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(54) PROCESS FOR PREPARING AZACYCLOALKANOYLAMINOTHIAZOLES

VERFAHREN ZUR HERSTELLUNG VON AZACYCLOALKANOYLAMINOTHIAZOLEN

PROCEDE DE PREPARATION D'AZACYCLOALCANOYLAMINOTHIAZOLES

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(73) Proprietor: **Bristol-Myers Squibb Company**
Princeton, NJ 08543-4000 (US)

(72) Inventors:
- **CHEN, Bang-Chi**
Plainsboro, NJ 08536 (US)
- **KIM, Kyoung, S.**
North Brunswick, NJ 08902 (US)
- **KIMBALL, S., David**
East Windsor, NJ 08520 (US)
- **MISRA, Raj, N.**
Hopewell, NJ 08525 (US)
- **SALVATI, Mark, E.**
Lawrenceville, NJ 08648 (US)
- **SUNDEEN, Joseph, E.**
Yardley, PA 19067 (US)
- **XIAO, Hai-Yun**
Princeton, NJ 08540 (US)
- **ZHAO, Rulin**
Pennington, NJ 08534 (US)

(74) Representative: **Hubert, Philippe et al**
Cabinet Beau de Loménie
158, rue de l'Université
75340 Paris Cédex 07 (FR)

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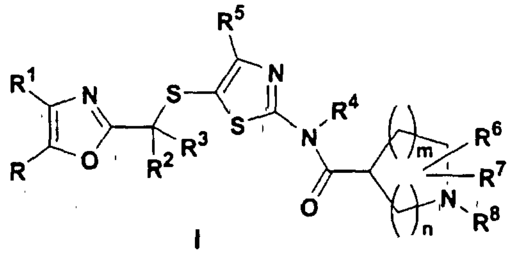
Description

[0001] The present invention concerns new processes for the preparation of 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazoles and analogs, inhibitors of cyclin dependent kinases.

[0002] The 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazole compounds of formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

R is alkyl, aryl or heteroaryl;
R^1, R^2, R^3, R^4 and R^5 are each independently hydrogen, alkyl, aryl or heteroaryl;
R^6 and R^7 are each independently hydrogen, alkyl, aryl, heteroaryl, halogen, hydroxy or alkoxy;
R^8 is hydrogen, alkyl, aryl, heteroaryl, $CONR^9R^{10}$, COR^{11} or $COOR^{12}$;
R^9, R^{10}, R^{11} and R^{12} are each independently hydrogen, alkyl or aryl;
m equals 0 to 5; and
n equals 0 to 5,

are novel, potent inhibitors of cyclin dependent kinases (cdks). They are useful in the therapy of proliferative diseases, for example, cancer, inflammation, autoimmune diseases such as arthritis, viral diseases, fungal diseases, chemotherapy-induced alopecia, neurodegenerative disorders such as Alzheimer's disease and cardiovascular disease. More specifically, the compounds of formula I are useful in the treatment of a variety of cancers such as bladder, breast, colon, kidney, liver and lung cancers.

[0003] WO 9924416 and corresponding U.S. Patent No. 6,040,321 describe the preparation of 5-(2-oxazolylalkylthio)-2-aminothiazoles, key intermediates in the synthesis of 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazoles of formula I, by reacting 5-acetylthio-2-acetylaminothiazole with a base followed by trapping the thiolate with a 2-oxazolylalkyl halide. Hydrolysis of the resulting 5-(2-oxazolylalkylthio)-2-acetylaminothiazole compounds afforded the 5-(2-oxazolylalkylthio)-2-aminothiazole key intermediates. The requisite 2-oxazolylalkyl halides were prepared by (i) reaction of β-hydroxy amines with α-chloroacyl chlorides followed by oxidation of the resulting β-hydroxy-α-chloroamides and subsequent oxazole ring formation (K. S. Kim *et al.*, WO 9924416, May 20, 1999) or (ii) reaction of α-diazo ketones with α-chloronitriles (K.S. Kim *et al.*, WO 9924416, May 20, 1999; T. Ibata *et al.*, *Bull. Chem. Soc. Japan* **1979**, *52,* 3597). Although a variety of 5-(2-oxazolylalkylthio)-2-aminothiazoles can be prepared by this method, this process is not amenable to large scale synthesis due to the commercial availability of the starting 5-acetylthio-2-acetylaminothiazole, the use of hazardous α-diazo ketones and expensive chromatographic separation of products.

[0004] Reaction of α-halo ketones with azide to give α-azido ketones has been previously reported in the literature (A. Hassner *et al., Angew Chem. Int. Ed. Engl.* **1986,** *25*, 478; M. G. Nair *et al.*, *J. Med. Chem.* **1980**, *23*, 899; H.-J. Ha *et al., Synth. Commun.* **1994**, *24*, 2557). Reaction of α-sulfonyloxy ketones with azide to give α-azido ketones has also been previously reported (T. Patonay *et al., J. Org. Chem.* **1994**, *59*, 2902; G. A. Revelli *et al., Synth. Commun.* **1993**, *23,* 1111).

[0005] Reduction of α-azido ketones to α-amino ketones has been described in the literature (H.-J. Ha *et al., Synth. Commun.* **1994**, *24,* 2557; J. P. Sanchez *et al., J. Heterocycl. Chem.* **1988**, *25*, 469; S. K. Boyer *et al., J. Org. Chem.* **1985**, *50,* 3408). Reaction of α-amino ketones with α-halo acyl halides to give the corresponding amides has further been described (G. T. Newbold *et al., J. Chem. Soc.* 1948, 1855; G. T. Newbold *et al.*, *J. Chem. Soc.* **1950**, 909).

[0006] Reaction of alkylthiouronium salts with alkyl halides to give sulfides has been previously reported (H. Chen *et al., Synth. Commun.* **1990**, *20,* 3313). Reaction of alkylthiols with 5-bromo-2-aminothiazole to give 5-alkylthio-2-aminothiazoles has been reported (J. B. Dickey *et al., J. Org. Chem.* **1959**, *24*, 187).

[0007] Scott and Wolf, Applied Microbiology, 1962, 10, 211-216 disclose the preparation of a number of quaternaries from hexamethylenetetramine and halohydrocarbons, prepared with a view to studying their antibacterial activity.

[0008] This invention concerns new efficient processes for the preparation of 5- (2-oxazolylalkylthio)-2-aminothiazoles.

The processes involve new strategies for the preparation of 2-oxazolylalkyl halides and 5-(2-oxazolylalkylthio)-2-aminothiazoles which include the method of making new key intermediate quaternary ammonium salts and 2-oxazolylalkyl sulfide derivatives. This invention further relates to processes for the preparation of 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazoles and analogs, inhibitors of cyclin dependent kinases.

[0009] The present invention relates to new, more efficient processes for the preparation of 5-(2-oxazolylalkylthio)-2-aminothiazoles with application to the synthesis of 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazoles and analogs, inhibitors of cyclin dependent kinases.

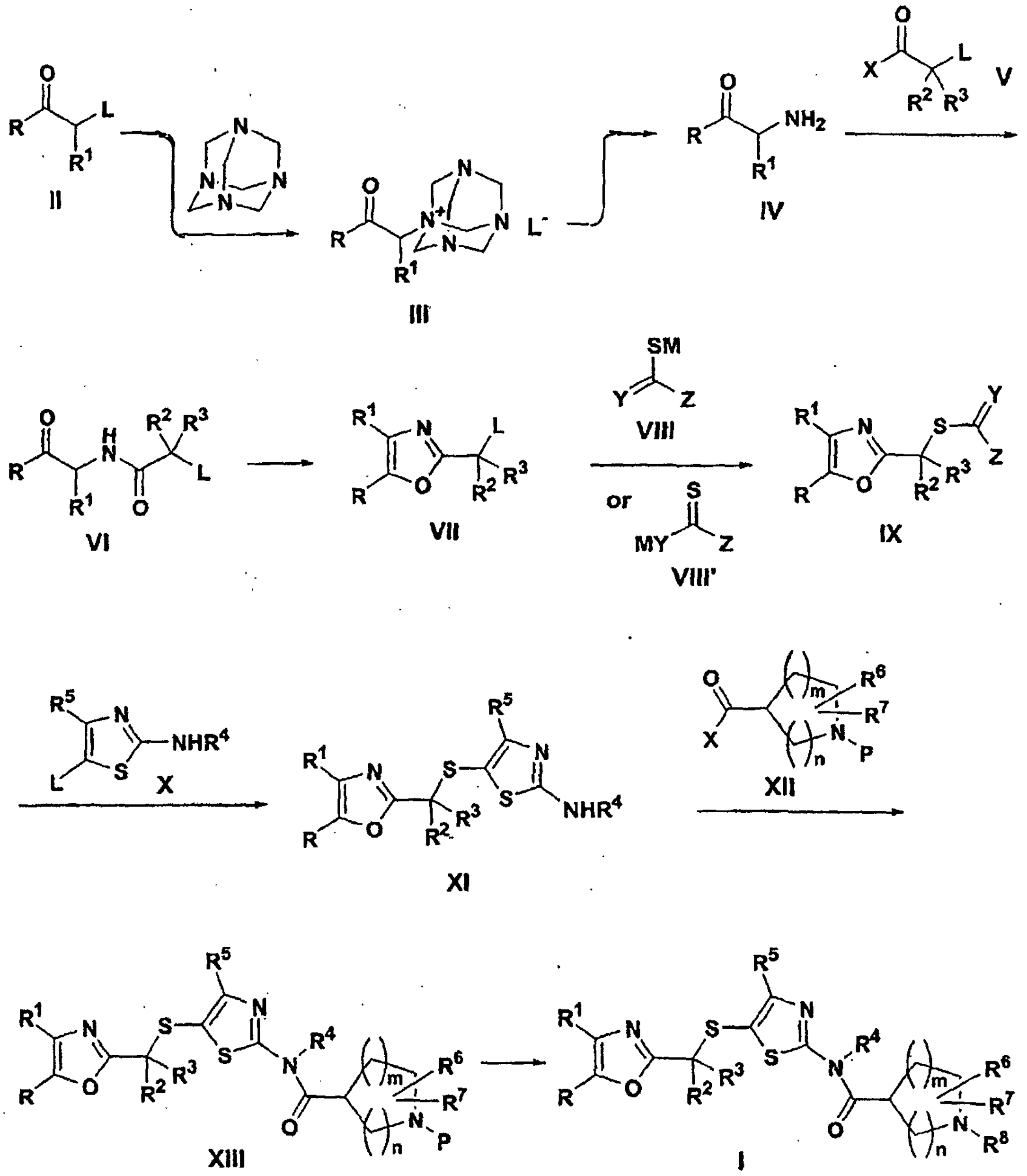
[0010] The α-amino ketones IV are prepared by reaction of α-halo ketones II with a cyclic alkylenetetramine such as hexamethylenetetramine and the like, followed by hydrolysis of the resulting, new quaternary ammonium salt III. This reaction provides excellent yields of the desired intermediate compound IV, above 90%, yet in a safer manner.

