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(71) Applicant (for all designated States except US): SYNGENTA LIMITED [GB/GB]; European Regional Centre, Priestley Road, Surrey Research Park, Guildford, Surrey GU2 7YH (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): DALLIMORE, Jonathan, Wesley, Paul [GB/GB]; Syngenta Limited, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY (GB). EL QACEMI, Myriem [FR/GB]; Syngenta Limited, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY (GB). WILLIAMS, John [GB/GB]; Syngenta Limited, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY (GB). KOZAKIEWICZ, Anthony, Marian [GB/GB]; Syngenta Limited, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY (GB).

(74) Agents: WARD, Steven, Paul et al.; Intellectual Property Department, Syngenta Limited, P.O. Box 3538, Jealott's

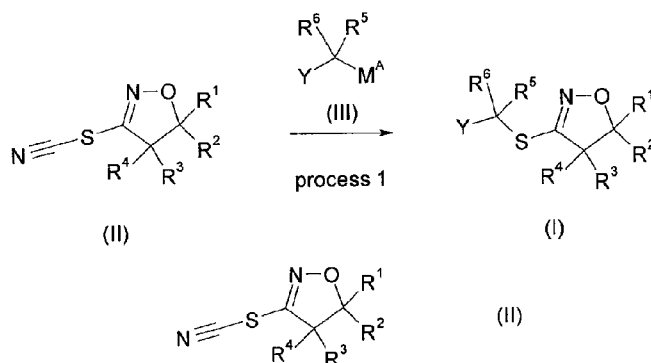
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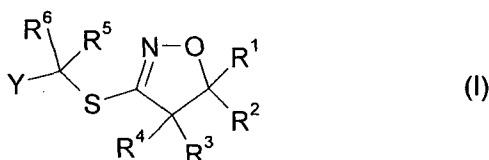
(57) Abstract: The present invention relates to a process for making isoxazoline herbicides (or isoxazoline herbicide precursors), to the intermediate used in this process, and to two processes for making the intermediate.

PROCESSES FOR MAKING ISOXAZOLINE DERIVATIVES

The present invention relates to a process for making isoxazoline herbicides (or isoxazoline herbicide precursors), to an intermediate to be used in this process and to several processes for making the intermediate.

Certain isoxazoline herbicides (and isoxazoline herbicide precursors) have been disclosed, for example, in EP 1,203,768 and EP 1,364,946. For example, 4,5-dihydro-5,5-dimethyl-3-[(phenylmethyl)thio]-isoxazole (CAS RN 326828-96-0) was disclosed as a herbicide and as an intermediate in the synthesis of 4,5-dihydro-5,5-dimethyl-3-[(phenylmethyl)sulfonyl]-isoxazole (CAS RN 326829-12-3) in EP 1,203,768. Therefore, the compounds of formula (I) are referred to as isoxazoline herbicides or as isoxazoline herbicide precursors. Routes to isoxazoline herbicides (or isoxazoline herbicide precursors) have been disclosed, for example, in EP 1,541,561. However, there is a need for further processes to isoxazoline herbicides (or isoxazoline herbicide precursors).

The present invention therefore provides a process for making a compound of formula (I)



where

R¹ and R² are independently hydrogen, C₁-C₈alkyl or C₃-C₁₀cycloalkyl or R¹ and R² join to form together with the carbon atom to which they are attached a C₃-C₁₀cycloalkyl ring;

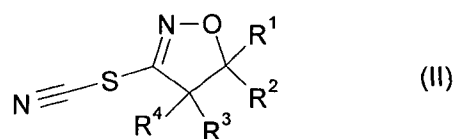
R³ and R⁴ are independently hydrogen or C₁-C₈alkyl or R³ and R⁴ join to form together with the carbon atom to which they are attached a C₃-C₁₀cycloalkyl ring;

R⁵ and R⁶ are independently hydrogen or C₁-C₈alkyl;

Y is aryl or aryl substituted by one to five R⁷, or heteroaryl or heteroaryl substituted by one to five R⁷; and

each R⁷ is independently cyano, nitro, halogen, C₁-C₈alkyl, C₁-C₈haloalkyl, C₁-C₈alkoxy- or C₁-C₈haloalkoxy-;

which comprises reacting a compound of formula (II)



where R^1 , R^2 , R^3 and R^4 are as defined for a compound of formula (I);
with a Grignard reagent of formula (III) thereof



where R^5 , R^6 and Y are as defined for a compound of formula (I) and M^A is MgBr or MgCl;

in the presence of an anhydrous solvent and under a protective atmosphere.

The compounds of formula (I) may exist in different geometric or optical isomers or tautomeric forms. This invention covers all such isomers and tautomers and mixtures thereof in all proportions as well as isotopic forms such as deuterated compounds.

