Br, -Cl, -OCH₃, -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN, -SCH₂CH₂SCN



30 Y represents -Br, -Cl, -OCH₃, -SCN, -OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN or -SCH₂CH₂SCN; X represents -Br, -Cl, -F, -CH₃, -OCH₃, -COOCH₃, -NO₂, -SCH₃, -SO₂CH₃ or -CF₃ and n is an integer of from 0-5, with the proviso that at least one of R or Y represents -SCN, OCH₂SCN, -SCH₂SCN, -OCH₂CH₂SCN or -SCH₂CH₂SCN and with further proviso that when R is





Y is -SCN or -SCH₂SCN.

23. The method as defined in Claim 22 wherein the compound is 4-phenyl-3-thiocyanatomethylthio-1,2,5-thiadiazole.

24. The method of Claim 22 wherein the compound is 4-chloro-3-thiocyanato-1,2,5-thiadiazole.

25. The method of Claim 22 wherein the compound is bis(thiocyanato)-1,2,5-thiadiazole.

26. The method of Claim 22 wherein the compound is 4-chloro-3-thiomethylthiocyanato-1,2,5-thiadiazole.

27. The method of Claim 22 wherein the compound is bis(thiomethylthiocyanato)-1,2,5-thiadiazole.

28. The method of Claim 22 wherein the compound is bis(thioethylthiocyanato)-1,2,5-thiadiazole.

29. The method of Claim 22 wherein the compound is 4-chloro-3-thiocyanatomethyloxo-1,2,5-thiadiazole.

30. The method of Claim 22 wherein the compound is 4-methoxy-3-thiocyanatomethyloxo-1,2,5-thiadiazole.

31. The method of Claim 22 wherein the compound is bis(thiocyanatomethyloxo)-1,2,5-thiadiazole.

