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PROCESS FOR THE PREPARATION OF DIHALOAZOLOPYRIMIDINES

BACKGROUND OF THE INVENTION

Dihaloazolopyrimidines are useful as intermediates in the preparation of a variety of agrochemical and pharmaceutical compounds. In particular, 5,7-dihalo-6-aryl-1,2,4-triazolo[1,5-a]pyrimidines are key intermediates in the preparation of fungicidal triazolopyrimidine derivatives which are described in EP-A2-550113.

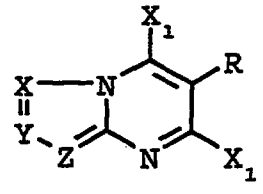
EP-A2-550113 describes a method for the preparation of 5,7-dihalo-6-aryl-1,2,4-triazolo[1,5-a]pyrimidines from malonic acid esters and 3-amino-1,2,4-triazole. However, that method is not entirely satisfactory because those pyrimidine compounds are obtained in low yield.

G. Fischer (Advances in Heterocyclic Chemistry, 1993, 57, 81-138) describes the formation of triazolopyrimidines from 1,3-dicarbonyl compounds and 3-amino-1,2,4-triazole, and states that refluxing in glacial acetic acid is "standard conditions". Y. Makisumi (Chem. Pharm. Bull., 1961, 9, 801-808) reports that under those conditions the condensation of diethyl malonate with 3-amino-1,2,4-triazole does not proceed. Makisumi discloses that the reaction could be carried out in the presence of sodium ethoxide in ethanol, and that the

product dihydroxytriazolopyrimidine could be converted to the corresponding dichlorotriazolopyrimidine using a large excess of phosphorus oxychloride. However, Makisumi's method is not entirely satisfactory for the preparation of dihaloazolopyrimidines because a large excess of phosphorus oxychloride is required and the overall yield of the reactions starting from diethyl malonate is often low.

SUMMARY OF THE INVENTION

The present invention provides an effective and efficient process for the preparation of a dihaloazolopyrimidine having the structural formula I



(I)

wherein

X_1 is chlorine or bromine;

R is phenyl optionally substituted with one or more halogen, nitro, cyano, C_1-C_6alkyl, C_1-C_6-haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_4alkoxycarbonyl, phenyl, phenoxy or benzyloxy groups,

naphthyl optionally substituted with one or more

halogen, nitro, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_4alkoxycarbonyl, phenyl, phenoxy or benzyloxy groups,

hydrogen,

C_1-C_6alkyl optionally substituted with one or more halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy or C_1-C_4haloalkoxy groups,

C_3-C_8cycloalkyl optionally substituted with one or more halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy or C_1-C_4haloalkoxy groups, or

C_2-C_6alkenyl optionally substituted with one or more halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy or C_1-C_4haloalkoxy groups;

X is CR_1 or N;

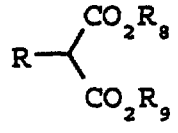
Y is CR_2 or N;

Z is CR_3 or N;

R_1, R_2 and R_3 are each independently hydrogen or C_1-C_6alkyl optionally substituted with one or more halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, amino, C_1-C_4alkylamino or di(C_1-C_4alkyl)amino groups, and

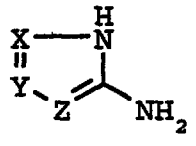
when R_1 and R_2 are taken together with the atoms to which they are attached, they may form a ring in which R_1R_2 is represented by the structure:

$-CR_4=CR_5-CR_6=CR_7-$ where R_4, R_5, R_6 and R_7 are each independently hydrogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy or C_1-C_4haloalkoxy, which process comprises: (a) reacting (1) a malonic acid ester having the structural formula II



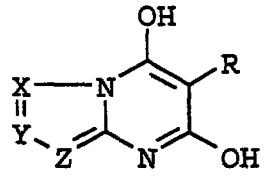
(II)

wherein R_8 and R_9 are each independently C_1-C_6alkyl, and R is as described above with (2) a heterocyclylamine having the structural formula III



III

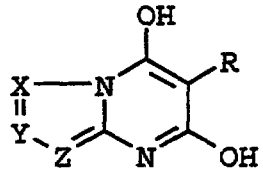
wherein X, Y and Z are as described above at a temperature of at least about 100°C to form an intermediate salt; (b) optionally acidifying the intermediate salt with aqueous acid to form a dihydroxyazolopyrimidine having the structural formula IV



(IV)

wherein R, X, Y and Z are as described above; and (c) halogenating the intermediate salt or dihydroxyazolopyrimidine with at least about two molar equivalents of a halogenating agent, e.g., phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride or phosphorus pentabromide or a suitable mixture thereof at a temperature of at least about 100°C.