Alkyl groups (either alone or as part of a larger group, such as alkoxy-) can be in the form of a straight or branched chain and are, for example, methyl, ethyl, propyl, prop-2-yl, butyl, but-2-yl, 2-methyl-prop-1-yl or 2-methyl-prop-2-yl. Unless indicated to the contrary, the alkyl groups are preferably C_1 - C_6 , more preferably C_1 - C_4 , most preferably C_1 - C_3 alkyl groups.

Halogen is fluorine, chlorine, bromine or iodine.

Haloalkyl groups (either alone or as part of a larger group, such as haloalkoxy-) are alkyl groups which are substituted by one or more of the same or different halogen atoms and are, for example, difluoromethyl, trifluoromethyl, chlorodifluoromethyl or 2,2,2-trifluoro-ethyl.

Cycloalkyl groups or carbocyclic rings can be in mono- or bi-cyclic form and are, for example, cyclopropyl, cyclobutyl, cyclohexyl and bicyclo[2.2.1]heptan-2-yl. The cycloalkyl groups are preferably C_3 - C_8 , more preferably C_3 - C_6 cycloalkyl groups.

Aryl groups are aromatic ring systems which can be in mono-, bi- or tricyclic form. Examples of such rings include phenyl, naphthyl, anthracenyl, indenyl or

phenanthrenyl. Unless indicated to the contrary, aryl groups are preferably phenyl and naphthyl, with phenyl being most preferred. Where an aryl moiety is said to be substituted, the aryl moiety is preferably substituted by one to four substituents, most preferably by one to three substituents.

Heteroaryl groups are aromatic ring systems containing at least one heteroatom and consisting either of a single ring or of two or more fused rings. Preferably, single rings will contain up to three heteroatoms and bicyclic systems up to four heteroatoms which will preferably be chosen from nitrogen, oxygen and sulfur. Examples of monocyclic groups include pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl. Examples of bicyclic groups include quinolinyl, cinnolinyl, quinoxalinyl, indolyl, indazolyl, benzimidazolyl, benzothiophenyl and benzothiazolyl. Unless indicated to the contrary, monocyclic heteroaryl groups are preferred, with pyrazolyl and triazolyl being most preferred. Where a heteroaryl moiety is said to be substituted, the heteroaryl moiety is preferably substituted by one to four substituents, most preferably by one to three substituents.

Preferred values of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , Y and R^7 for the compounds of formula (I) and (II) are, in any combination, as set out below.

Preferably R^1 is C_1 - C_8 alkyl or C_3 - C_{10} cycloalkyl, more preferably C_1 - C_8 alkyl, even more preferably methyl or ethyl, most preferably methyl.

Preferably R^2 is C_1 - C_8 alkyl or C_3 - C_{10} cycloalkyl, more preferably C_1 - C_8 alkyl, even more preferably methyl or ethyl, most preferably methyl.

Preferably R^3 is hydrogen or C_1 - C_8 alkyl, more preferably hydrogen.

Preferably R^4 is hydrogen or C_1 - C_8 alkyl, more preferably hydrogen.

Preferably R^5 is hydrogen.

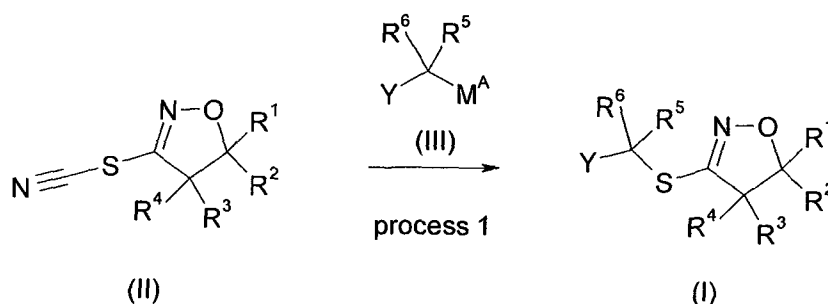
Preferably R^6 is hydrogen.

Preferably Y is phenyl or phenyl substituted by one to five R^7 , or heteroaryl or heteroaryl substituted by one to five R^7 (where heteroaryl is pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl or thiadiazolyl), more preferably phenyl or phenyl substituted by one to five R^7 , or heteroaryl or heteroaryl substituted by one to five R^7 (where heteroaryl is pyrazolyl or triazolyl), even more preferably phenyl or phenyl substituted by one to five R^7 , most preferably phenyl.

Preferably each R^7 is independently halogen, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, C_1 - C_8 alkoxy- or C_1 - C_8 haloalkoxy-, more preferably chloro, fluoro, methyl, ethyl, trifluoromethyl, methoxy, difluoromethoxy- or trifluoromethoxy-.