[0011] Thereafter, reacting the α-amino ketones IV with an α-halo acyl halide V in the presence of a base or, alternatively, coupling the α-amino ketones IV with an α-halo acid, produces the corresponding amides VI. Then, ring closure of VI with a dehydrating reagent affords 2-oxazolylalkyl halides VII. When a conventional dehydrating reagent such as trihalophosphorus oxide like $POCl_3$ is used, product isolation is difficult due to the formation of large amounts of hydrochloric and phosphoric acids. Thus, the process of the present invention preferably utilizes the Burgess' reagent which produces excellent yields and permits easy, safe product isolation from water.

[0012] Subsequent treatment of 2-oxazolylalkyl halides VII with sulfur-containing reagent VIII or VIII' affords new key intermediate compounds, 2-oxazolylalkyl sulfides IX. Coupling of IX with 5-halo-2-aminothiazole X gives 5(2-oxazolylalkylthio)-2-aminothiazoles XI. Coupling of XI with an azacycloalkanoic acid derivative XII affords thiazolyl amides XIII, which may be deprotected (in the case where P is a protecting group, *e.g.*, Boc) to give 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazoles I, where R^8 is hydrogen, inhibitors of cyclin dependent kinases.

[0013] The above-described reactions are illustrated in the below Scheme 1.

Scheme 1



[0014] In formulas I-XIII of Scheme 1, the following terms apply:

R is alkyl, aryl or heteroaryl;
R^1, R^2, R^3, R^4 and R^5 are each independently hydrogen, alkyl, aryl or heteroaryl;
R^6 and R^7 are each independently hydrogen, alkyl, aryl, heteroaryl, halogen, hydroxy or alkoxy;
R^8 is hydrogen, alkyl, aryl, heteroaryl, $CONR^9R^{10}$, COR^{11} or $COOR^{12}$;
R^9, R^{10}, R^{11} and R^{12} are each independently hydrogen, alkyl or aryl;
L is halogen or sulfonate (RSO_2O-, CF_3SO_2O-, *etc.*);
M is hydrogen, Li, Na, K, Cs or quaternary ammonium (R_4N);
X is hydroxy, halogen or acyloxy (RCOO-, ROCOO-, *etc.*);
Y is O, S, NH, N-alkyl, N-aryl or N-acyl;
Z is hydrogen, alkyl, aryl, O-alkyl, O-aryl, S-alkyl, S-aryl, NH_2, N-alkyl, N-aryl or N-acyl;
P is a nitrogen-protecting group (Boc, Cbz, R_3Si, *etc.*);

m equals 0 to 5; and
n equals 0 to 5.

[0015] Listed below are definitions of various terms used to describe the compounds involved in the processes of the present invention. These definitions apply to the terms as they are used throughout the specification (unless specifically indicated otherwise) either individually or as part of a larger group. It should be noted that any heteroatom with unsatisfied valences is assumed to have the hydrogen atom to satisfy the valences.

[0016] The term "alkyl" or "alk" (*i.e.,* derivative forms of alkyl) refers to optionally substituted straight chain, branched or cyclic monovalent alkane (saturated hydrocarbon) derived radicals containing from 1 to 12 carbon atoms. When substituted, alkyl groups may be substituted with up to four substituent groups at any available point of attachment. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The alkyl can be optionally substituted with one or more halogens or alkyl groups such as, for example, trifluoromethyl, 4,4-dimethylpentyl, 2,2,4-trimethylpentyl, *etc.*

[0017] The term "aryl" or derivative forms thereof refers to monocyclic or bicyclic aromatic rings, *e.g.*, phenyl, substituted phenyl and the like, as well as groups which are fused, *e.g.*, napthyl, phenanthrenyl and the like, containing from 6 to 30 carbon atoms. An aryl group can thus contain at least one ring having 6 atoms, with up to five such rings being present, containing up to 22 or 30 atoms therein, depending upon optionally alternating (resonating) double bonds between carbon atoms or suitable heteroatoms. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, anthryl, biphenyl and the like.

[0018] The term "acyl" refers to the radical RCO-, taken alone or in combination, for example, with oxygen, nitrogen, sulfur, *etc.* The term "halogen" or "halo" refers to chlorine, bromine, fluorine or iodine, with bromine being the preferred halogen.

[0019] The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one or two additional carbon atoms is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms, said heteroaryl group being optionally substituted as described herein. Exemplary heteroaryl groups include, but are not limited to, thienyl, furyl, pyrrolyl, pyridinyl, imidazolyl, pyrrolidinyl, piperidinyl, thiazolyl, oxazolyl, triazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyrazinyl, pyridazinyl, pyrimidinal, triazinylazepinyl, indplyl, isoindolyl, quinolinyl, isoquinolinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzoxadiazolyl, benzofurazanyl, *etc.* The heteroaryl groups can be optionally substituted by one or more groups which include, but are not limited to, halogen, alkyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, trifluoromethyl, cycloalkyl, nitro, cyano, amino, alkylS(O)$_m$ (where m = 0, 1 or 2), thiol and the like.

[0020] When a functional group is termed "protected," this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds involved in the present processes will be recognized from the specification taking into account the level of skill in the art, and with reference to standard textbooks such as T. W. Greene *et al.*, Protective Groups in Organic Synthesis, Wiley, N.Y. (1991).

[0021] The term "pharmaceutically acceptable salt" refers to those salts of the biologically active compounds which do not significantly or adversely affect the pharmaceutical properties of the compounds such as, for example, toxicity, efficacy, *etc.* and include those salts which are conventionally employed in the pharmaceutical industry. Suitable examples of salts include, but are not limited to, those formed with inorganic or organic acids such as hydrochloride, hydrobromide, sulfate, phosphate, *etc.* Also included, particularly for the intermediate compounds of the invention, are salts which are unsuitable for pharmaceutical utility but which can be employed otherwise, for example, for isolation or purification of free active compounds or their pharmaceutically acceptable salts.

[0022] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of the compounds employed in the processes of the invention embraces all possible stereoisomers and their mixtures. The definition further embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by conventional methods such as, for example, salt formation with an optically active acid followed by crystallization.

[0023] It should be understood that solvates (*e.g.*, hydrates) of the compounds of formula I and the intermediate compounds are also within the scope of the present invention. Methods of solvation are generally known in the art. Therefore, the compounds useful in the processes of this invention may be in the free or hydrate form.

[0024] As set forth in Scheme 1, the processes for the preparation of 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazoles and analogs involve the following transformations:

(a) reacting an α-substituted ketone II like the α-halo ketone with a cyclic alkylenetetramine such as, for example, hexamethylenetetramine in a suitable solvent or solvent mixtures to give a new quaternary ammonium salt III.

The α-halo ketone includes α-halo aliphatic and α-halo aromatic ketones. The preferred α-halo ketones are α-halo pinacolones with α-bromo pinacolone most preferred. A sulfonate, for example, RSO_2O- (where R is alkyl, aryl or heteroaryl), CF_3SO_2O- and the like, may be substituted for the halogen in the α-position. Suitable solvent(s) include solvents such as hydrocarbons, ethers, amides, for example, dimethylformamide, ketones, *etc.*, or mixtures thereof, with ketones such as acetone preferred for reaction (a)

(b) reacting the quaternary ammonium salt III obtained in step (a) with an acid in a suitable solvent or solvent mixtures to give an α-amino ketone IV.

The acid in reaction (b) includes, but is not limited to, protic acids such as HCl, HBr, HI, H_2SO_4, H_3PO_4, *etc.*, with HCl preferred. Suitable solvent(s) in reaction (b) include solvents such as hydrocarbons, ethers, alcohols and the like, or mixtures thereof, with alcohol such as ethanol preferred. The α-amino ketone product may be isolated as the salt or free base forms.

(c) reacting (acylating) the α-amino ketone IV or its acid salt obtained in step (b) with an α-substituted acyl derivative V such as, for example, an α-halo acyl halide, in the presence of a base and in a suitable solvent or solvent mixtures to give an amide VI.

The α-halo acyl halide V includes α-alkyl or aryl substituted or unsubstituted α-halo acyl halide with the latter preferred. The most preferred α-halo acyl halide is α-chloroacetyl chloride. The base used in the reaction includes, but is not limited to, aromatic and aliphatic organic amines with the latter preferred. The most preferred base is triethylamine. Suitable solvent(s) include aprotic solvents such as hydrocarbons, halogenated hydrocarbons, ethers, esters and the like, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred. Alternatively, the reaction can be carried out using an α-substituted acid instead of the α-substituted acyl derivative and then employing a coupling reagent such as a water-soluble diimide like carbodiimide, haloformate, thionyl halide, *etc.* In either reaction, a sulfonate, for example, RSO_2O- (where R is an alkyl, aryl or heteroaryl), CF_3SO_2O- and the like, may be substituted for the halogen in the α-position of the α-halo acyl halide or the α-halo acid reactants which are illustrated.

(d) reacting the amide VI obtained in step (c) with a dehydrating reagent in a suitable solvent or solvent mixtures to give the cyclized 2-oxazolylalkyl derivative VII such as, for example, the 2-oxazolylalkyl halide.

Advantageously, the reaction is carried out using (methoxycarbonylsulfamoyl)triethylammonium hydroxide (Burgess' reagent) as the dehydrating reagent. Suitable solvent(s) include hydrocarbons, halogenated hydrocarbons, ethers and the like, or mixtures thereof. Most preferred is the use of the Burgess' reagent in tetrahydrofuran. Suitable dehydrating reagents also include, but are not limited to, other bases, acids, acid anhydrides and the like, such as, *e.g.*, concentrated sulfuric acid, polyphosphoric acid, *etc.* Although less conveniently, the dehydrating reagent, for instance, can be trihalophosphorus oxide such as tribromophosphorus oxide or trichlorophosphorus oxide, alone or with a solvent like toluene.

(e) reacting the 2-oxazolylalkyl derivative VII obtained in step (d) with a sulfur-containing reagent VIII or VIII' in a suitable solvent or solvent mixtures to give 2-oxazolylalkyl sulfide IX, a new key intermediate compound.

The sulfur-containing reagent includes N-substituted or unsubstituted thioureas, thio acids or salts such as thioacetic acid or its salt, xanthic acids or salts such as ethylxanthic acid potassium salt. Unsubstituted thiourea is preferred. Suitable solvent(s) include hydrocarbons, halogenated hydrocarbons, ethers, esters, amides, alcohols and the like, or mixtures thereof, with alcohol such as methanol or ethanol preferred.