The present invention also provides an effective and efficient process for the preparation of a dihydroxyazolopyrimidine having the structural formula IV



(IV)

wherein R, X, Y and Z are as described above. This product (IV) is produced by the above-described procedure wherein the intermediate salt is acidified; the product (IV) then may be isolated, if desired.

It is, therefore, an object of the present invention to provide an efficient new process for the preparation of dihaloazolopyrimidines.

It is another object of the present invention to provide a novel process for preparing dihydroxyazolopyrimidines.

Other objects and advantages of the present invention will be apparent to those skilled in the art from the following description and the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

In one preferred embodiment of the present invention, a malonic acid ester represented by formula II is reacted with at least about one molar equivalent of a heterocyclylamine represented by formula III, preferably in a temperature range of about 120°C to 200°C, more preferably about 150°C to 180°C, and optionally in the presence of a base and/or solvent to form an intermediate salt. The intermediate salt is halogenated with at least about two molar equivalents of phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride or phosphorus pentabromide, or a suitable mixture thereof, preferably in a temperature range of about 120°C to 150°C.

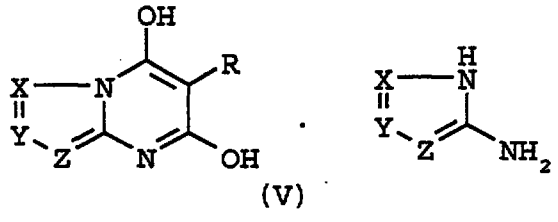
Advantageously, it has now been found that dihaloazolopyrimidines may be obtained in high yield and good purity by the effective and efficient process of the present invention. In contrast, dihaloazolopyrimidines are obtained in comparatively low yield when prepared according to art methods.

A further advantage of the present invention is that the inventive process may be conducted in one pot when the intermediate salt is not acidified. A one pot reaction sequence is highly desirable because it avoids the isolation of intermediate compounds and significantly reduces the amount of chemical waste produced.

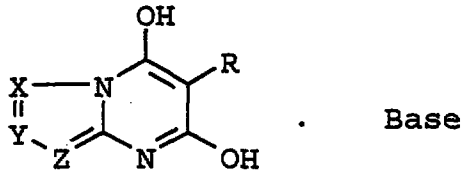
In another preferred embodiment of the present invention, the intermediate salt is prepared in the presence of added base. The base is preferably pres in an amount of at least about one molar equivalent relative to the malonic acid ester. Bases suitab use in the process of the present invention inc tertiary amines such as tri(C_2-C_6alkyl)amines

substituted pyridines, quinoline, substituted quinolines, and ureas; alkali metal hydroxides such as sodium hydroxide and potassium hydroxide; alkaline earth metal hydroxides such as calcium hydroxide and magnesium hydroxide; alkali metal C_1-C_6alkoxides such as sodium ethoxide and potassium tert-butoxide; alkaline earth metal C_1-C_6alkoxides such as magnesium ethoxide; alkali metal carbonates such as sodium carbonate and potassium carbonate; and alkaline earth metal carbonates such as calcium carbonate. Preferred bases include tri(C_2-C_6alkyl)amines such as triethylamine and tributylamine, pyridine, 4-(N,N-dimethylamino)pyridine, quinoline, and N,N,N',N'-tetramethylurea with triethylamine and tributylamine being more preferred.

The intermediate salt of this invention is represented by structural formula V when prepared in the absence of added base, and structural formula VI when prepared in the presence of added base:



(V)



Base

(VI)

wherein R, X, Y and Z are as described above and "Base" represents the added base.

