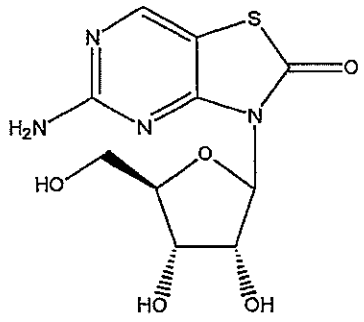
# NOVEL PROCESS FOR THE PREPARATION OF 5-AMINO-3H-THIAZOLO[4,5-*d*]PYRIMIDIN-2-ONE

## FIELD OF THE INVENTION

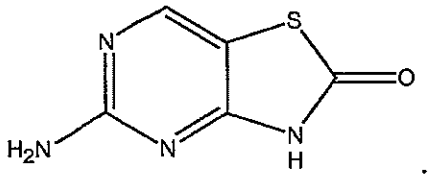
[0001] The present invention relates to a process for the preparation of the title compound, 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one, which is a useful intermediate in the preparation of certain thiazolo[4,5-*d*]pyrimidine nucleosides, which can have utility as immunomodulators.

## BACKGROUND

[0002] A variety of D- and L-purine nucleoside analogs have been explored for use as immunomodulators. A class of nucleoside analogs that can have utility for such purpose are thiazolo[4,5-*d*]pyrimidine nucleosides, such as those compounds disclosed in United States Published Application No. 2005/0070556, assigned to Anadys Pharmaceuticals, Inc., the entire disclosure of which is incorporated herein by reference. These compounds include, for example, 5-Amino-3-β-D-ribofuranosyl-3*H*-thiazolo[4,5-*d*]pyrimidin-2-one of formula




[0003] A useful intermediate in the preparation of this and other thiazolo[4,5-*d*]pyrimidine nucleosides is the pyrimidine base, 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one of formula

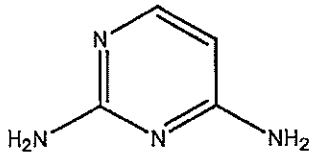


**[0004]** It would be desirable to provide an efficient and cost-effective process for the preparation of this compound. The present invention provides such a process.

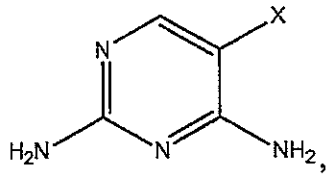
## SUMMARY OF THE INVENTION

**[0005]** The invention is directed to a process for the preparation of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one. The process comprises:

(i) halogenating a 2,4-diaminopyrimidine of formula

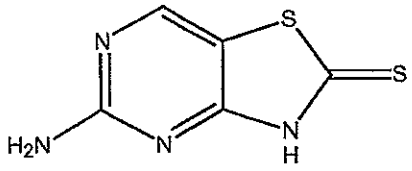


to form a 2,4-diamino-5-halo-pyrimidine of formula



wherein X represents halo selected from F, Cl, Br, and I;

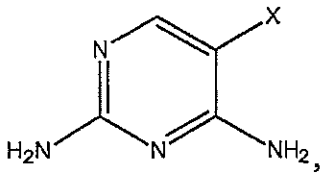
(ii) cyclocondensing the 2,4-diamino-5-halo-pyrimidine to form 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione of formula



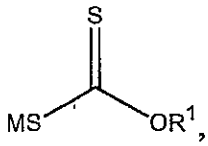
; and

(iii) oxidizing the 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione to form 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one.

**[0006]** In one embodiment, the invention is directed to a process for cyclocondensing a 2,4-diamino-5-halo-pyrimidine of formula



wherein X is halo selected from F, Cl, Br, and I, to form 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione, wherein the cyclocondensation is carried out in the presence of a xanthogenate compound having the formula



wherein M is a metal cation and $R^1$ is an alkyl group; and

wherein the reaction comprises heating the above reactants under nitrogen in the presence of an inert solvent.

**[0007]** In another embodiment, the invention is directed to a process for oxidizing 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione to form 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one, wherein the process comprises reacting 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione with an oxidizing agent under basic conditions and a subsequent acidic hydrolysis to give the desired 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one.