(f) reacting the 2-oxazolylalkyl sulfide IX obtained in step (e) with a 5-halo-2-aminothiazole X in the presence of a base and in a suitable solvent or solvent mixtures to give 5-(2-oxazolylalkylthio)-2-aminothiazole XI.

The 5-halo-2-aminothiazole includes 4,N-substituted or unsubstituted 5-halo-2-aminothiazoles with 5-bromo-2-aminothiazole preferred. A suitable base includes, but is not limited to, metal hydroxide, metal alkoxides, metal carbonates and aqueous amines such as ammonium hydroxide. Sodium hydroxide is preferred. Suitable solvent(s) include solvents such as hydrocarbons, halogenated hydrocarbons, ethers, esters, amides, alcohols and the like, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred.

(g) reacting the 5-(2-oxazolylalkylthio)-2-aminothiazole XI obtained in step (f) with an azacycloalkanoic acid derivative XII in the presence of a coupling reagent in a suitable solvent or solvent mixtures to give thiazolyl amide XIII.

The azacycloalkanoic acid derivative includes N-protected derivatives, for example, N-protected isonipecotic acid or N-protected nipecotic acid. The preferred nitrogen-protecting groups are Boc, Cbz, silicon derivatives and the like with Boc being the most preferred. The coupling reagent includes, but is not limited to, water-soluble carbodiimides, haloformates and the like, with carbodiimides such as alkylcarbodiimides being preferred. Suitable solvent (s) include solvents such as hydrocarbons, halogenated hydrocarbons, ethers, esters, amides, *etc.*, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred.

(h) reacting the thiazolyl amide XIII obtained in step (g) with a deprotecting reagent in a suitable solvent or solvent mixtures to give a desired 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazole I (where R^8 is hydrogen).

[0025] The choice of the deprotecting reagent is based on the nature of the protecting group (P). For the Boc protecting group, the preferred deprotecting reagent is an acid such as hydrochloric acid or trifluoroacetic acid and suitable solvent (s) for such deprotecting reaction include solvents such as hydrocarbons, halogenated hydrocarbons, ethers, esters, amides and the like, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred.

[0026] The starting compounds of Scheme 1 are commercially available or may be prepared by methods known to one of ordinary skill in the art.

[0027] To further illustrate Scheme 1, in a process to make 5-(5-t-butyl-2-oxazolylmethylthio)-2-azacycloalkanoylaminothiazoles and analogs thereof, for example, the α-amino pinacolone IV (R = Bu-t, R^1 = H) is prepared by reaction of α-bromo pinacolone II (R = Bu-t, R^1 = H, L = Br) with hexamethylenetetramine followed by hydrolysis of the resulting quaternary ammonium salt III (R = Bu-t, R^1 = H, L = Br). Coupling of α-amino pinacolone IV (R = Bu-t, R^1 = H) with an α-chloroacetyl chloride V ($R^2 = R^3$ = H, L = X = Cl) produces amide VI (R = Bu-t, $R^1 = R^2 = R^3$ = H, L = Cl). Ring closure of VI with a dehydrating reagent affords 5-t-butyl-2-oxazolylmethyl chloride VII (R = Bu-t, $R^1 = R^2 = R^3$ = H, L = Cl). Treatment of VII with sulfur-containing reagent VIII or VIII' such as thiourea affords 5-t-butyl-2-oxazolylalkyl sulfide IX (R = Bu-t, $R^1 = R^2 = R^3$ = H, Y = NH, Z = NH_2). Coupling of IX with 5-bromo-2-aminothiazole X ($R^4=R^5$=H, L=Br) gives 5-(5-t-butyl-2-oxazolylmethylthio)-2-aminothiazole XI (R = Bu-t, $R^1 = R^2 = R^3 = R^4 = R^5$ = H). Coupling of XI with N-Boc azacycloalkanoic acid XII (X = OH, $R^6 = R^7$ = H, m = 0, n = 2, P = Boc), affords thiazolyl amide XIII (R = Bu-t, $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = R^7$ = H, m = 0, n = 2, P = Boc), which after deprotection, gives rise to the desired 5-(5-t-butyl-2-oxazolylmethylthio)-2-azacycloalkanoylaminothiazole I (R = Bu-t, $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = R^8$ = H, m = 0, n = 2), or an analog thereof.

[0028] The present invention further includes two novel key intermediate compounds of formulae III and IX which have been produced from the new processes to synthesize 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazoles of formula I.

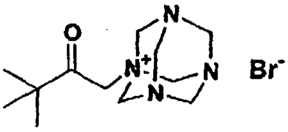
[0029] The following examples demonstrate certain aspects of the present invention. However, it is to be understood that these examples are for illustration only and do not purport to be wholly definitive as to conditions and scope of this invention. It should be appreciated that when typical reaction conditions (*e.g.*, temperature, reaction times, *etc.*) have been given, the conditions both above and below the specified ranges can also be used, though generally less conveniently. The examples are conducted at room temperature (about 23°C to about 28°C) and at atmospheric pressure. All parts and percents referred to herein are on a weight basis and all temperatures are expressed in degrees centigrade unless otherwise specified.

[0030] A further understanding of the invention may be obtained from the non-limiting examples which follow below.

EXAMPLE 2

A Preparation of α-Hexamethylenetetramino-pinacolone Bromide

[0031]

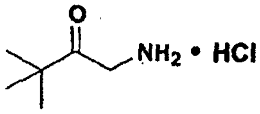


[0032] α-Bromo-pinacolone (179 g, 1 mol, 1 eq) was combined in 2 L of acetone with hexamethylenetetramine (154.21 g, 1.1 mol, 1.1 eq) and the reaction stirred under N_2 at room temperature for 26 hours. The resulting slurry was filtered, the filter cake was washed with ether (3 x 50 mL) and dried *in vacuo* at 50°C overnight to provide 330 g (100%) of the title compound containing 7% hexamethylenetetramine. HPLC R.T.=0.17 min (Phenomenex Inc., 5 μm C18 column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

EXAMPLE 4

B' Preparation of α-Amino-pinacolone Hydrochloride

[0033]

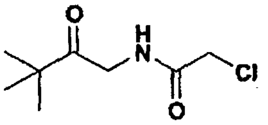


[0034] α-Hexamethylenetetramino-pinacolone bromide (400 g, 1.254 mol, 1 eq) was combined in 2 L of ethanol with 12 N aqueous HCl (439 mL, 5.26 mol, 4.2 eq). The reaction was stirred at 75°C for 1 hour and then allowed to cool to room temperature, the resulting slurry filtered, the filtrate concentrated *in vacuo* and isopropyl alcohol was added. The solution was filtered again. Addition of 1.2 L of ether caused the desired material to precipitate from solution. The material was filtered, washed with ether (2 x 300 mL), and dried *in vacuo* at 50°C overnight to provide 184.1 g (97%) of the title compound.

EXAMPLE 5

C. Preparation of α-N-(2-Chloroacetylamino)-pinacolone

[0035]

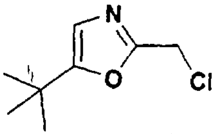


[0036] The title compound of Example 4 (130.96 g, 0.8637 mol, 1 eq) was dissolved in 3.025 L of CH_2Cl_2 under N_2 at -5°C. Triethylamine (301 mL, 2.16 mol, 2.5 eq) was added, followed by chloroacetyl chloride (75.7 mL, 0.450 mol, 1.1 eq) in 175 mL of CH_2Cl_2. The resulting slurry was stirred at -5 to -10°C for 2 hours. Water (1.575 L) was added, followed by 175 mL of concentrated HCl. The organic phase was washed a second time with 1.75 L of 10% aqueous HCl, and then with 500 mL of water. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to provide 155.26 g (93.8%) of the title compound. HPLC R.T.=2.27 min (Phenomenex Inc., 5 μm C18 column 4.6 x 50 mm, 10-90% aqueous methanol, over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

EXAMPLE 6

D. Preparation of 5-(t-Butyl)-2-oxazolylmethyl Chloride

[0037]



[0038] The title compound of Example 5 (180.13 g, 0.9398 mol, 1 eq) was combined with phosphorus oxychloride (262 mL, 2.8109 mol, 3 eq) under N_2. The reaction was heated at 105°C for 1 hour, the mixture was cooled to room temperature, and quenched with 1.3 kg of ice. The aqueous phase was extracted with ethyl acetate (1 L, then 2 x 500 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ (4 x 1 L) which was back-extracted several times with ethyl acetate. The organic phases were combined, washed with saturated aqueous $NaHCO_3$ (500 mL) followed by saturated aqueous NaCl (300 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oil. The crude material was distilled under high vacuum at 100°C to provide 155.92 g (96%) of the title compound. HPLC R.T.=3.62 min (Phenomenex Inc., 5 μm C18 column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

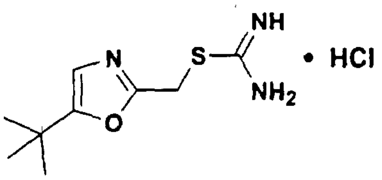
[0039] Alternatively, the title compound of Example 5 (10.0 g, 52.17 mmol, 1 eq.) in 50 mL of tetrahydrofuran (THF) was combined with (methoxycarbonylsulfamyl)-triethylammonium hydroxide (Burgess' reagent, 105.70 mmol, 2.03 eq., generated in situ from 9.2 mL of chlorosulfonyl isocyanate, 4.4 mL of methanol and 14.8 mL of triethylamine in 100 mL

THF). The reaction was heated to 45°C for 1.5 hours. After cooling to room temperature, the reaction was quenched with water (50 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (2 x 50 mL) and water (50 mL), dried over $MgSO_4$ and passed through a small silica gel plug. The solvent was removed to give an oil which was taken up in a mixture of 15 mL heptane and 90 mL of t-butyl methyl ether, and then washed with 0.2 N HCl (2 x 25 mL), saturated brine (25 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave 10.9 g of the title compound.

EXAMPLE 7

E. Preparation of 5-(t-Butyl)-2-oxazolylmethyl Thiouronium Hydrochloride

[0040]

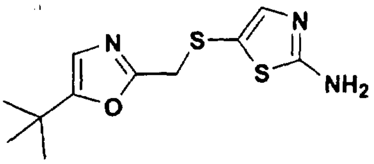


[0041] The title compound of Example 6 (1.77 g, 10.2 mmol, 1.02 eq) was combined with thiourea (0.76 g, 9.98 mmol, 1 eq) under N_2 in 10 mL of absolute ethanol. The reaction was heated at reflux for 1.5 hours. The mixture was cooled to room temperature and concentrated *in vacuo*. Trituration of the resulting crude material with t-butyl methyl ether provided 2.32 g (93%) of the title compound. HPLC R.T.=2.05 min (Phenomenex Inc., 5 μm C18 column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm); ^1H NMR (d_6-DMSO): δ 9.48 (s, 3H), 6.85 (s, 1H), 4.73 (s, 2H), 1.24 (s, 9H).