In a further preferred embodiment of the present invention, a solvent is present. Solvents suitable for use in the process of the present invention have a boiling point of at least about 80°C and include aromatic hydrocarbons such as mesitylene, toluene, xylenes and mixtures thereof; chlorinated aromatic hydrocarbons such as mono- and dihalobenzenes and mixtures thereof; polynuclear aromatic hydrcarbons such as naphthalene, alkylnaphthalenes and mixtures thereof; alcohols such as butanol; and mixtures thereof. The solvent of the present invention preferably has a boiling point range of about 80°C to 220°C, more preferably about 120°C to 180°C. Mesitylene is one of the preferred solvents of the present invention.

The reaction between the malonic acid ester and the hetercyclylamine is preferably performed at a pressure of about one atmosphere or higher. If the reaction includes a solvent having a boiling point (defined at normal atmospheric pressure) lower than the reaction temperature, the reaction pressure must be elevated so that the solvent boiling point is elevated to at least the reaction temperature.

In some embodiments of the inventive process, an aqueous acid is used to acidify the intermediate salt. Aqueous acids suitable for use include aqueous mineral acids such as hydro-chloric acid, hydrobromic acid and sulfuric acid, and aqueous organic acids such as trifluoroacetic acid with hydrochloric acid, hydrobromic acid, and sulfuric acid being preferred.

The halogenation reaction may comprise reacting the intermediate salt or the dihydroxyazolopyrimidine with a suitable halogenating agent under conditions that produce the desired dihaloazolopyrimidine. Any halogenating agent and conditions known in the art may be used.

Preferably, the halogenating agent and conditions are those described herein for the preferred embodiments of the present invention. Advantageously, the halogenation reaction may be conducted at atmospheric pressure or at a pressure greater than atmospheric pressure. The term "a suitable mixture thereof", as used in the specification and claims with regard to the halogenating agents described herein, is defined as a phosphorus oxychloride and phosphorus pentachloride mixture or a phosphorus oxybromide and phosphorus pentabromide mixture.

The process of the present invention is especially useful for the preparation of dihaloazolopyrimidines wherein

X_1 is chlorine;

R is phenyl optionally substituted with one or more halogen, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4-alkoxy, C_1-C_4haloalkoxy, phenyl, phenoxy or benzyloxy groups, or

naphthyl;

X is CR_1 or N;

Y is CR_2;

Z is N; and

R_1 and R_2 are each independently hydrogen, and when R_1 and R_2 are taken together with the atoms to which they are attached, they may form a ring in which R_1R_2 is represented by the structure: -CH=CH-CH=CH-.

Advantageously, the present invention is particularly useful for the preparation of 5,7-dihalo-6-aryl-1,2,4-triazolo[1,5-a]pyrimidines of formula I wherein

X_1 is chlorine;

R is phenyl optionally substituted with one or more halogen, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4-alkoxy or C_1-C_4haloalkoxy groups;

X and Z are N; and

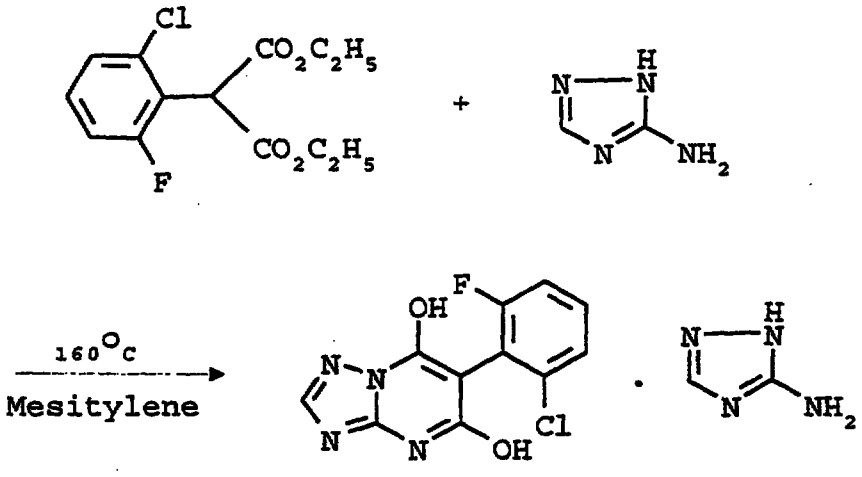
Y is CH.