Scheme A shows the process for making a compound of formula (I) from a compound of formula (II) (process 1).

Scheme A



Process 1:

Compounds of formula (I) can be made by reacting a thiocyanato-isoxazoline of formula (II) where R^1 , R^2 , R^3 and R^4 are as defined for a compound of formula (I) with a Grignard reagent of formula (III) where R^5 , R^6 and Y are as defined for a compound of formula (I) and M^A is MgBr or MgCl, in the presence of an anhydrous solvent and under a protective atmosphere.

Grignard reagents of formula (III) are commercially available or can be made by methods known to the person skilled in the art. It is preferred that M^A is MgBr.

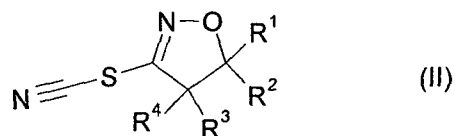
The solvent can be any anhydrous solvent which does not react with the Grignard reagent, for example an anhydrous ether, such as anhydrous tetrahydrofuran.

The atmosphere can be any gas which does not react with the Grignard reagent, for example a nitrogen atmosphere or an argon atmosphere. It is preferred that atmosphere is a nitrogen atmosphere.

The reaction is preferably carried out at a temperature of from -20°C to $+70^\circ\text{C}$, more preferably of from -5°C to ambient temperature, most preferably at 0°C .

Similar reactions of thiocyanato-substituted heterocycles with benzylic Grignard reagents have been described in the literature, for example, in *Chemical & Pharmaceutical Bulletin*, 37, 618 (1989).

Compounds of formula (II) are novel and as such form a further aspect of the invention. Therefore, the invention provides a compound of formula (II)



where R^1 , R^2 , R^3 and R^4 are as defined for a compound of formula (I).

The compounds of formula (II) may exist in different geometric or optical isomers or tautomeric forms. This invention covers all such isomers and tautomers and mixtures thereof in all proportions as well as isotopic forms such as deuterated compounds.

Examples of compounds of formula (II) which illustrate the present invention are given in Table 1.

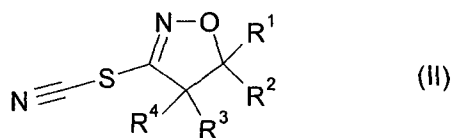
Table 1:

Table 1 provides 2 compounds of formula (II) where R^1 , R^2 , R^3 and R^4 have the values specified.

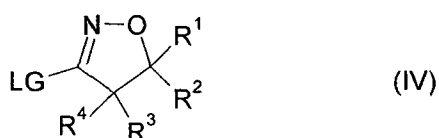
Compound Number	R^1	R^2	R^3	R^4
II-1	Me	Me	H	H
II-2	Me	Et	H	H

The present invention also provides processes for making a compound of formula (II).

Firstly, the present invention provides a process for making a compound of formula (II)

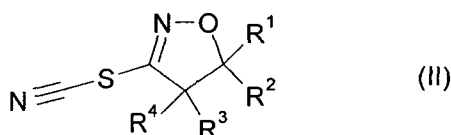


where R^1 , R^2 , R^3 and R^4 are as defined for a compound of formula (I);
which comprises reacting an isoxazoline derivative of formula (IV) or a salt thereof

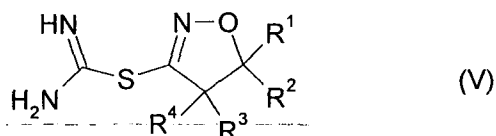


where R^1 , R^2 , R^3 and R^4 are as defined for a compound of formula (I) and LG is a leaving group;
with a thiocyanate salt in the presence of an acid and in the presence of a solvent.

Secondly, the present invention provides a process for making a compound of formula (II)