EXAMPLE 8

F. Preparation of 5-[5-(t-Butyl)-2-oxazolylmethylthio]-2-aminothiazole

[0042]

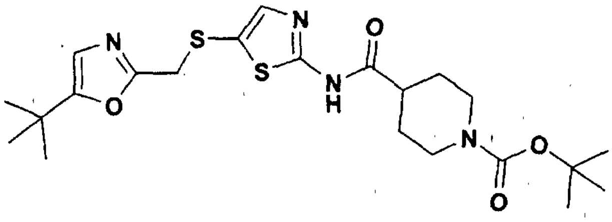


[0043] The title compound of Example 7 (1.25 g, 5 mmol, 1 eq) was added to a mixture of NaOH (3.0 g, 75 mmol, 15 eq), water (10 mL), toluene (10 mL) and tetrabutylammonium sulfate (50 mg, 0.086 mmol, 0.017 eq). 5-Bromo-2-aminothiazole hydrobromide (1.70 g, 5 mmol, 1 eq) was added and the reaction was stirred at room temperature for 14.5 hours. The mixture was diluted with water and extracted twice with ethyl acetate, the organic extracts washed with water (4 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide 1.1 g (82%) of the title compound. HPLC 86.3% at 2.75 min (Phenomenex Inc., 5 μm C18 column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm); ^1H NMR ($CDCl_3$): δ 6.97 (s, 1H), 6.59 (s, 1H), 5.40 (br s, 2H), 3.89 (s, 2H), 1.27 (s, 9H).

EXAMPLE 9

G. Preparation of 5-[5-(t-Butyl)-2-oxazolylmethylthio]-2-[(N-t-butoxycarbonyl)azacycloalkanoyl]aminothiazole

[0044]

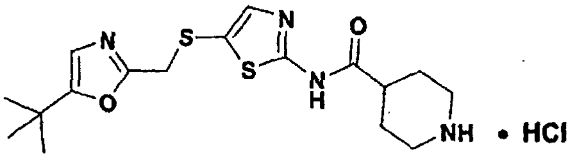


[0045] The title compound of Example 8 (9.6 g, 35.6 mmol) was dissolved in N,N-dimethylformamide (36 mL) and CH_2Cl_2 (100 mL), to which was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (13.8 g, 72 mmol, 2 eq), N-t-butoxycarbonyl-azacycloalkanoic acid (12.6 g, 55 mmol, 1.5 eq), and 4-(dimethylamino)pyridine (2 g, 16 mmol, 0.45 eq). The clear reaction mixture became cloudy as it was stirred at room temperature for 3.5 hours. Water (300 mL) and ethyl acetate (200 mL) were added and the resulting precipitate was removed by filtration. The filtrate was extracted with ethyl acetate, the organic extracts dried over $MgSO_4$ and concentrated *in vacuo* to provide a yellow solid which was combined with the precipitate obtained by filtration. The solid was boiled in a mixture of ethanol, acetone and water for 20 minutes, filtered, washed with an ethanol/water mixture and dried to give 16.6 g (97%) of the title compound.

EXAMPLE 10

H. Preparation of 5-[5-(t-Butyl)-2-oxazolylmethylthio]-2-(azacycloalkanoyl)aminothiazole hydrochloride

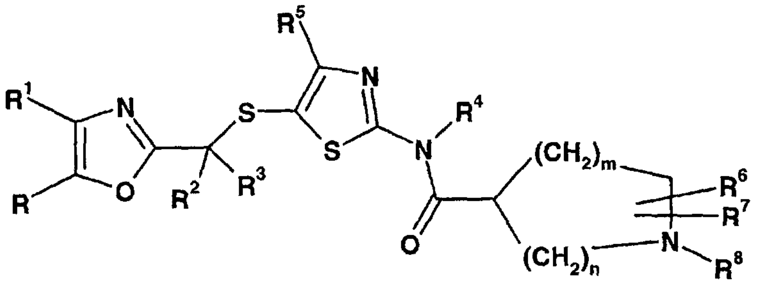
[0046]



[0047] The title compound of Example 9 (16.6 g) was dissolved in 150 mL of CH_2Cl_2, trifluoroacetic acid (30 mL) was added dropwise, and the mixture was stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo*, diluted with water (300 mL), cooled in ice, made basic with sodium hydroxide, and the resulting solid filtered and recrystallized from ethanol, water and methanol to provide 11.2 g (83%) of the title compound as a yellow solid. The white solid hydrochloride could be obtained by addition of 18 mL of IN aqueous HCl to 7 g of this material in methanol. MS: 381 $[M+H]^+$; HPLC: 100% at 3.12 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

Claims

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

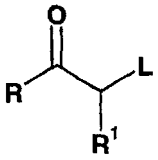


I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R is alkyl, aryl or heteroaryl;
R^1, R^2, R^3, R^4 and R^5 are each independently hydrogen, alkyl, aryl or heteroaryl;
R^6 and R^7 are each independently hydrogen, alkyl, aryl, heteroaryl, halogen, hydroxy or alkoxy;
R^8 is hydrogen, alkyl, aryl, heteroaryl, $CONR^9R^{10}$, COR^{11} or $COOR^{12}$;
R^9, R^{10}, R^{11} and R^{12} are each independently hydrogen, alkyl or aryl;
wherein, in each of the above definitions, "alkyl" refers to straight chain, branched or cyclic monovalent alkane-derived radicals containing from 1 to 12 carbon atoms, which may be substituted with up to four substituent groups at any point of attachment,
m equals 0 to 5; and
n equals 0 to 5;
which comprises the steps of:

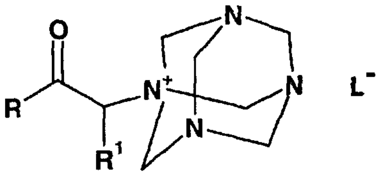
(a) reacting an α-substituted ketone having the formula II



II

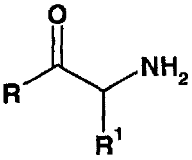
wherein:

R and R^1 are as described hereinabove; and
L is halogen or sulfonate; with a cyclic alkylenetetramine in a suitable solvent or solvent mixture to form a quaternary ammonium salt having the formula III



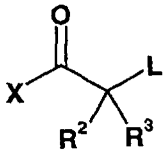
III

(b) reacting the quaternary ammonium salt having the formula III with an acid in a suitable solvent or solvent mixture to form an α-amino ketone having the formula IV



IV

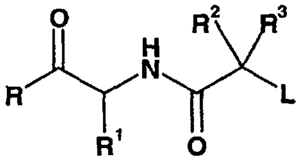
(c) reacting the α-amino ketone with an α-substituted acyl derivative having the formula V



V

wherein:

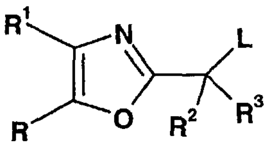
R^2, R^3 and L are as described hereinabove; and
X is hydroxy, halogen or acyloxy;
in the presence of a base in a suitable solvent or solvent mixture to form an amide having the formula VI



VI

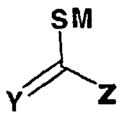
or, alternatively, reacting the α-amino ketone with an α-substituted acid in the presence of a coupling reagent to form the corresponding amide having the formula VI;

(d) reacting the amide having the formula VI with a dehydrating reagent in a suitable solvent or solvent mixture to give a 2-oxazolylalkyl derivative having the formula VII



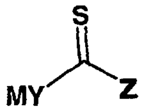
VII

(e) reacting the 2-oxazolylalkyl derivative having the formula VII with a sulfur-containing reagent of formula VIII or VIII'



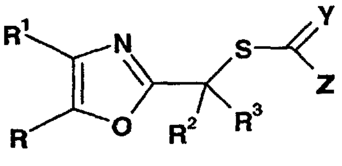
VIII

or



VIII'

wherein
M is hydrogen, Li, Na, K, Cs or quaternary ammonium (R_4N);
Y is oxygen, sulfur, NH, N-alkyl, N-aryl or N-acyl; and
Z is hydrogen, alkyl, aryl, O-alkyl, O-aryl, S-alkyl, S-aryl, NH_2, N-alkyl, N-aryl or N-acyl;
in a suitable solvent or solvent mixture to give a 2-oxazolylalkyl sulfide compound having the formula IX

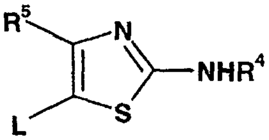


IX

wherein

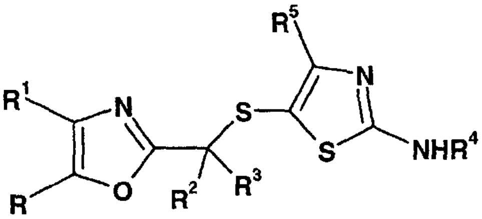
Y and Z are as defined above;

(f) reacting the 2-oxazolylalkyl sulfide having the formula IX with a 5-halo-2-aminothiazole compound having the formula X



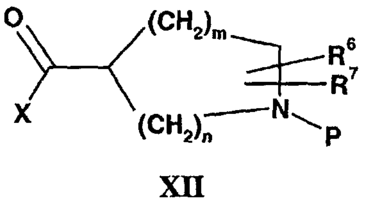
X

in the presence of a base in a suitable solvent or solvent mixture to give a 5-(2-oxazolylmethylthio)-2-aminothiazole compound having the formula XI



XI

(g) reacting the 5-(2-oxazolylmethylthio)-2-aminothiazole having the formula XI with an with an azacycloalkanoic acid derivative having the formula XII



XII

wherein:

- R^6, R^7 and X are as described hereinabove;
- P is a nitrogen-protecting group;
- m equals 0 to 5; and
- n equals 0 to 5;
- in the presence of a coupling reagent in a suitable solvent or solvent mixture to form a thiazolyl amide; and

(h) reacting the thiazolyl amide with a deprotecting reagent in a suitable solvent or solvent mixture to form the compound of formula I.

2. The process as recited in Claim 1, wherein the α-substituted ketone in step (a) is an α-halo ketone.

3. The process as recited in Claim 2, wherein the α-halo ketone is an α-halo aliphatic ketone or an α-halo aromatic ketone.