The process of the present invention can produce surprisingly high yields of dihydroxyazolopyrimidines and dihaloazolopyrimidines. One key factor is the temperature of the reaction between the malonic acid ester and the heterocyclylamine. The use of a base and/or solvent may also enhance the yield in some embodiments. Those skilled in the art will be able, without undue experimentation, to select a favorable combination of temperature and optional base and/or solvent for any particular embodiment within the scope of this invention, upon consideration of the foregoing description of the preferred embodiments and the Examples that follow.

In order to facilitate a further understanding of the invention, the following illustrative examples are presented. The invention is not limited to the specific embodiments described or illustrated, but encompasses the full scope of the appended claims.

EXAMPLE 1

Preparation of 5,7-Dihydroxy-6-(2-chloro-6-fluorophenyl)-1,2,4-triazolo[1,5-a]pyrimidine, 3-amino-1,2,4-triazole salt



A mixture of diethyl (2-chloro-6-fluorophenyl)-malonate (29 g, 0.1 mol), 3-amino-1,2,4-triazole (8.4 g, 0.1 mol), and the solvent mesitylene (10 mL) is heated at 160°C for 7 hours and filtered to obtain a solid. The solid is washed with diisopropyl ether and dried to give the title product as a solid (18 g, 50% yield, mp 260-266°C).

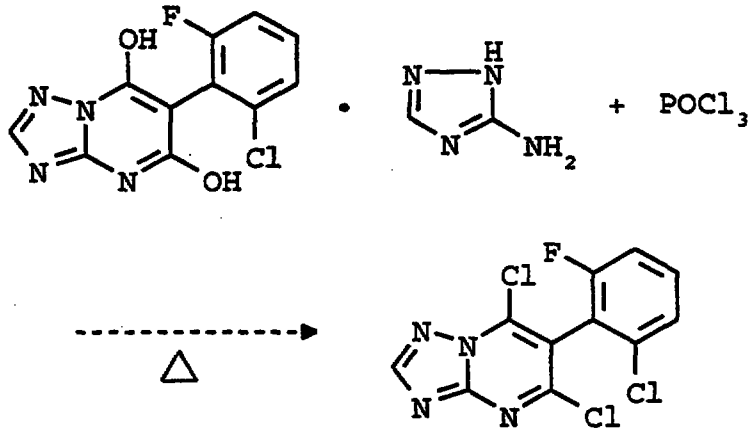
Following essentially the same procedure, but using the appropriate solvent and/or base, the 5,7-dihydroxy-6-(2-chloro-6-fluorophenyl)-1,2,4-triazolo[1,5-a]pyrimidine salts shown in Table I are obtained.

TABLE I

Solvent	Base	Temperature °C	% Yield	Salt
mesitylene	no added base	160	50	3-amino-1,2,4-triazole
mesitylene	triethylamine	160	32	triethylamine
SHELLSOL®	no added base	180	48	3-amino-1,2,4-triazole
toluene	triethylamine	170	64	triethylamine
no added solvent	triethylamine	160	64	triethylamine
no added solvent	quinoline	180	20	quinoline

EXAMPLE 2

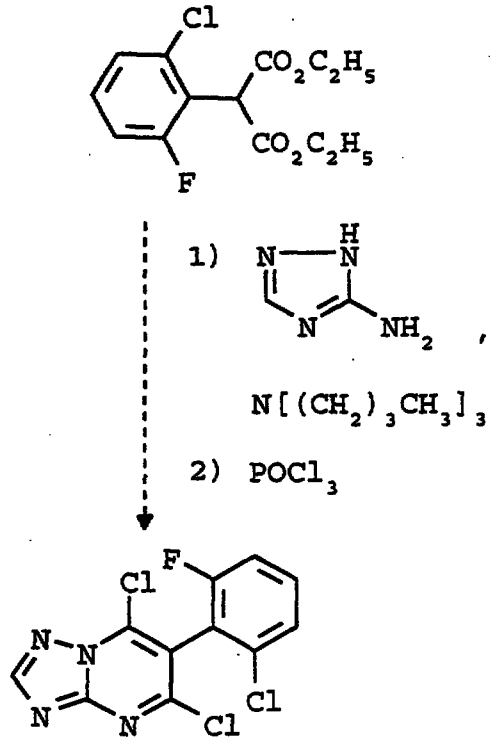
Preparation of 5,7-Dichloro-6-(2-chloro-6-fluorophenyl)-1,2,4-triazolo[1,5-a]pyrimidine