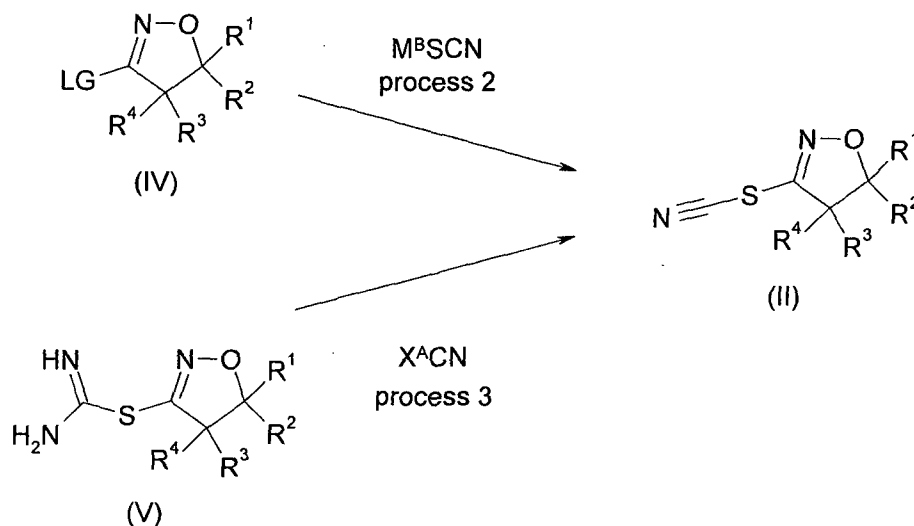
where R^1 , R^2 , R^3 and R^4 are as defined for a compound of formula (I);
which comprises reacting an isothiuronium-isoxazoline of formula (V) or a salt thereof



where R^1 , R^2 , R^3 and R^4 are as defined for a compound of formula (I);
with a cyanogen salt in the presence of a base and in the presence a solvent.

Scheme B shows the processes for making a compound of formula (II) (process 2, process 3).

Scheme B



Process 2:

Compounds of formula (II) as defined for process 1 can be made by reacting an isoxazoline derivative of formula (IV) or a salt thereof where R^1 , R^2 , R^3 and R^4 are as defined for a compound of formula (I) and LG is a leaving group, with a thiocyanate salt in the presence of an acid and in the presence of a solvent.

The leaving group can be any chemical group which can be readily displaced by a nucleophile. The leaving group can be, for example, a halogen atom, such as a bromo group or a chloro group, or a nitro group, or a sulfonyl, such as methylsulfonyl or phenylsulfonyl. It is preferred that the leaving group is chloro or nitro.

The preparation of certain bromo-isoxazolines is described, for example, in WO 2006/038657.

The preparation of certain chloro-isoxazolines is described, for example, in EP 1,203,768.

The preparation of certain nitro-isoxazolines is described, for example, in WO 2001/046163.

The preparation of certain methylsulfonyl-isoxazolines is described, for example, in EP 1,203,768.

The preparation of certain phenylsulfonyl-isoxazolines is described, for example, in WO 2007/071900.

The thiocyanate salt is of the formula $M^B\text{SCN}$ where M^B is a metal cation, for example an alkali metal cation, such as a sodium cation or a potassium cation. It is preferred that M^B is a sodium cation. Thiocyanate salts of the formula $M^B\text{SCN}$ are commercially available.

The acid can be any acid which facilitates the reaction, for example an organic acid, such as formic acid, acetic acid or trifluoroacetic acid, or an inorganic acid, such as aqueous hydrochloric acid. It is preferred that the acid is formic acid.

The solvent can be any solvent which does not react with the isoxazoline derivative, for example dichloromethane, ethanol, or an excess of the organic acid which is used to facilitate the reaction. It is preferred that the solvent is an excess of formic acid.

The reaction is preferably carried out at a temperature of from 0°C to 200°C, more preferably of from 0°C to 100°C, most preferably at ambient temperature.

Similar reactions have been described in the literature with various outcomes. A thiocyanato-substituted heterocycle was obtained, for example, in *Bioorganic & Medicinal Chemistry Letters*, 17, 225, (2007), an isothiocyanato-substituted heterocycle was obtained, for example, in *Monatshefte fuer Chemie*, 135, 45, (2004), and a mixture of thiocyanato-substituted heterocycle and of isothiocyanato-substituted heterocycle was obtained, for example, in *Yakugaku Zasshi*, 108, 437, (1988).

Process 3:

Compounds of formula (II) as defined for process 1 can be made by reacting an isothiuronium-isoxazoline of formula (V) or a salt thereof where R^1 , R^2 , R^3 and R^4 are as defined for a compound of formula (I), with a cyanogen salt in the presence of a base and in the presence a solvent.

The preparation of isothiuronium-isoxazolines is described, for example, in EP 1,829,868. The isothiuronium-isoxazoline is usually isolated as a salt, for example the hydrochloric acid salt.

The cyanogen salt is of formula $X^A\text{CN}$ where X^A is a halide, such as chloride or a bromide. It is preferred that X^A is bromide. Cyanogen salts of formula $X^A\text{CN}$ are commercially available.

The base can be any base which facilitates the reaction, for example a carbonate, such as potassium carbonate, sodium carbonate or potassium hydrogen carbonate, or a hydroxide, such as potassium hydroxide, or an alkoxide, such as sodium alkoxide. It is preferred that the base is potassium carbonate.