4. The process as recited in Claim 3, wherein the α-halo ketone is an α-halo pinacolone.

5. The process as recited in Claim 4, wherein the α-halo pinacolone is α-bromo pinacolone.

6. The process as recited in Claim 1, wherein the solvent in step (a) is a hydrocarbon, an ether, an amide, a ketone or a mixture thereof.

7. The process as recited in Claim 6, wherein the solvent is the ketone and the ketone is acetone.

8. The process as recited in Claim 1, wherein the cyclic alkylenetetramine in step (a) is hexamethylenetetramine.

9. The process as recited in Claim 1, wherein the acid in step (b) is HCl, HBr, HI, H_2SO_4 or H_3PO_4.

10. The process as recited in Claim 9, wherein the acid is HCl.

11. The process as recited in Claim 1, wherein the solvent in step (b) is a hydrocarbon, an ether, an alcohol or a mixture thereof.

12. The process as recited in Claim 11, wherein the solvent is the alcohol and the alcohol is ethanol.

13. The process as recited in Claim 1, further comprising isolating the α-amino ketone product as the salt or free base form before performing step (c).

14. The process as recited in Claim 1, wherein the α-substituted acyl derivative in step (c) is an α-halo acyl halide.

15. The process as recited in Claim 14, wherein the α-halo acyl halide is α-chloroacetyl chloride.

16. The process as recited in Claim 1, wherein the base in step (c) is an aromatic organic amine or an aliphatic organic amine.

17. The process as recited in Claim 16, wherein the base is the aliphatic organic amine and the aliphatic organic amine is triethylamine.

18. The process as recited in Claim 1, wherein the α-substituted acid in step (c) is an α-halo acid halide and the coupling reagent is water-soluble.

19. The process as recited in Claim 18, wherein the coupling reagent is a carbodiimide, a haloformate or a thionyl halide.

20. The process as recited in Claim 1, wherein the dehydrating reagent in step (d) is an acid, an acid anhydride or a base.

21. The process as recited in Claim 1, wherein the dehydrating reagent in step (d) is concentrated sulfuric acid, polyphosphoric acid, trichlorophosphorus oxide, tribromophosphorus oxide or (methoxycarbonylsulfamoyl)triethylammonium hydroxide.

22. The process as recited in Claim 21, wherein the dehydrating reagent is (methoxycarbonylsulfamoyl)triethylammonium hydroxide.

23. The process as recited in Claim 1, wherein the solvent in step (d) is tetrahydrofuran.

24. The process as recited in Claim 1, wherein the dehydrating reagent in step (d) is (methoxycarbonylsulfamoyl) triethylammonium hydroxide and the solvent is tetrahydrofuran.

25. The process as recited in Claim 1, wherein the sulfur-containing reagent in step (e) is an N-substituted thiourea, an unsubstituted thiourea, a thio acid or a salt thereof, or a xanthic acid or a salt thereof.

26. The process as recited in Claim 25, wherein the sulfur-containing reagent is thiourea, thioacetic acid or the salt thereof, or ethylxanthic acid potassium salt.

27. The process as recited in Claim 1, wherein the 5-halo-2-aminothiazole compound in step (f) is 5-bromo-2-aminothiazole.

28. The process as recited in Claim 1, wherein the base in step (f) is a metal hydroxide, a metal alkoxide, a metal carbonate or an aqueous amine.

29. The process as recited in Claim 28, wherein the base is the metal hydroxide and the metal hydroxide is sodium hydroxide.

30. The process as recited in Claim 1, wherein the solvent in step (f) is a hydrocarbon, a halogenated hydrocarbon, an ether, an ester, an amide, an alcohol or a mixture thereof.

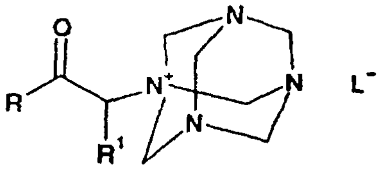
31. The process as recited in Claim 30, wherein the solvent is the halogenated hydrocarbon and the halogenated hydrocarbon is dichloromethane.

32. The process as recited in Claim 1, wherein the nitrogen-protecting group in step (g) is Boc or Cbz.

33. The process as recited in Claim 1, wherein the coupling reagent in step (g) is a carbodiimide, a haloformate or a thionyl halide.

34. The process as recited in Claim 33, wherein the coupling reagent is the carbodiimide and the carbodiimide is an alkylcarbodiimide.

35. A process for the preparation of a compound having the formula III

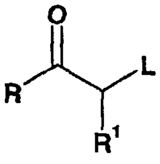


III

or a salt thereof, wherein:

R is alkyl;
R^1 is hydrogen, alkyl, aryl or heteroaryl; and
L is halogen or a sulfonate;

wherein, in each of the above definitions, "alkyl" refers to straight chain, branched or cyclic monovalent alkane-derived radicals containing from 1 to 12 carbon atoms, which may be substituted with up to four substituent groups at any point of attachment, which comprises reacting an α-substituted ketone having the formula II



II

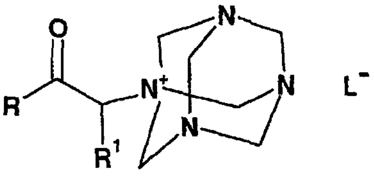
wherein:

R, R^1 and L are as described hereinabove;
with a cyclic alkylenetetramine in a suitable solvent or solvent mixture to form the compound of formula III,

wherein the solvent or solvent mixture comprises a ketone.

36. The process as recited in Claim 35, wherein the ketone is acetone.

37. A process for the preparation of a compound having the formula III

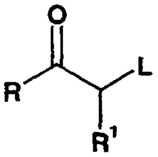


III

or a salt thereof, wherein:

R is t-butyl;
R^1 is hydrogen, alkyl, aryl or heteroaryl; and
L is halogen or a sulfonate;

wherein "alkyl" refers to straight chain, branched or cyclic monovalent alkane-derived radicals containing from 1 to 12 carbon atoms, which may be substituted with up to four substituent groups at any point of attachment,
which comprises reacting an α-substituted ketone having the formula II



II

wherein:

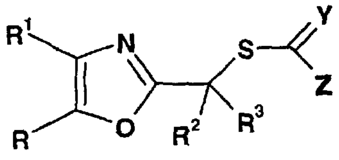
R, R^1 and L are as described hereinabove;
with a cyclic alkylenetetramine in a suitable solvent or solvent mixture to form the compound of formula III.

38. The process as recited in Claim 37, wherein the α-substituted ketone is an α-halo pinacolone.

39. The process as recited in Claim 38, wherein the α-halo pinacolone is α-bromo pinacolone.

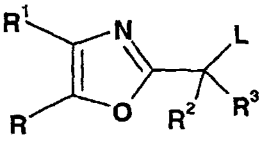
40. The process as recited in Claim 35 or Claim 37, wherein the cyclic alkylenetetramine is hexamethylenetetramine.

41. A process for the preparation of a compound having the formula IX



IX

or a salt thereof, wherein/
R is alkyl, aryl or heteroaryl;
R^1, R^2 and R^3 are each independently hydrogen, alkyl, aryl or heteroaryl;
Y is O, S, NH, N-alkyl, N-aryl or N-acyl; and
Z is hydrogen, alkyl, aryl, O-alkyl, O-aryl, S-alkyl, S-aryl, NH_2, N-alkyl, N-aryl or N-acyl;
wherein, in each of the above definitions, "alkyl" refers to straight chain, branched or cyclic monovalent alkane-derived radicals containing from 1 to 12 carbon atoms, which may be substituted with up to four substituent groups at any point of attachment, which comprises reacting a 2-oxazolylalkyl derivative having the formula VII



VII

wherein:

R, R^1, R^2 and R^3 are as described hereinabove; and
L is halogen or sulfonate;
with a sulfur-containing reagent in a suitable solvent or a solvent mixture to form the compound of formula IX.

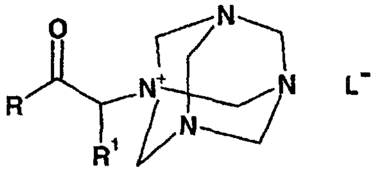
42. The process as recited in Claim 41, wherein the sulfur-containing reagent is an N-substituted thiourea, an unsubstituted thiourea, a thio acid or a salt thereof, or a xanthic acid or a salt thereof.

43. The process as recited in Claim 42, wherein the sulfur-containing reagent is thiourea, thioacetic acid or the salt thereof, or ethylxanthic acid potassium salt.

44. The process as recited in Claim 41, wherein the solvent is a hydrocarbon, a halogenated hydrocarbon, an ether, an ester, an amide, an alcohol or a mixture thereof.

45. The process as recited in Claim 44, wherein the solvent is the alcohol and the alcohol is methanol or ethanol.

46. A compound having the formula III



III

or a salt thereof, wherein:

R is t-butyl;
R^1 is hydrogen, alkyl, aryl or heteroaryl; and
L is halogen or a sulfonate,

wherein "alkyl" refers to straight chain, branched or cyclic monovalent alkane-derived radicals containing from 1 to 12 carbon atoms, which may be substituted with up to four substituent groups at any point of attachment.

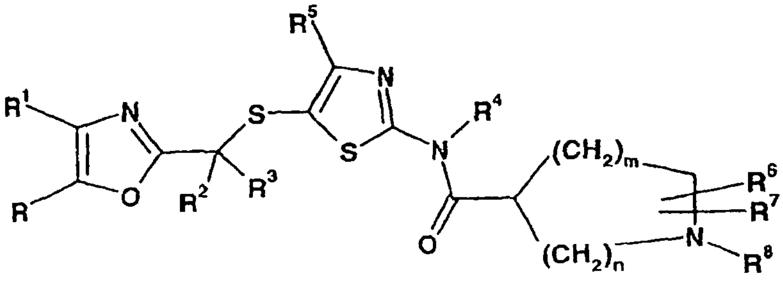
47. The compound as recited in Claim 46, wherein R^1 is hydrogen.