## DETAILED DESCRIPTION OF THE INVENTION

**[0008]** The present invention provides a novel process for the manufacture and purification of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one, a useful intermediate in the preparation of thiazolo[4,5-*d*]pyrimidine nucleosides, such as 5-amino-3-β-D-ribofuranosyl-3*H*-thiazolo[4,5-*d*]pyrimidin-2-one. The process involves the conversion of 2,4-diaminopyrimidine to 2,4-diamino-5-halo-pyrimidine followed by a cyclocondensation to afford 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione, and subsequent oxidation to the title compound.

[0009] The process can be made to be operationally simple, efficient, and robust, resulting in high overall yield and high throughput. For example, the three-step process of the invention can result in a yield of over 50%. In addition, the process can be made to be environmentally friendly, with low overall amounts of waste materials. Moreover, the process involves the use of inexpensive reagents, can be practiced without the use of chromatography, and can be amendable to scale-up. In this regard, the starting material for the process, 2,4-diaminopyrimidine, is relatively inexpensive and is commercially available in bulk quantities.

[0010] As used herein, the term "halogen" refers to fluorine, chlorine, bromine, and iodine and the term "halo" refers to substituents of the same.

[0011] As used herein, the term "alkyl" includes saturated monovalent hydrocarbon radicals having straight, branched, or cyclic moieties (including fused and bridged bicyclic and spirocyclic moieties), or a combination of the foregoing moieties. For an alkyl group to have cyclic moieties, the group must have at least three carbon atoms. Particularly notable alkyl groups include methyl, ethyl, propyl, and butyl.

[0012] The compounds of the invention may exhibit the phenomenon of tautomerism. While each formula drawing provided cannot expressly depict all possible tautomeric forms, it is to be understood that each formula is intended to represent any tautomeric form of the depicted compound and are not to be limited merely to a specific compound form depicted by the formula drawings. For example (as shown below), it is understood for the below formula that regardless of whether or not the substituents are shown in their enol or their keto form, they represent the same compound.




[0013] As used herein, the term "metal cation" refers to a cationic metal ion. Particularly notable metal cations are those of group 1A of the periodic table, including cations of lithium (Li), sodium (Na), and potassium (K).

**[0014]** As used herein, the term "inert solvent" refers to any solvent that can dissolve but will not significantly react with the reactants of a given reaction or reaction system. For example, in the cyclocondensation 2,4-diamino-5-halo-pyrimidine to form

**[0015]** 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione, suitable inert solvents can, for example, include N,N-Dimethylformamide (DMF), N,N-Dimethylacetamide (DMAc) and N-methyl pyrolidinone (NMP).

**[0016]** As used herein, the term "oxidizing agent" refers to a substance or species that gains electrons in a chemical reaction. For example, in the oxidation of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione to form 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one, suitable oxidizing agents can, for example, include hydrogen peroxide ($H_2O_2$), urea, hydrogen peroxide ($NH_2CONH_2.H_2O_2$), and sodium hypochlorite (NaClO).

**[0017]** The first step of a process falling within the scope of the invention involves halogenation of 2,4-diaminopyrimidine to form 2,4-diamino-5-halo-pyrimidine. This step can, for example, be carried out by first dissolving 2,4-diaminopyrimidine in a suitable solvent and then introducing a halogenating agent to the reaction mixture.

**[0018]** The temperature of reaction mixture in this step can, for example, range from about -20° C to 50° C, such as from about 0° C to room temperature (about 25° C). In addition, the molar ratio of 2, 4-diaminopyrimidine to halogenating agent can, for example, range from about 1.0:1.5 to 1.0:1.0, such as about 1.0:1.1 to 1.0:1.0. The volume of solvent per gram of 2,4-diaminopyrimidine can, for example, range from about 5 ml to 100 ml, such as about 10 ml to 30 ml.

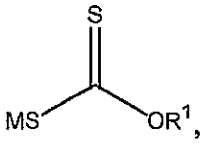
**[0019]** Examples of suitable solvents include tetrahydrofuran (THF), acetonitrile, methanol, ethanol, water and acetic acid. Preferred solvents include THF and acetic acid. Examples of halogenating agents include $Br_2$, $Cl_2$, $F_2$, $I_2$, and pyridinium tribromide ($PyHBr_3$). Preferred halogenating agents include $Br_2$ and $PyHBr_3$. When $Br_2$ or $PyHBr_3$ are used as halogenating agents, the compound produced in this first step is 2,4-diamino-5-bromo-pyrimidine.