A mixture of 5,7-dihydroxy-6-(2-chloro-6-fluorophenyl)-1,2,4-triazolo[1,5-a]pyrimidine, 3-amino-1,2,4-triazole salt (34.8 g, 0.095 mol), and phosphorus oxychloride (100 mL) is heated in an autoclave at 140°C (2.8 bar) for 4 hours and excess phosphorus oxychloride is removed by distillation. The resultant reaction mixture is cooled to room temperature and poured into a water/dichloromethane mixture (300 mL, 1:1) while maintaining the temperature of the mixture below 30°C. The organic phase is separated, dried over anhydrous sodium sulfate, and concentrated in vacuo to obtain an oil which crystallizes overnight to give the title product as a solid (22.4 g, 74% yield, mp 118-120°C).

EXAMPLE 3

Preparation of 5,7-Dichloro-6-(2-chloro-6-fluorophenyl)-1,2,4-triazolo[1,5-a]pyrimidine

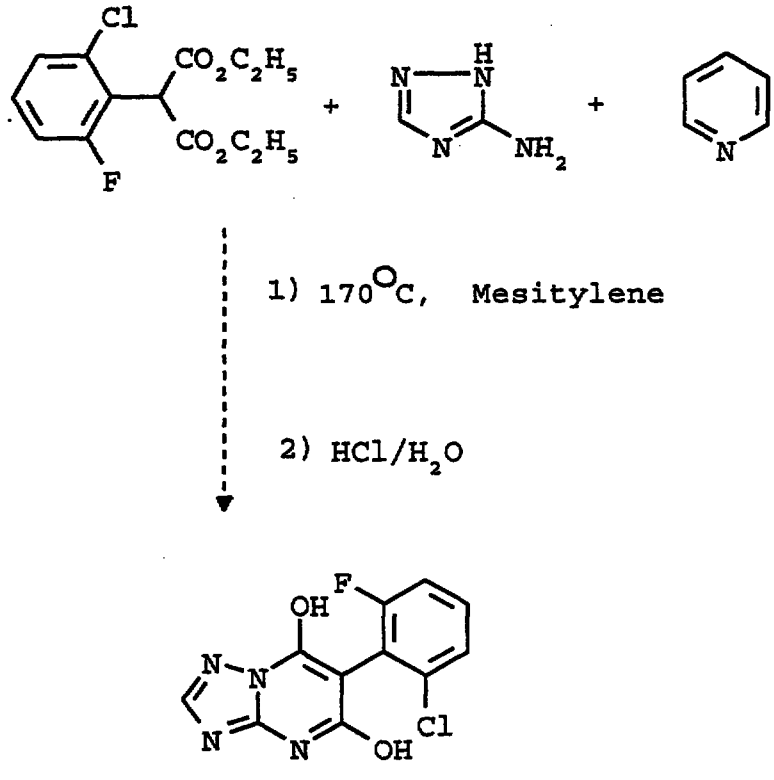


A mixture of 3-amino-1,2,4-triazole (12.6 g, 0.15 mol), diethyl (2-chloro-6-fluorophenyl)malonate (47.6 g, 0.15 mol), and tributyl amine (27.8 g, 0.15 mol) is heated at 170°C while allowing ethanol generated during the reaction to distill off. After 2 hours, residual ethanol is removed with a slow nitrogen stream for 30 minutes. The reaction mixture is then cooled to 130°C and phosphorus oxychloride (69 g, 0.45 mol) is added

dropwise over 20 minutes. The resultant clear, brown solution is refluxed for 6 hours, cooled to room temperature, and slowly added to a toluene/water (5:6) mixture (1,100 mL) with stirring. The organic phase is separated, washed sequentially with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate and concentrated <u>in vacuo</u> to give a brown, viscous oil (44.5 g) which contains 90% of the title product (83% yield).