48. The compound as recited in Claim 47, wherein L is halogen.

49. The compound as recited in Claim 46, wherein the compound is α-hexamethylenetetramino-pinacolone bromide.

Patentansprüche

1. Ein Verfahren für die Herstellung einer Verbindung mit der Formel I

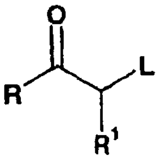


I

oder einem pharmazeutisch akzeptablen Salz oder Solvat davon, worin:

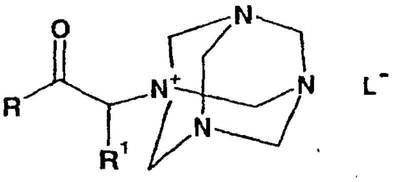
R Alkyl, Aryl oder Heteroaryl ist;
R^1, R^2, R^3, R^4 und R^5 jeweils unabhängig voneinander Wasserstoff, Alkyl, Aryl oder Heteroaryl sind;
R^6 und R^7 unabhängig voneinander Wasserstoff, Alkyl, Aryl, Heteroaryl, Halogen, Hydroxy oder Alkoxy sind;
R^8 Wasserstoff, Alkyl, Aryl, Heteroaryl, $CONR^9R^{10}$, COR^{11} oder $COOR^{12}$ ist;
R^9, R^{10}, R^{11} und R^{12} unabhängig voneinander Wasserstoff, Alkyl oder Aryl sind;
worin, in jeder der obigen Definitionen, "Alkyl" sich auf ein geradkettiges, verzweigtes oder cyclisches monovalentes, von Alkanen stammendes Radikal bezieht, welches von 1 bis 12 Kohlenstoffatome enthält, die mit bis zu 4 Substituenten-Gruppen an beliebiger Stelle bezüglich der Anbringung substituiert sein können,
m entspricht 0 bis 5; und
n entspricht 0 bis 5;
welches die Schritte umfasst:

(a) reagieren eines α-substituierten Ketons mit der Formel II



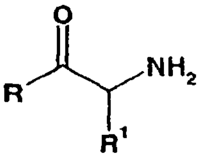
II

worin R und R^1 wie hierin oben beschrieben sind; und
L Halogen oder Sulfonat ist; mit einem cyclischen Alkylentetramin in einem geeigneten Lösungsmittel oder einer Lösungsmittelmischung, um ein quaternäres Ammoniumsalz mit der Formel III



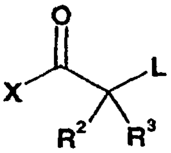
III

zu bilden;
(b) reagieren des quaternären Ammoniumsalzes mit der Formel III mit einer Säure in einem geeigneten Lösungsmittel oder einer Lösungsmittelmischung, um ein α-Aminoketon mit der Formel IV



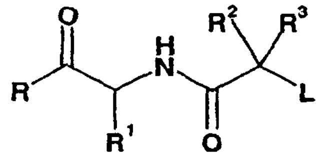
IV

zu bilden;
(c) reagieren des α-Aminoketons mit einem α-substituierten Acylderivat mit der Formel V



V

worin R^2, R^3 und L wie hierin oben beschrieben sind; und
X Hydroxy, Halogen oder Acyloxy ist;
in der Gegenwart einer Base in einen geeigneten Lösungsmittel oder Lösungsmittelgemisch, um ein Amid mit der Formel VI

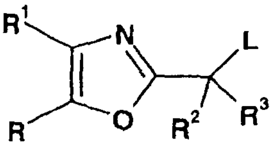


VI

zu bilden;

oder, alternativ, reagieren des α-Aminoketons mit einer α-substituierten Säure in der Gegenwart eines Kupplungsreagenz, um das korrespondierende Amid mit der Formel VI zu bilden;

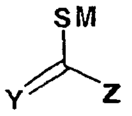
(d) reagieren des Amids mit der Formel VI mit einem Dehydratisierungsreagenz in einem geeigneten Lösungsmittel oder Lösungsmittelgemisch, um ein 2-Oxazolylalkylderivat mit der Formel VII



VII

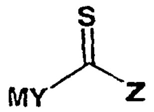
zu ergeben;

(e) reagieren des 2-Oxazolylalkylderivates mit der Formel VII mit einem Schwefel-enthaltenden Reagenz der Formeln VIII oder VIII'



VIII

oder

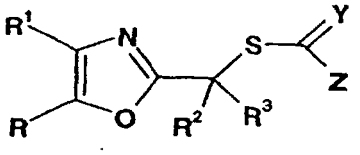


VIII'

worin M gleich Wasserstoff, Li, Na, K, Cs, oder quaternäres Ammonium (R_4N) ist;

Y gleich Sauerstoff, Schwefel, NH, N-Alkyl, N-Aryl oder N-Acyl ist; und

Z gleich Wasserstoff, Alkyl, Aryl, O-Alkyl, O-Aryl, S-Akyl, S-Aryl, NH_2, N-Alkyl, N-Aryl oder N-Acyl ist; in einem geeigneten Lösungsmittel oder Lösungsmittelgemisch, um eine 2-Oxazolylalkylsulfidverbindung mit der Formel IX

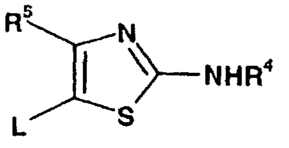


IX

zu ergeben,

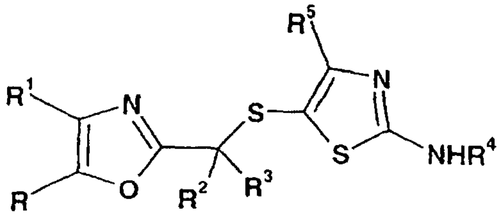
worin Y und Z wie oben definiert sind;

(f) Reagieren des 2-Oxazolylalkylsulfids mit der Formel IX mit einer 5-Halogen-2-Aminothiazol-Verbindung mit der Formel X



X

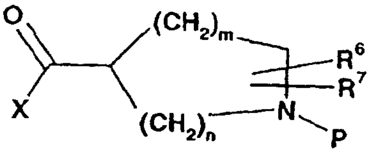
in der Gegenwart einer Base in einem geeigneten Lösungsmittel oder Lösungsmittelgemisch, um eine 5-(2-Oxazolylmethylthio)-2-aminothiazolverbindung mit der Formel XI



XI

zu ergeben;

(g) reagieren des 5-(2-Oxazolylmethylthio)-2-aminothiazol mit der Formel XI mit einem Azacycloalkansäurederivat mit der Formel XII



XII

worin:

R⁶, R⁷ und X wie oben hierin beschrieben sind;
P eine Stickstoff-Schutzgruppe ist;
m gleich 0 bis 5 ist; und
n gleich 0 bis 5 ist;
in der Gegenwart eines Kupplungsreagenz in einem geeigneten Lösungsmittel oder Lösungsmittelgemisch, um ein Thiazolylamid zu bilden; und

(h) reagieren des Thiazolylamids mit einem Entschützungs-Reagenz in einem geeigneten Lösungsmittel oder Lösungsmittelgemisch, um die Verbindung von Formel I zu bilden.

2. Das Verfahren, wie in Anspruch 1 angegeben, worin das α-subsituierte Keton in Schritt (a) ein α-Halogen-Keton ist.

3. Das Verfahren, wie in Anspruch 2 angegeben, worin das α-Halogenketon ein aliphatisches α-Halogen-Keton oder ein aromatisches α-Halogen-Keton ist.

4. Das Verfahren, wie in Anspruch 3 angegeben, worin das α-Halogenketon ein α-Halogenpinacolon ist.

5. Das Verfahren, wie in Anspruch 4 angegeben, worin das α-Halogenpinacolon ein α-Brompinacolon ist.

6. Das Verfahren, wie in Anspruch 1 angegeben, worin das Lösungsmittel in Schritt (a) ein Kohlenwasserstoff, ein Ether, ein Amid, ein Keton oder eine Mischung davon ist.

7. Das Verfahren, wie in Anspruch 6 angegeben, worin das Lösungsmittel das Keton ist und das Keton Aceton ist.

8. Das Verfahren, wie in Anspruch 1 angegeben, worin das cyclische Alkylentetramin in Schritt (a) ein Hexamethylentetramin ist.

9. Das Verfahren, wie in Anspruch 1 angegeben, worin die Säure in Schritt (b) HCl, HBr, HI, H_2SO_4 oder H_3PO_4 ist.

10. Das Verfahren, wie in Anspruch 9 angegeben, worin die Säure HCl ist.

11. Das Verfahren, wie in Anspruch 1 angegeben, worin das Lösungsmittel in Schritt (b) ein Kohlenwasserstoff, ein Ether, ein Alkohol oder eine Mischung davon ist.

12. Das Verfahren, wie in Anspruch 11 angegeben, worin das Lösungsmittel der Alkohol und der Alkohol Ethanol ist.

13. Das Verfahren, wie in Anspruch 1 angegeben, ferner umfassend ein Isolieren des α-Aminoketonprodukts in der Salz- oder freien Basenform vor Durchführung von Schritt (c).

14. Das Verfahren, wie in Anspruch 1 angegeben, worin das α-substituierte Acylderivat in Schritt (c) ein α-Halogenacylhalogenid ist.

15. Das Verfahren wie in Anspruch 14 angegeben, worin das α-Halogenacylhalogenid ein α-Chloroacetylchlorid ist.

16. Das Verfahren, wie in Anspruch 1 angegeben, worin die Base in Schritt (c) ein aromatisches organisches Amin oder ein aliphatisches organisches Amin ist.

17. Das Verfahren, wie in Anspruch 16 angegeben, worin die Base das aliphatische organische Amin ist und das aliphatische organische Amin Triethylamin ist.

18. Das Verfahren, wie in Anspruch 1 angegeben, worin die α-substituierte Säure in Schritt (c) ein α-Säurehalogenid ist und das Kupplungsreagenz wasserlöslich ist.

19. Das Verfahren, wie in Anspruch 18 angegeben, worin das Kupplungsreagenz Carbodiimid, ein Halogenformiat oder ein Thionylhalogenid ist.

20. Das Verfahren, wie in Anspruch 1 angegeben, worin das dehydratisierende Reagenz in Schritt (d) eine Säure, ein Säureanhydrid oder eine Base ist.

21. Das Verfahren, wie in Anspruch 1 angegeben, worin das dehydratisierende Reagenz in Schritt (d) konzentrierte Schwefelsäure, Polyphosphorsäure, Trichlorphosphoroxid, Tribromphosphoroxid oder (Methoxycarbonylsulfamoyl) triethyl-ammoniumhydroxid ist.

22. Das Verfahren, wie in Anspruch 21 angegeben, worin das dehydratisierende Reagenz (Methoxycarbonylsulfamyl) triethyl-ammoniumhydroxid ist.

23. Das Verfahren, wie in Anspruch 1 angegeben, worin das Lösungsmittel in Schritt (d) Tetrahydofuran ist.

24. Das Verfahren, wie in Anspruch 1 angegeben, worin das dehydratisierende Reagenz in Schritt (d) (Methoxycarbonylsulfamyl)triethyl-ammoniumhydroxid und das Lösungsmittel Tetrahydrofuran ist.

25. Das Verfahren, wie in Anspruch 1 angegeben, worin das Schwefel-enthaltende Reagenz in Schritt (e) ein N-substituierter Thioharnstoff, ein unsubstituierter Thioharnstoff, eine Thiosäure oder ein Salz davon oder eine Xanthogensäure oder ein Salz davon ist.