**[0020]** The reaction product from this first step can be separated from the reaction mixture by any means known to those skilled in the art. For example, the reaction product can be separated from the reaction mixture by filtration, neutralization, filtration and washing with a solvent (for example, water) and/or a combination of these.

**[0021]** Alternately, the reaction product from this first step can be neutralized, concentrated and carried on to the next step without isolation.

**[0022]** Other methods of halogenating substituted pyrimidine compounds have been disclosed in, for example, English *et al., J Am. Chem. Soc'y*, 68, 453-58 (1946).

**[0023]** The next step of a process falling within the scope of the invention involves cyclocondensation 2,4-diamino-5-halo-pyrimidine to form 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione. This step can, for example, be carried out by reacting a 2,4-diamino-5-halo-pyrimidine, such as 2,4-diamino-5-bromo-pyrimidine, with a xanthogenate compound having the general formula:




**[0024]** wherein M represents a metal cation and $R^1$ is an alkyl group. Such a reaction can, for example, be carried out by dissolving both reagents in an inert solvent, with heating, under $N_2$ for a specified period of time.

**[0025]** The temperature of reaction solution in this step can, for example, range from about 50° C to 200° C. In another embodiment, the temperature range for this step is about 130° C to 180° C. In addition, the molar ratio of 2,4-diamino-5-halo-pyrimidine to the xanthogenate compound can, for example, range from about 1:10 to 1:1, such as from about 1:2 to 1:1. The volume of solvent per gram of 2,4-diamino-5-halo-pyrimidine can, for example, range from about 5 ml to 100 ml, such as about 10 ml to 40 ml.

**[0026]** Examples of suitable inert solvents include DMF ,NMP, DMAc (Dimethylacetamide), DMSO (Dimethylsulfoxide), Dimethylsulfone and Sufolane(tetramethylene sulfone).

**[0027]** With regard to the xanthogenate compound, examples of suitable metal cations include potassium and sodium. Examples of alkyl groups include methyl and ethyl. A preferred xanthogenate compound is potassium ethyl xanthogenate.

**[0028]** The reaction product from this step can be separated from the reaction mixture by any means known to those skilled in the art. For example, the reaction product can be separated from the reaction mixture by addition of water, neutralization, filtration, washing with a solvent (for example, water and/or ethanol), and/or a combination of these.

**[0029]** The next step of a process falling within the scope of the invention involves oxidation of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione to form the title compound, 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one. This step can, for example, be carried out by reacting 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione with an oxidizing agent under basic conditions, and a subsequent acidic hydrolysis.

**[0030]** The temperature of the reaction solution in this step can, for example, range from about 0° C to 100° C. In another embodiment, the temperature ranges from about 20° C to 90° C.

**[0031]** In addition, the molar ratio of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione to oxidizing agent can, for example, range from about 1:5 to 1:1, such as from about 1:3 to 1:2. The volume of solvent per gram of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione can, for example, range from about 5 ml to 100 ml, such as from about 10 ml to 30 ml.

**[0032]** In at least one embodiment of the invention, the basic conditions under which 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione is reacted with an oxidizing agent can be provided by first dissolving a base, such as an inorganic base, in water followed by adding 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione to the resulting solution. An oxidizing agent can then be added to the solution. The molar ratio of base to 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione can, for example, range from about 1:5 to 1:1, such as from about 1:3 to 1:1.

[0033] Examples of bases that can be used include but not limited to inorganic bases, such as NaOH and KOH. Examples of oxidizing agents include but not limited to hydrogen peroxide, urea hydrogen peroxide, and sodium hypochlorite. Acids that can be used in the hydrolysis include any suitable acid, for example, HCl (including concentrated HCl).

[0034] The reaction product from this step, which is the title compound, can be separated from the reaction mixture by any means known to those skilled in the art. For example, the reaction product can be separated from the reaction mixture by filtration, neutralization with base, filtration and washing with a solvent (for example, water and/or acetonitrile), and/or a combination of these.