EXAMPLE 4

Preparation of 5,7-Dihydroxy-6-(2-chloro-6-fluorophenyl)-1,2,4-triazolo[1,5-a]pyrimidine -



A mixture of diethyl (2-chloro-6-fluorophenyl)-malonate (7.3 g, 0.025 mol), 3-amino-1,2,4-triazole (2.1 g, 0.025 mol), mesitylene (20 mL), and pyridine (5 mL) is refluxed for 7 hours at 170°C, cooled to room temperature, and decanted to obtain a solid. A solution of the solid in water (50 mL) is acidified with concentrated hydrochloric acid (5 mL), and the resultant precipitate is collected, washed with water, and dried to give the title product as a solid (5 g, 71% yield, mp 220°C).

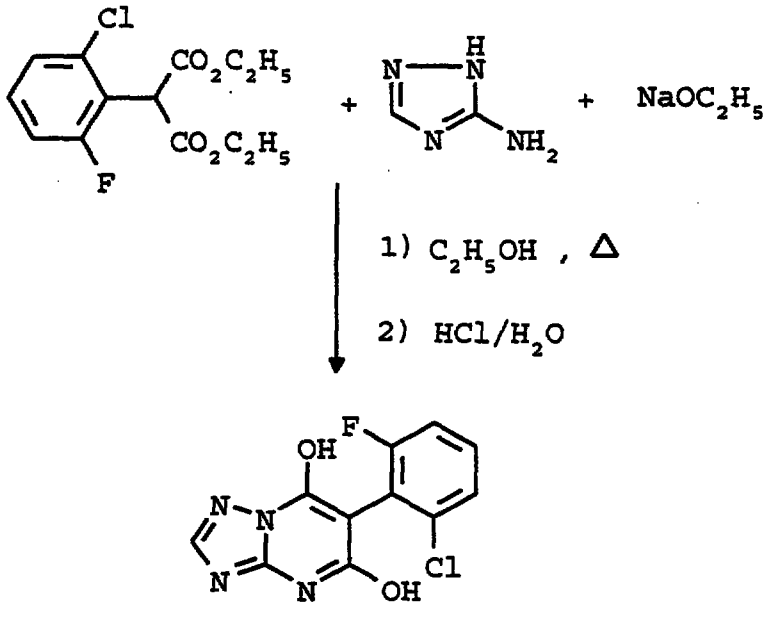
Following essentially the same procedure, but using the appropriate solvent and/or base, 5,7-dihydroxy-6-(2-chloro-6-fluorophenyl)-1,2,4-triazolo[1,5-a]pyrimidine is obtained in the yields shown in Table II.

TABLE II

Solvent	Base	Temperature °C	% Yield
mesitylene	sodium hydroxide	170	27
mesitylene	potassium tert-butoxide	170	28
mesitylene	4-(N,N-dimethylamino)pyridine	150	61
mesitylene	quinoline	180	48
mesitylene	sodium ethoxide	170	55
SHELLSOL®	pyridine	180	38
no added solvent	pyridine	160	42
no added solvent	N,N,N',N'-tetramethylurea	170	50