26. Das Verfahren, wie in Anspruch 25 angegeben, worin das Schwefel-enthaltende Reagenz Thioharnstoff, Thioessigsäure oder ein Salz davon oder Ethylxanthogenat-Kaliumsalz ist.

27. Das Verfahren, wie in Anspruch 1 angegeben, worin die 5-Halogen-2-aminothiazolverbindung in Schritt (f) 5-Brom-2-aminothiazol ist.

28. Das Verfahren, wie in Anspruch 1 angegeben, worin die Base in Schritt (f) ein Metallhydroxid, ein Metallalkoxid, ein Metallcarbonat oder ein wässriges Amin ist.

29. Das Verfahren, wie in Anspruch 28 angegeben, worin die Base das Metallhydroxid und das Metallhydroxid Natriumhydroxid ist.

30. Das Verfahren, wie in Anspruch 1 angegeben, worin das Lösungsmittel in Schritt (f) ein Kohlenwasserstoff, ein halogenierter Kohlenwasserstoff, ein Ether, ein Ester, ein Amid, ein Alkohol oder eine Mischung davon ist.

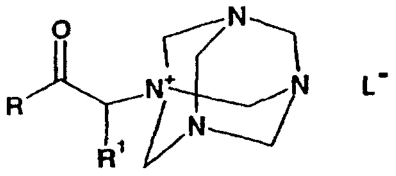
31. Das Verfahren, wie in Anspruch 30 angegeben, worin das Lösungsmittel der halogenierte Kohlenwasserstoff ist und der halogenierte Kohlenwasserstoff Dichlormethan ist.

32. Das Verfahren, wie in Anspruch 1 angegeben, worin die Stickstoffschutzgruppe in Schritt (g) Boc oder Cbz ist.

33. Das Verfahren, wie in Anspruch 1 angegeben, worin das Kupplungsreagenz in Schritt (g) ein Carbodiimid, ein Halogenformiat oder ein Thionylhalogenid ist.

34. Das Verfahren wie in Anspruch 33 angegeben, worin das Kupplungsreagenz das Carbodiimid ist und das Carbodiimid ein Alkylcarbodiimid ist.

35. Ein Verfahren für die Herstellung einer Verbindung mit der Formel III

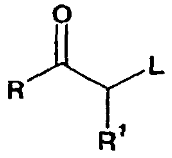


III

oder einem Salz davon, worin:

R Alkyl ist;
R^1 Wasserstoff, Alkyl, Aryl oder Heteroaryl ist; und
L Halogen oder Sulfonat ist;

worin, in jeder der obigen Definitionein, "Alkyl" sich auf ein geradkettiges, verzweigtes oder cyclisch monovalentes, von Alkanen stammendes Radikal bezieht, welches von 1 bis 12 Kohlenstoffatome enthält, welches mit bis zu 4 Substituentengruppen an einer beliebigen Stelle bezüglich der Anbringung substituiert sein kann, welches ein reagieren eines α-substituierten Ketons mit der Formel II



II

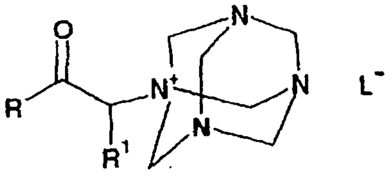
umfasst, worin:

R, R^1 und L wie hierin oben beschrieben sind;
mit einem cyclischen Alkylentetramin in einem geeigneten Lösungsmittel oder Lösungsmittelgemisch, um eine Verbindung der Formel III zu bilden,

worin das Lösungsmittel oder das Lösungsmittelgemisch ein Keton umfasst.

36. Das Verfahren wie in Anspruch 35 angegeben, worin das Keton Aceton ist.

37. Ein Verfahren für die Herstellung einer Verbindung mit der Formel III

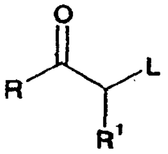


III

oder einem Salz davon, worin:

R t-Butyl ist;
R^1 Wasserstoff, Alkyl, Aryl oder Heteroaryl ist; und
L Halogen oder Sulfonat ist;

worin Alkyl sich auf ein geradkettiges, verzweigtes oder cyclisch monovalentes, von Alkanen stammendes Radikal bezieht, welches von 1 bis 12 Kohlenstoffatome enthält, welches mit bis zu 4 Substituentengruppen an einer beliebigen Stelle bezüglich der Anbringung substituiert sein kann,
welches ein reagieren eines α-substituierten Keton mit der Formel II



II

umfasst, worin:

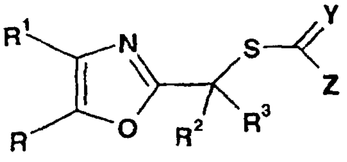
R, R^1 und L wie oben beschrieben sind;
mit einem cyclischen Alkylentetramin in einem geeigneten Lösungsmittel oder Lösungsmittelgemisch, um eine Verbindung der Formel III zu bilden.

38. Das Verfahren, wie in Anspruch 37 angegeben, worin das α-substituierte Keton ein α-Halogenpinacolon ist.

39. Das Verfahren, wie in Anspruch 38 angegeben, worin das α-Halogenpinacolon ein α-Brompinacolon ist.

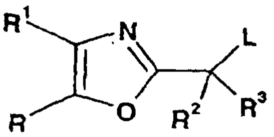
40. Das Verfahren, wie in Anspruch 35 oder 37 angegeben, worin das cyclische Alkylentetramin Hexamethylentetramin ist.

41. Ein Verfahren für die Herstellung einer Verbindung mit Formel IX



IX

oder eines Salz davon, worin
R Alkylaryl oder Heteroaryl ist;
R^1, R^2 und R^3 jeweils unabhängig voneinander Wasserstoff, Alkyl, Arly oder Heteroaryl sind;
Y gleich O, NH, N-Alkyl, N-Aryl oder N-Acyl ist; und
Z gleich Wasserstoff, Alkylyl, O-Alkyl, O-Aryl, S-Alkyl, S-Aryl, NH_2, N-Alkyl, N-Aryl oder N-Acyl ist;
worin, in jeder der obigen Definitionen, "Alkyl" sich auf ein geradkettiges, verzweigtes oder cyclisch monovalentes, von Alkanen stammendes Radikal bezieht, welches von 1 bis 12 Kohlenstoffatome enthält, welches mit bis zu 4 Substituentengruppen an einer beliebigen Stelle bezüglich der Anbringung substituiert sein kann,
welches ein reagieren eines 2-Oxazolylderivats mit der Formel VII



VII

umfasst, worin:

R, R^1, R^2 und R^3 wie hierin oben beschrieben sind; und
L Halogen oder Sulfonat ist;
mit einem Schwefel-enthaltenden Reagenz in einem geeigneten Lösungsmittel oder Lösungsmittelgemisch, um eine Verbindung mit Formel IX zu bilden.

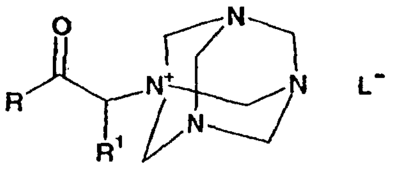
42. Das Verfahren wie in Anspruch 41 angegeben, worin das Schwefel-enthaltende Reagenz einen N-substituierten Thioharnstoff, ein unsubstituierter Thioharnstoff, eine Thiosäure oder ein Salz davon oder ein Xanthogensäure oder ein Salz davon ist.

43. Das Verfahren, wie in Anspruch 42 angegeben, worin das Schwefel-enthaltende Reagenz Thioharnstoff, Thioessigsäure oder ein Salz davon oder Ethylxanthogenat-Kaliumsalz ist.

44. Das Verfahren, wie in Anspruch 41 angegeben, worin das Lösungsmittel ein Kohlenwasserstoff, ein halogenierter Kohlenwasserstoff, ein Ether, ein Ester, ein Amid, ein Alkohol oder eine Mischung davon ist.

45. Das Verfahren, wie in Anspruch 44 angegeben, worin das Lösungsmittel der Alkohol ist und der Alkohol Methanol oder Ethanol ist.

46. Eine Verbindung mit der Formel III



III

oder ein Salz davon worin:

R tert-Butyl ist;
R^1 Wasserstoff, Alkyl, Arly oder Heteroaryl ist; und
L Halogen oder Sulfonat ist, worin "Akyl" sich auf ein geradkettiges, verzweigtes oder cyclisch monovalentes, von Alkanen stammendes Radikal bezieht, welches von 1 bis 12 Kohlenstoffatome enthält, welches mit bis zu 4 Substituentengruppen an einer beliebigen Stelle bezüglich der Anbringung substituiert sein kann.

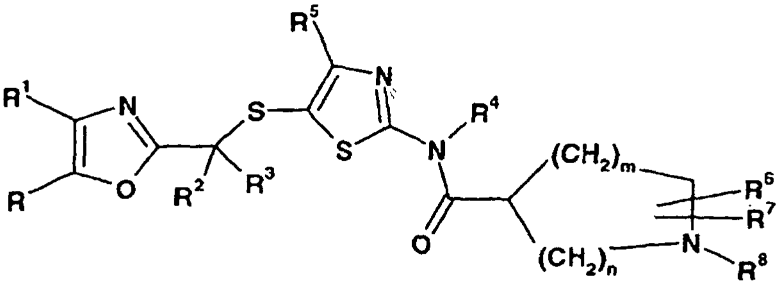
47. Die Verbindung, wie in Anspruch 46 angegeben, worin R^1 Wasserstoff ist.