[0035] In one embodiment of the invention the title compound can be made without the use of chromatography separation or purification for each of the three individual process steps.

[0036] The following non-limiting examples illustrate the present invention.

Preparation of Compounds

[0038] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company or Lancaster Synthesis Ltd. and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) were purchased from Aldrich in Sure Seal bottles and used as received.

[0039] The reactions set forth below were done generally under a positive pressure of argon or nitrogen at an ambient temperature (unless otherwise stated) in anhydrous solvents. The reactions were assayed by TLC and/or analyzed by LC-MS and terminated as judged by the consumption of starting material. Analytical thin layer chromatography (TLC) was performed on glass-backed silica gel 60 $F_{254}$ 0.2 mm plates (EM Science), and visualized with UV light (254 nm) followed by heat.

[0040] $^{1}$H-NMR spectra and $^{13}$C-NMR were recorded on a Varian Mercury-VX400 instrument operating at 400 MHz. NMR spectra were obtained as $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.27 ppm and 77.00 ppm), $CD_3OD$ (3.4 and 4.8 ppm and 49.3 ppm), DMSO-$d_6$, or internally tetramethylsilane (0.00 ppm) when appropriate. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[0041] Mass spectra reported are (+)-ES or APCI (+) LC/MS conducted by the Analytical Chemistry Department of Anadys Pharmaceuticals, Inc.

[0042] The described synthetic pathways and experimental procedures utilize many common chemical abbreviations, THF (tetrahydrofuran), DMF (N,N-dimethylformamide), EtOAc (ethyl acetate), DMSO (dimethyl sulfoxide), MeCN (acetonitrile), MeOH (methanol), HPLC (high pressure liquid chromatography), TLC (thin layer chromatography), $Br_2$ (bromine), $H_2O_2$ (hydrogen peroxide) and the like.

## EXAMPLE 1

### Step 1: Halogenation to 2,4-diamino-5-bromo-pyrimidine

[0043] To a stirring mixture of 2,4-diaminopyrimidine (25 g, 0.23 mol, 1.0 eq) in acetic acid (375 ml) was added $Br_2$ (36.3 g, 0.23 mol, 1.0 eq) at room temperature. The resulting mixture was stirred at room temperature (about 25° C) for 2 hours and then filtered. The yellow solid was mixed with water (250 ml) and the pH of the resulting mixture was adjusted to 8-9 using 50% NaOH solution. Stirring was continued at room temperature for 30 min and the mixture was filtered, washed with water, and then dried under vacuum to give 38 g (87%) of 2,4-diamino-5-bromo-pyrimidine as a white solid. $^{1}$H NMR (400 MHz, $d_6$-DMSO) δ 6.06 (s, 2H, ex. $D_2O$), 6.50 (br, 2H, ex. $D_2O$), 7.76 (s, 1H); MS (+)-ES $[M+H]^+$ *m/z* 191.

**Step 2: Cyclocondensation to 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione**

[0044] A solution of 2,4-diamino-5-bromo-pyrimidine (9.5 g, 50 mmol, 1.0 eq) and potassium ethyl xanthogenate (16 g, 100 mmol. 2 eq) in DMF (300 ml) was heated up to reflux for 10 hours under $N_2$. The reaction solution was cooled down to room temperature and water (600 ml) was added. The pH of the solution was then adjusted to about 5 using $H_2SO_4$ (2 ml) and the resulting suspension was stirred at 50-60° C for 30 min., cooled to about 30° C, filtered and washed with water. The product was dried under vacuum at 50-60° C to give 8.2 g (89%) of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione as a yellow solid. $^1$H NMR (400 MHz, $d_6$-DMSO). δ 6.91 (s, 2H, ex. $D_2O$), 8.34 (s, 1H), 12.3 (br, 1H, ex. $D_2O$); MS (+)-ES $[M+H]^+$ *m/z* 185.