The solvent can be any solvent which does not react with the isothiuronium-isoxazoline, polar solvents such as ethanol, acetonitrile, dimethylformamide, water or a mixture of thereof, being particularly preferred. It is preferred that the solvent is acetonitrile or a mixture of acetonitrile and water.

The reaction is preferably carried out at a temperature of from 0°C to 200°C, more preferably of from 0°C to 100°C, most preferably at ambient temperature.

Similar reactions have been described in, for example, *Chemical and Pharmaceutical Bulletin*, 12, 182, (1964), *Journal fuer Praktische Chemie (Leipzig)*, 326, 159 (1984), and *Tetrahedron Letters*, 32, 2505 (1991).

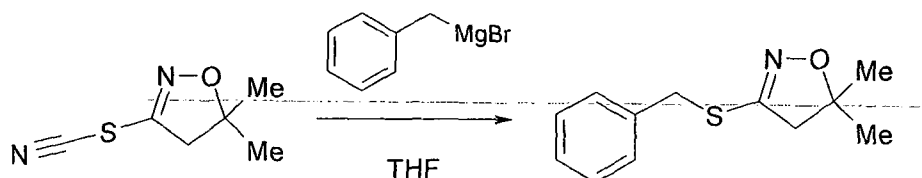
The following Examples further illustrate, but do not limit, the invention.

Preparation Examples

The following abbreviations were used throughout this section: s = singlet; bs = broad singlet; d = doublet; dd = double doublet; dt = double triplet; t = triplet, tt = triple triplet, q = quartet, sept = septet; m = multiplet; Me = methyl; Et = ethyl; Pr = propyl; Bu = butyl.

1. Process 1

Example 1.1: Preparation of 3-benzylsulfanyl-5,5-dimethyl-4,5-dihydro-isoxazole

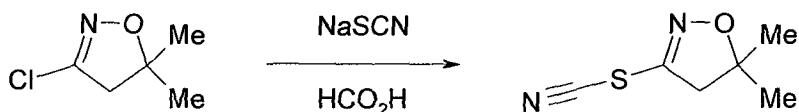


To a stirred solution of 5,5-dimethyl-3-thiocyanato-4,5-dihydro-isoxazole (Example 2.1 - Example 2.5 and Example 3.1 - Example 3.2) (250 mg, 1.6 mmol) in

anhydrous tetrahydrofuran ("THF") (3 ml) was added benzyl magnesium chloride (2M in tetrahydrofuran) (0.9 ml, 1.8 mmol) dropwise over a period of 5 minutes at 0°C under a nitrogen atmosphere. An additional amount of anhydrous tetrahydrofuran (6 ml) was added at 0°C. After 5 minutes the reaction mixture was poured into water and the mixture extracted with diethyl ether. The organic extract was dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate / hexane 1:4 to 1:0) to give the title compound as a yellow solid (304 mg, 83% yield). ¹H-NMR (CDCl₃, 400 MHz): 1.41 (s, 6H), 2.78 (s, 2H), 4.27 (s, 2H), 7.32 (m, 5H) ppm.

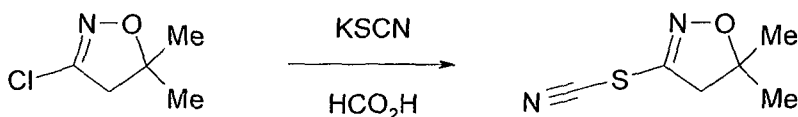
2. Process 2

Example 2.1: Preparation of 5,5-dimethyl-3-thiocyanato-4,5-dihydro-isoxazole



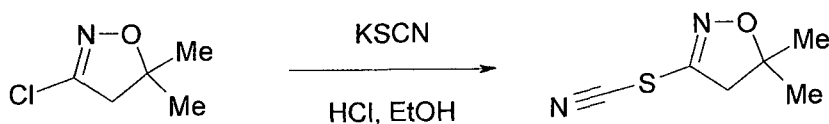
To a solution of 3-chloro-5,5-dimethyl-4,5-dihydro-isoxazole (preparation described, for example, in WO 2007/096576) (2.00 g, 15 mmol) in formic acid (12 ml) was added sodium thiocyanate (1.46 g, 18 mmol) in one portion at ambient temperature. The reaction mixture was stirred at ambient temperature for 4 hours. The reaction mixture was diluted with ethyl acetate, washed with aqueous sodium hydrogen carbonate (saturated), dried over magnesium sulfate and concentrated to give the title compound as an orange oil (2.05 g, 88% yield). ¹H-NMR (CDCl₃, 400 MHz): 1.50 (s, 6H), 3.1 (s, 2H) ppm.