COMPARATIVE EXAMPLE

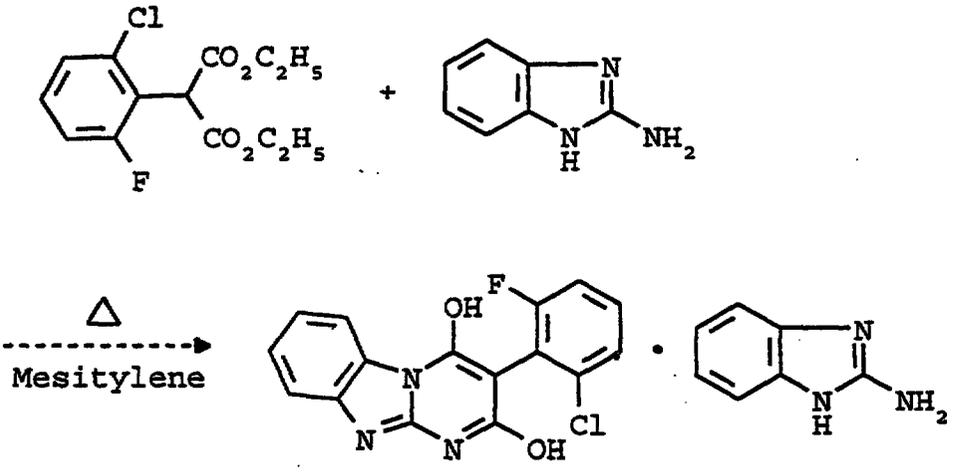
Preparation of 5,7-Dihydroxy-6-(2-chloro-6-fluorophenyl)-1,2,4-triazolo[1,5-a]pyrimidine



Diethyl (2-chloro-6-fluorophenyl)malonate (108 g, 0.37 mol) and 3-amino-1,2,4-triazole (31.2 g, 0.37 mol) are added to a sodium ethoxide solution (previously prepared by dissolving sodium (8.5 g, 0.37 mol) in ethanol (250 mL)). The resultant reaction mixture is refluxed for 50 hours, cooled to room temperature and filtered to obtain a solid which is washed with diisopropyl ether. A solution of the washed solid in water is acidified with concentrated hydrochloric acid, and the resultant precipitate is collected, washed with water and dried to give the title product as a solid (15.7 g, 14.5% yield, mp 215°C).

EXAMPLE 5

Preparation of 5,7-Dihydroxy-6-(2-chloro-6-fluorophenyl)benzimidazopyrimidine, 2-aminobenzimidazole salt

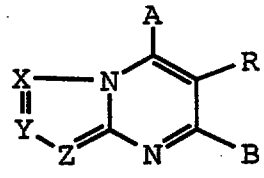


A mixture of diethyl (2-chloro-6-fluorophenyl)-malonate (5.8 g, 0.02 mol) and mesitylene is heated to reflux, treated portionwise over 2 hours with 2-amino-benzimidazole (2.7 g, 0.02 mol), refluxed for 4 hours, cooled to room temperature and diluted with acetone. The resultant mixture is filtered to give the title product as white crystals (5.1 g, 55% yield, mp 313-325°C).

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CLAIMS:

1. A process for the preparation of a compound having the structural formula



(IA)

wherein

A and B are both OH or Cl or Br.

R is phenyl optionally substituted with one or more substituents the same or different selected from halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6-haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_4alkoxycarbonyl, phenyl, phenoxy and benzyloxy,

naphthyl optionally substituted with one or more substituents the same or different selected from halogen, nitro, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_4-alkoxycarbonyl, phenyl, phenoxy and benzyloxy,

hydrogen,

C_1-C_6alkyl optionally substituted with one or more substituents the same or different selected from halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4halo-alkyl, C_1-C_4alkoxy and C_1-C_4haloalkoxy,

C_3-C_6cycloalkyl optionally substituted with one or more substituents the same or different selected from halogen, nitro, cyano, C_1-C_4 alkyl, C_1-C_4-haloalkyl, C_1-C_4alkoxy and C_1-C_4haloalkoxy,

or

C_2-C_6alkenyl optionally substituted with one or more substituents the same or different selected from halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy and C_1-C_4haloalkoxy;

X is CR_1 or N;

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Y is CR_2 or N;

Z is CR_3 or N;

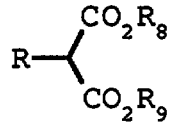
R_1, R_2 and R_3 are each independently hydrogen or C_1-C_6alkyl optionally substituted with one or more substituents the same or diffrent selected from halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, amino, C_1-C_4alkylamino and di(C_1-C_4alkyl)amino, and

when R_1 and R_2 are taken together with the atoms to which they are attached, they may form a ring in which R_2 is represented by the structure:

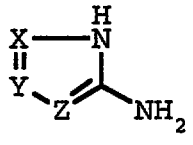
$-CR_4=CR_5-CR_6=CR_7-$ where R_4, R_5, R_6 and R_7 are each independently hydrogen, nitro, cyano, C_1C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy or C_1-C_4haloalkoxy;

which process comprises:

(a) reacting (1) a malonic acid ester having the structural formula



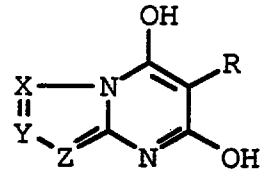
wherein R_8 and R_9 are each independently C_1-C_6alkyl, and R is as defined above with (2) a heterocyclylamine having the structural formula



wherein X, Y and Z are as defined above at a temperature of at least 100°C to form a intermediate base salt of a compound of formula IA wherein A and B are both OH, and optionally acidifying with aqueous acid to give the corresponding free hydroxy compound having the structural formula

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wherein R, X, Y and Z are as described above,
and if desired

(b) halogenating the intermediate salt or dihydroxyazolopyrimidine from step (a) with at least two molar equivalents of a halogenating agent to give a compound of formula IA wherein A and B are both halogen.

2. The process according to Claim 1 wherein said halogenating agent is selected from phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride, phosphorus pentabromide and a suitable mixture thereof, and wherein said halogenating step is performed at a temperature of at least 100°C.

3. The process according to Claim 1 or Claim 2 wherein said malonic acid ester is reacted with said heterocyclylamine at a temperature of 120°C to 200°C.

4. The process according to any one of Claims 1 to 3 wherein said malonic acid ester is reacted with said heterocyclylamine in the presence of a base.

5. The process according to Claim 4 wherein said base is present in an amount of at least one molar equivalent relative to said malonic acid ester.

6. The process according to Claim 4 wherein said base comprises a tertiary amine, an alkali metal hydroxide, an alkaline earth metal hydroxide, an alkali metal C_1-C_6alkoxide, an alkaline earth metal C_1-C_6alkoxide, an alkali metal carbonate,or an alkaline earth metal carbonate.

7. The process according to Claim 6 wherein said tertiary amine comprises tri (C_2-C_6alkyl)amine, pyridine, a substituted pyridine, quinoline, a substituted quinoline, and N,N,N',N'-tetramethylurea.

8. The process according to any one of Claims 1 to 7 wherein said malonic acid ester is reacted with said heterocyclylamine in the presence of a solvent.

9. The process according to Claim 8 wherein said solvent has a boiling point of 80°C to 220°C.

10. The process according to Claim 8 wherein said solvent comprises the group consisting of an aromatic hydrocarbon, a chlorinated aromatic hydrocarbon, a polynuclear aromatic hydrocarbon, an alcohol, and mixtures thereof, and the boiling point of the solvent is at least 80°C.

11. The process according to Claim 10 wherein said aromatic hydrocarbon is selected from mesitylene, toluene, a xylene, and mixtures thereof, said polynuclear aromatic hydrocarbon is selected from naphthalene, an alkylnaphthalene, and mixtures thereof, and said alcohol is butanol.

12. The process according to any one of Claims 1 to 11 wherein said heterocyclylamine is present in an amount of at least one molar equivalent relative to said malonic acid ester.

13. The process according to any one of Claims 1 to 12 wherein said aqueous acid is an aqueous mineral acid selected from the group consisting of hydrochloric acid, hydrobromic acid, and sulfuric acid.

14. The process according to any one of Claims 1 to 13 wherein said halogenation is conducted at a pressure greater than one atmosphere.

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15. The process according to any one of Claims 1 to 14 wherein R is phenyl optionally substituted with one or more substituents the same or diffrent selected from halogen, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4-alkoxy, C_1-C_4haloalkoxy, phenyl, phenoxy and benzyloxy; or naphthyl;

X is CR_1 or N;

Y is CR_2;

Z is N; and

R_1 and R_2 are each independently hydrogen, and when R_1 and R_2 are taken together with the atoms to which they are attached, they may form a ring in which R_1R_2 is represented by the structure: -CH=CH-CH=CH-.