**Step 3: Oxidation to 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one**

[0045] Procedure A: To a solution of NaOH (0.6 g, 15 mmol, 3 eq) in water (20 ml) was added 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione (0.92 g, 5 mmol, 1.0 eq). The mixture was stirred to dissolve. An aqueous solution of $H_2O_2$ (0.68 g, 2.3 ml (30%), 20 mmol, 4 eq) was slowly added dropwise to the above solution, keeping the temperature below 50° C. The reaction was then cooled down to room temperature (about 25° C). Concentrated HCl (37%, 6 ml) was added to the above solution until the pH is less than 1. The mixture is stirred at room temperature for 30 minutes. Celite (2 g) was added to the suspension and the suspension was filtered and washed with water (10 ml). To the filtrate was added 50% NaOH solution to adjust the pH to 5-5.5, stirred for 30 minutes, filtered, washed with water, and dried at 50° C under vacuum to give 0.52 g (62%) of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one as a pale yellow solid. $^1$H NMR (400 MHz, $d_6$-DMSO) δ 6.70 (s, 2H, ex. $D_2O$), 8.2 (s, 1H), 12.2 (br s, 1H, ex. $D_2O$); MS (+)-ES $[M+H]^+$ *m/z* 169.

[0046] Alternately, the procedure for Step 3 can be done using urea hydrogen peroxide instead of hydrogen peroxide:

[0047] Procedure B: To a solution of NaOH (0.6 g, 15 mmol, 3 eq) in water (20 ml) was added 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione (0.92 g, 5 mmol, 1.0 eq). The mixture was stirred to dissolve. Urea hydrogen peroxide (2.8 g, 30 mmol, 6 eq) was slowly added dropwise to the above solution, keeping the temperature below 50° C. The reaction was then cooled down to room temperature (about 25° C). Concentrated HCl (37%, 6 ml) was added to the above solution until the pH is less than 1. The mixture is stirred at room temperature for 30 minutes. Celite (2 g) was added to the solution and the solution was filtered and washed with water (10 ml). To the filtrate was added 50% NaOH solution to adjust the pH to 5-5.5. The solution was heated up to 50-60° C for 30 minutes. The resulting solution was cooled down to room temperature, filtered, and washed with water, dried at 50° C under vacuum to give 0.56 g (67%) of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one as a pale yellow solid. $^1$H NMR, HPLC and LCMS analyses of this product are identical to the product described from Procedure A in Step 2 of Example 1 above.

## EXAMPLE 2

### Step 1: Halogenation to 2,4-diamino-5-bromo-pyrimidine

[0048] To a mixture of 2,4-diaminopyrimidine (5.5 g, 0.05 mol, 1.0 eq.) and THF (200 ml) was added pyridinium tribromide (17.5 g, 0.055 mol, 1.1 eq) at 0° C in three portions. The resulting mixture was stirred at about 0° C for two hours, filtered and washed with THF (20 ml). The yellow solid was mixed with water (100 ml) and the resulting mixture was neutralized with 10% NaOH solution to a pH of about 7. Stirring was continued at room temperature for 30 minutes, after which the mixture was filtered, washed with water (2x20 ml) and dried under vacuum at 50° C to give 8.2 g (87%) of 2,4-diamino-5-bromo-pyrimidine as a white solid. $^1$H NMR, HPLC and LCMS analyses of this product are identical to the product described in Step 1 of Example 1.

**Step 2: Cyclocondensation to 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione**

[0049] A solution of 2,4-diamino-5-bromo-pyrimidine (0.95 g, 5 mmol, 1.0 eq) and potassium ethyl xanthogenate (1.6 g, 10 mmol. 2.0 eq) in DMF (30 ml)heated up to reflux for 10 hours under $N_2$. The reaction solution was cooled down to room temperature (about 25° C) and water (30 ml) was added to the solution. The pH of the solution was adjusted to about 5 with 3.6 N $H_2SO_4$. The resulting mixture was heated up to 50-60° C for 1 hour, cooled to room temperature stirred for 2 hours, filtered, washed with water (20 ml) and ethanol (20 ml) and dried to give 0.8 g (87%) of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione as a yellow solid. $^1$H NMR, HPLC and LCMS analyses of this product are identical to the product described in Step 2 of Example 1.