Example 2.2: Alternative preparation of 5,5-dimethyl-3-thiocyanato-4,5-dihydro-isoxazole



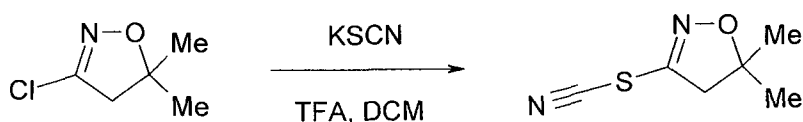
Potassium thiocyanate (1.75 g, 18 mmol) and 3-chloro-5,5-dimethyl-4,5-dihydro-isoxazole (preparation described, for example, in WO 2007/096576) (2.01g, 15 mmol) were suspended in formic acid (12 ml, 318 mmol) and the reaction mixture stirred at ambient temperature for 7 hours. The reaction mixture was diluted with diethyl ether and the mixture washed successively with water, aqueous sodium hydroxide (4M) and brine, dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (eluent: diethyl ether / hexane 0:1 to 1:19) to give a colorless oil (2.0 g, 89% yield).

Example 2.3: Alternative preparation of 5,5-dimethyl-3-thiocyanato-4,5-dihydro-isoxazole



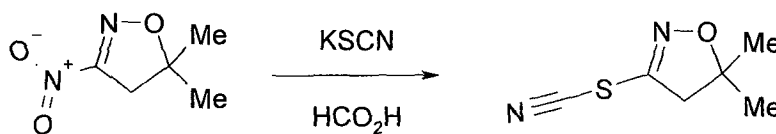
Potassium thiocyanate (160 mg, 1.65 mmol) was suspended in ethanol (3 ml) and 3-chloro-5,5-dimethyl-4,5-dihydro-isoxazole (preparation described, for example, in WO 2007/096576) (2.01g, 15 mmol) was added with stirring at ambient temperature. Aqueous hydrochloric acid (36% w/v) (0.03 ml) was added and the reaction mixture stirred at ambient temperature for 2 hours. Additional aqueous hydrochloric acid (concentrated) (0.5 ml) was added and the reaction mixture stirred at ambient temperature for 30 minutes and then stored at ambient temperature for 16 hours. ¹H-NMR (CDCl₃, 400 MHz) analysis of a sample showed that the title compound was formed in 55% yield and that the remainder of the material was starting material.

Example 2.4: Alternative preparation of 5,5-dimethyl-3-thiocyanato-4,5-dihydro-isoxazole



Potassium thiocyanate (160 mg, 1.65 mmol) and 3-chloro-5,5-dimethyl-4,5-dihydro-isoxazole (preparation described, for example, in WO 2007/096576) (210 mg, 1.57 mmol) were suspended in dichloromethane (3.0 ml). Trifluoroacetic acid ("TFA") (0.11 ml) was added and the reaction mixture stirred at ambient temperature for 9 hours. The reaction mixture was stored at ambient temperature for 15 hours. The reaction mixture was quenched by addition of water and washed with aqueous sodium hydrogen carbonate (saturated). The phases were separated and the aqueous phase extracted with diethyl ether. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (eluent: diethyl ether / hexane 0:1 to 1:9) to afford the title compound (170 mg, 66% yield).

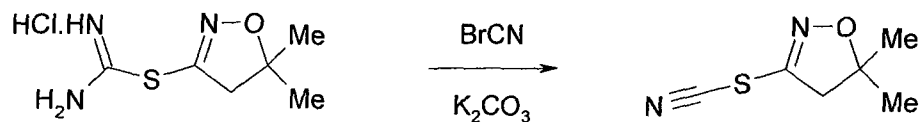
Example 2.5: Alternative preparation of 5,5-dimethyl-3-thiocyanato-4,5-dihydro-isoxazole



To a stirred solution of 5,5-dimethyl-3-nitro-4,5-dihydro-isoxazole (Example 4.1) (432 mg, 3.0 mmol) in formic acid (12 ml) was added potassium thiocyanate (388 g, 4.0 mmol) in one portion at ambient temperature. The reaction mixture was heated at 70°C for 1 hour. The reaction mixture was allowed to cool to ambient temperature and diluted with ethyl acetate, washed with aqueous sodium hydrogen carbonate (saturated), dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate / hexane 1:6) to give the title compound as a yellow oil (320 mg, 68% yield).

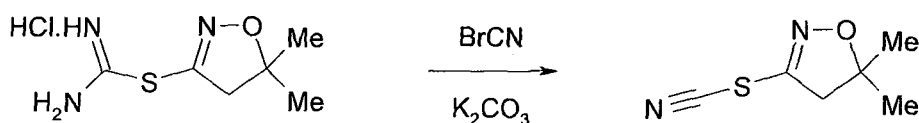
3. Process 3

Example 3.1: Alternative preparation of 5,5-dimethyl-3-thiocyanato-4,5-dihydro-isoxazole



To a suspension of 2-(5,5-dimethyl-4,5-dihydro-isoxazol-3-yl)-isothioureahydrochloride (preparation described, for example, in EP 1,829,868) (20.6 g, 0.1 mol) and potassium carbonate (28.0 g, 0.2 mol) in acetonitrile (200 ml) was added cyanogen bromide (17.0 g, 0.16 mol) in one portion at ambient temperature. The reaction mixture was stirred at ambient temperature for 37 hours. The reaction mixture was filtered and the filtrate concentrated. The residue was triturated with a mixture of hexane and diethyl ether (1:1) (200 ml). The resulting suspension was filtered and the filtrate concentrated. The residue was purified by column chromatography on silica gel (eluent: diethyl ether / hexane 1:1) to give the title compound as an oil (10.5 g, 67% yield).

Example 3.2: Alternative preparation of 5,5-dimethyl-3-thiocyanato-4,5-dihydro-isoxazole

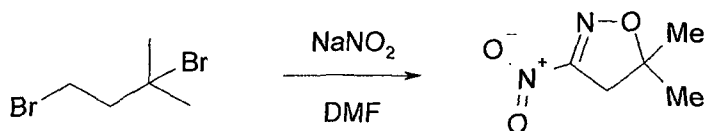


To a suspension of 2-(5,5-dimethyl-4,5-dihydro-isoxazol-3-yl)-isothioureahydrochloride (preparation described, for example, in EP 1,829,868) (20.6 g, 0.10 mol) and potassium carbonate (27.2 g, 0.20 mol) in acetonitrile (400 ml) was added cyanogen bromide (15.3 g, 0.15 mol) in one portion at ambient temperature followed by water (10 ml). The reaction mixture was stirred at ambient temperature for 34 hours. The reaction mixture was filtered and the filtrate concentrated. The residue was partitioned between water (1 l) and diethyl ether (1 l), the phases were separated and the organic extract washed with water (1 l), dried over magnesium sulfate and concentrated. The residue was

purified by column chromatography on silica gel (eluent: diethyl ether / hexane 1:1) to give the title compound as a pale yellow liquid (11.8 g, 76% yield).

4. Preparation of intermediates

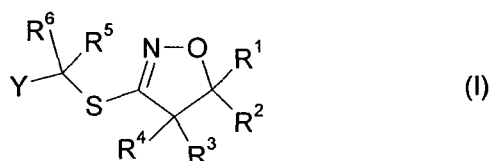
Example 4.1: Preparation of 5,5-dimethyl-3-nitro-4,5-dihydro-isoxazole



To a suspension of sodium nitrite (2.07 g, 30 mmol) in dimethylformamide ("DMF") (15 ml) was added 1,3 dibromo-3-methylbutane (commercially available) (2.30 g, 10 mmol) dropwise over a period of 5 minutes at ambient temperature. The reaction mixture was heated at 50°C for 1 hour. The reaction mixture was concentrated, diluted with diethyl ether, filtered through a plug of cellulose (such as Hyflo Super-Cel®) and concentrated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate / hexane 1:6) to give the title compound as a yellow oil (465 mg, 32% yield). ¹H-NMR (CDCl₃, 400 MHz): 1.58 (s, 6H), 3.26 (s, 2H) ppm.

CLAIMS:

1. A process for making a compound of formula (I)



where

R^1 and R^2 are independently hydrogen, C_1 - C_8 alkyl or C_3 - C_{10} cycloalkyl or R^1 and R^2 join to form together with the carbon atom to which they are attached a C_3 - C_{10} cycloalkyl ring;

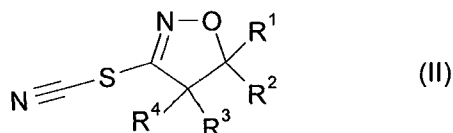
R^3 and R^4 are independently hydrogen or C_1 - C_8 alkyl or R^3 and R^4 join to form together with the carbon atom to which they are attached a C_3 - C_{10} cycloalkyl ring;

R^5 and R^6 are independently hydrogen or C_1 - C_8 alkyl;

Y is aryl or aryl substituted by one to five R^7 or heteroaryl or heteroaryl substituted by one to five R^7 ; and

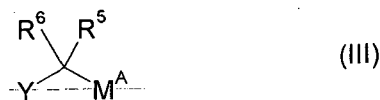
each R^7 is independently cyano, nitro, halogen, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, C_1 - C_8 alkoxy- or C_1 - C_8 haloalkoxy-;

which comprises reacting a compound of formula (II)



where R^1 , R^2 , R^3 and R^4 are as defined for a compound of formula (I);

with a Grignard reagent of formula (III)

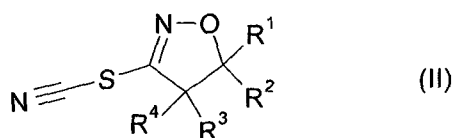


where R^5 , R^6 and Y are as defined for a compound of formula (I) and M^A is MgBr or MgCl;

in the presence of an anhydrous solvent and under a protective atmosphere.