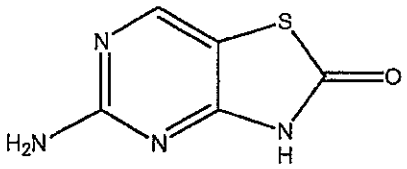
**Step 3: Oxidation to 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one**

[0050] 5-Amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione (0.24 g, 1.3 mmol, 1.0eq) was dissolved in 8 ml water containing 0.1 g NaOH (2.5 mmol, 2.5 eq). The resulting solution was heated to 80° C. A solution of sodium hypochlorite (NaClO) (4.4 ml, 10-13% solution, 5 eq) was added slowly to the above solution at about 80° C and stirring was continued at 80-90° C for 30 minutes. The solution was cooled down to about 70° C and a concentrated HCl solution (0.3 ml, 37%, 2.3 eq.) was added, after which the resulting solution was heated to 80-90° C for one hour. The reaction mixture was cooled down to room temperature and filtered through a pad of celite. The pH of the filtrate was adjusted to 5-5.5 using 10% NaOH solution. The resulting mixture was heated up to 60° C for 1 hour, cooled to room temperature and stirred for at least two hours, filtered and washed with water and acetonitrile to afford 0.06 g (27%) of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one as a pale yellow solid. $^1$H NMR, HPLC and LCMS analyses of this product are identical to the product described in Step 3 of Example 1.

[0051] It is to be understood that the foregoing description is exemplary and explanatory in nature, and is intended to illustrate the invention and its preferred embodiments. Through routine experimentation, the artisan will recognize apparent modifications and variations that may be made without departing from the spirit of the invention. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

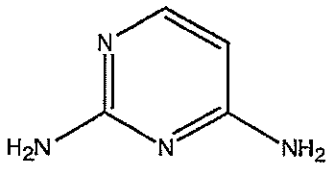
What is claimed is:

1. A process for the preparation of 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one of formula

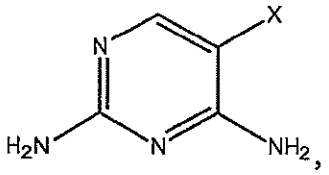


comprising:

(i) halogenating a 2,4-diaminopyrimidine of formula

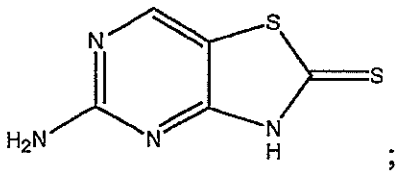


to form 2,4-diamino-5-halo-pyrimidine of formula



wherein X represents halo selected from F, Cl, Br, and I;

(ii) cyclocondensing the 2,4-diamino-5-halo-pyrimidine to form 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione of formula



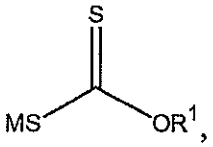
; and

(iii) oxidizing the 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione to form 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-one.

2. The process of claim 1, wherein X is selected from Br and Cl.

3. The process of claim 2, wherein X is Br.

4. The process of claim 1, wherein the cyclocondensation step is carried out in the presence of a xanthogenate compound having the formula:




wherein M represents a metal cation and $R^1$ is an alkyl group.

5. The process of claim 4, wherein M is selected from a potassium cation and a sodium cation and $R^1$ is selected from a methyl group and an ethyl group.

6. The process of claim 5, wherein M is a potassium cation and $R^1$ is an ethyl group.

7. The process of claim 1, wherein the oxidizing step comprises reacting 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione with an oxidizing agent under basic conditions and a subsequent acidic hydrolysis.

8. The process of claim 7, wherein the oxidizing agent is selected from hydrogen peroxide, urea hydrogen peroxide, and sodium hypochlorite.

9. The process of claim 8, wherein the oxidizing agent is hydrogen peroxide.

10. The process of claim 4, wherein X is selected from Cl and Br, M is selected from a potassium cation and a sodium cation, $R^1$ is selected from a methyl group and an ethyl group, and the oxidation step comprises reacting 5-amino-3H-thiazolo[4,5-*d*]pyrimidin-2-thione with an oxidizing agent under basic conditions and a subsequent acidic hydrolysis.

11. The process of claim 10, wherein X is Br, M is a potassium cation, $R^1$ is an ethyl group, and the oxidizing agent is hydrogen peroxide.