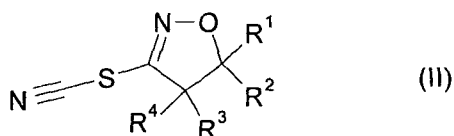
2. A process according to claim 1 where a process according to claim 4 or claim 5 precedes the process of claim 1.

3. A compound of formula (II)



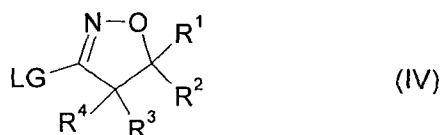
where R^1 , R^2 , R^3 and R^4 are as defined in claim 1.

4. A process for making a compound of formula (II)



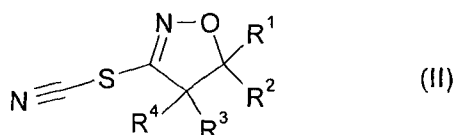
where R^1 , R^2 , R^3 and R^4 are as defined in claim 1;

which comprises reacting an isoxazoline derivative of formula (IV) or a salt thereof



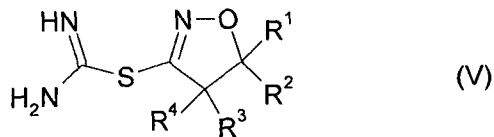
where R^1 , R^2 , R^3 and R^4 are as defined in claim 1 and LG is a leaving group;
with a thiocyanate salt in the presence of an acid and in the presence of a solvent.

5. A process for making a compound of formula (II)



where R^1 , R^2 , R^3 and R^4 are as defined in claim 1;

which comprises reacting an isothiuronium-isoxazoline of formula (V) or a salt thereof



where R^1 , R^2 , R^3 and R^4 are as defined in claim 1;

with a cyanogen salt in the presence of a base and in the presence a solvent.

6. A process according to any one of claims 1, 2, 4 or 5 or a compound according to claim 3 where R^1 and R^2 are C_1 - C_8 alkyl, R^3 , R^4 , R^5 and R^6 are hydrogen and Y is phenyl or phenyl substituted by one to five R^7 , or heteroaryl or heteroaryl substituted by one to five R^7 (where heteroaryl is pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl or thiadiazolyl).

7. A process according to claim 6 or a compound according to claim 6 where R^1 and R^2 are C_1 - C_8 alkyl, R^3 , R^4 , R^5 and R^6 are hydrogen and Y is phenyl or phenyl substituted by one to five R^7 .

8. A process according to claim 7 or a compound according to claim 7 where R^1 and R^2 are methyl, R^3 , R^4 , R^5 and R^6 are hydrogen and Y is phenyl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/000607

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D261/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 364 946 A1 (KUMIAI CHEMICAL INDUSTRY CO [JP]; IHARA CHEMICAL IND CO [JP]) 26 November 2003 (2003-11-26) cited in the application page 147 - paragraph 46 -----	1-8
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Y	EP 1 203 768 A1 (KUMIAI CHEMICAL INDUSTRY CO [JP] KUMIAI CHEMICAL INDUSTRY CO [JP]; IHA) 8 May 2002 (2002-05-08) cited in the application page 33 - paragraph 27 ----- -/--	1-8

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

30 July 2010

Date of mailing of the international search report

13/08/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Jeanjean, Fabien

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/000607

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	PAKULSKI Z ET AL: "Reaction of sugar thiocyanates with Grignard reagents. New synthesis of thioglycosides" TETRAHEDRON 1994 GB LNKD- DOI:10.1016/S0040-4020(01)87009-5, vol. 50, no. 9, 1994, pages 2975-2992, XP002593922 ISSN: 0040-4020 pages 2977-297; table 1 -----	1-8
Y	NAGASAKI IZURU ET AL: "SYNTHESIS OF ALKYLTHIO- AND ARYLTHIOHETEROARENES BY REGIOSELECTIVE GRIGNARD REACTION OF THIOCYANATOHETEROARENES" HETEROCYCLES, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 51, no. 5, 1 January 1999 (1999-01-01), pages 1015-1024, XP001525237 ISSN: 0385-5414 page 1016 -----	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2010/000607

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