48. Die Verbindung, wie in Anspruch 47 angegeben, worin L Halogen ist.

49. Die Verbindung, wie in Anspruch 46 angegeben, worin die Verbindung ein α-Hexamethylentetramino-pinacolon-bromid ist.

Revendications

1. Procédé pour la préparation d'un composé ayant la formule I

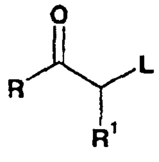


I

ou d'un sel ou d'un solvate de celui-ci pharmaceutiquement acceptable, où
R est un alkyle, un aryle ou un hétéroaryle ;
R^1, R^2, R^3, R^4 et R^5 sont, chacun de façon indépendante, un hydrogène, un alkyle, un aryle ou un hétéroaryle ;
R^6 et R^7 sont, chacun de façon indépendante, un hydrogène, un alkyle, un aryle, un hétéroaryle, un halogène, un hydroxy ou un alcoxy ;
R^8 est un hydrogène, un alkyle, un aryle, un hétéroaryle, $CONR^9R^{10}$, COR^{11} ou $COOR^{12}$;
R^9, R^{10}, R^{11} et R^{12} sont, chacun de façon indépendante, un hydrogène, un alkyle ou aryle ;
où, dans chacune des définitions ci-dessus, « alkyle » désigne des restes dérivés d'alcanes monovalents à chaîne linéaire, ramifiés ou cycliques contenant 1 à 12 atomes de carbone, qui peuvent être substitués par jusqu'à quatre groupes substituants en tout point d'attachement,
m est égal à 0 à 5 ; et

n est égal à 0 à 5 ;
qui comprend les étapes de :

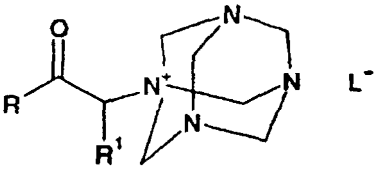
(a) réaction d'une cétone α-substituée de formule II



II

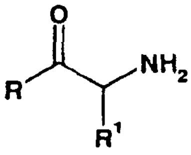
où :

R et R^1 sont tels que décrits ci-dessus ; et
L est un halogène ou un sulfonate ; avec une alkylènetétramine cyclique dans un solvant ou un mélange de solvants approprié pour former un sel d'ammonium quaternaire ayant la formule III



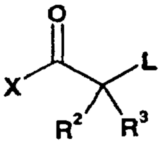
III

(b) réaction du sel d'ammonium quaternaire de formule III avec un acide dans un solvant ou un mélange de solvants approprié pour former une α-amino cétone de formule IV



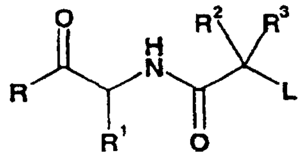
IV

(c) réaction de l'α-amino cétone avec un dérivé acyle α-substitué de formule V



V

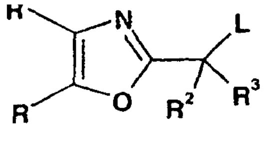
où
R^2, R^3 et L sont tels que décrits ci-dessus ; et
X est un hydroxy, un halogène ou un acyloxy ;
en présence d'une base dans un solvant ou un mélange de solvants approprié pour former un amide de formule VI



VI

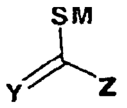
ou, selon une autre possibilité, réaction de l'α-amino cétone avec un acide α-substitué en présence d'un réactif de couplage pour former l'amide correspondant de formule VI ;

(d) réaction de l'amide de formule VI avec un réactif déshydratant dans un solvant ou un mélange de solvants approprié pour former un dérivé 2-oxazolylalkyle de formule VII



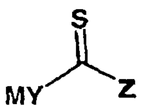
VII

(e) réaction du dérivé 2-oxazolylalkyle de formule VII avec un réactif contenant du soufre, de formule VIII ou VIII'



VIII

ou



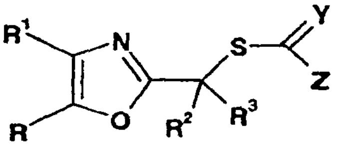
VIII'

où

M est un hydrogène, Li, Na, K, Cs ou un ammonium quaternaire (R_4N) ;

Y est un oxygène, un soufre, NH, N-alkyle, N-aryle ou N-acyle ; et

Z est un hydrogène, un alkyle, un aryle, O-alkyle, O-aryle, S-alkyle, S-aryle, NH_2, N-alkyle, N-aryle ou N-acyle ; dans un solvant ou un mélange de solvants approprié pour former un composé sulfure de 2-oxazolylalkyle de formule IX

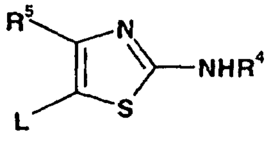


IX

où

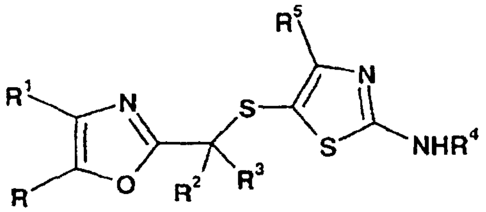
Y et Z sont tels que définis ci-dessus ;

(f) réaction du sulfure de 2-oxazolylalkyle de formule IX avec un composé 5-halogéno-2-aminothiazole de formule X



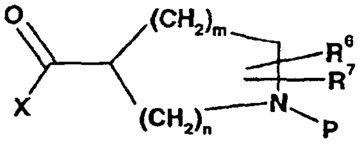
X

en présence d'une base dans un solvant ou un mélange de solvants approprié pour former un composé 5-(2-oxazolylméthylthio)-2-aminothiazole de formule XI



XI

(g) réaction du 5-(2-oxazolylméthylthio)-2-aminothiazole de formule XI avec un dérivé d'acide azacycloalcanoïque de formule XII



XII

où :

R^6, R^7 et X sont tels que décrits ci-dessus ;
P est un groupe protecteur d'azote ;
m est égal à 0 à 5 ; et
n est égal à 0 à 5 ;
en présence d'un réactif de couplage dans un solvant ou un mélange de solvants approprié pour former un thiazolylamide ; et

(h) réaction du thiazolylamide avec un réactif de déprotection dans un solvant ou un mélange de solvants approprié pour former le composé de formule I.

2. Procédé selon la revendication 1, dans lequel la cétone α-substituée dans l'étape (a) est une α-halogénocétone.

3. Procédé selon la revendication 2, dans lequel l'α-halogénocétone est une α-halogénocétone aliphatique ou une α-halogénocétone aromatique.

4. Procédé selon la revendication 3, dans lequel l'α-halogénocétone est une α-halogénopinacolone.

5. Procédé selon la revendication 4, dans lequel l'α-halogénopinacolone est l'α-bromopinacolone.

6. Procédé selon la revendication 1, dans lequel le solvant dans l'étape (a) est un hydrocarbure, un éther, un amide, une cétone, ou un mélange de ceux-ci.

7. Procédé selon la revendication 6, dans lequel le solvant est la cétone, et la cétone est l'acétone.

8. Procédé selon la revendication 1, dans lequel l'alkylènetétramine cyclique dans l'étape (a) est l'hexaméthylènetétramine.

9. Procédé selon la revendication 1, dans lequel l'acide dans l'étape (b) est HCl, HBr, HI, H_2SO_4 ou H_3PO_4.

10. Procédé selon la revendication 9, dans lequel l'acide est HCl.

11. Procédé selon la revendication 1, dans lequel le solvant dans l'étape (b) est un hydrocarbure, un éther, un alcool ou un mélange de ceux-ci.

12. Procédé selon la revendication 11, dans lequel le solvant est l'alcool et l'alcool est l'éthanol.

13. Procédé selon la revendication 1, comprenant en outre l'isolement du produit α-aminocétone sous forme de sel ou de base libre avant la réalisation de l'étape (c).

14. Procédé selon la revendication 1, dans lequel le dérivé acyle α-substitué dans l'étape (c) est un halogénure d'α-halogénoacyle.

15. Procédé selon la revendication 14, dans lequel l'halogénure d'α-halogénoacyle est le chlorure d'α-chloroacétyle.

16. Procédé selon la revendication 1, dans lequel la base dans l'étape (c) est une amine organique aromatique ou une amine organique aliphatique.

17. Procédé selon la revendication 16, dans lequel la base est l'amine organique aliphatique et l'amine organique aliphatique est la triéthylamine.

18. Procédé selon la revendication 1, dans lequel l'acide α-substitué dans l'étape (c) est un halogénure d'α-halogénoacide et le réactif de couplage est soluble dans l'eau.

19. Procédé selon la revendication 18, dans lequel le réactif de couplage est un carbodiimide, un halogénoformiate ou un halogénure de thionyle.

20. Procédé selon la revendication 1, dans lequel le réactif déshydratant dans l'étape (d) est un acide, un anhydride d'acide ou une base.

21. Procédé selon la revendication 1, dans lequel le réactif déshydratant dans l'étape (d) est l'acide sulfurique concentré, l'acide polyphosphorique, l'oxyde trichlorophosphoreux, l'oxyde tribromophosphoreux ou l'hydroxyde de (méthoxycarbonylsulfamoyl)triéthylammonium.

22. Procédé selon la revendication 21, dans lequel le réactif déshydratant est l'hydroxyde de (méthoxycarbonylsulfamoyl) triéthylammonium.

23. Procédé selon la revendication 1, dans lequel le solvant dans l'étape (d) est le tétrahydrofurane.

24. Procédé selon la revendication 1, dans lequel le réactif déshydratant dans l'étape (d) est l'hydroxyde de (méthoxycarbonylsulfamoyl)-triéthylammonium et le solvant est le tétrahydrofurane.

25. Procédé selon la revendication 1, dans lequel le réactif contenant du soufre dans l'étape (e) est une thiourée N-substituée, une thiourée non-substituée, un thioacide ou un sel de celui-ci, ou un acide xanthique ou un sel de celui-ci.

26. Procédé selon la revendication 25, dans lequel le réactif contenant du soufre est la thiourée, l'acide thioacétique ou un sel de celui-ci, ou le sel de potassium de l'acide éthylxanthique.

27. Procédé selon la revendication 1, dans lequel le composé 5-halogéno-2-aminothiazole dans l'étape (f) est le 5-bromo-2-aminothiazole.

28. Procédé selon la revendication 1, dans lequel la base dans l'étape (f) est un hydroxyde de métal, un alcoolate de métal, un carbonate de métal ou une amine aqueuse.

29. Procédé selon la revendication 28, dans lequel la base est l'hydroxyde de métal et l'hydroxyde de métal est l'hydroxyde de sodium.

30. Procédé selon la revendication 1, dans lequel le solvant dans l'étape (f) est un hydrocarbure, un hydrocarbure halogéné, un éther, un ester, un amide, un alcool ou un mélange de ceux-ci.

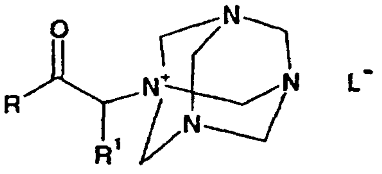
31. Procédé selon la revendication 30, dans lequel le solvant est l'hydrocarbure halogéné et l'hydrocarbure halogéné est le dichlorométhane.

32. Procédé selon la revendication 1, dans lequel le groupe protecteur d'azote dans l'étape (g) est Boc ou Cbz.

33. Procédé selon la revendication 1, dans lequel le réactif de couplage dans l'étape (g) est un carbodiimide, un halogénoformiate ou un halogénure de thionyle.

34. Procédé selon la revendication 33, dans lequel le réactif de couplage est le carbodiimide et le carbodiimide est un alkylcarbodiimide.

35. Procédé pour la préparation d'un composé ayant la formule III

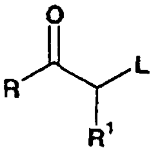


III

ou d'un sel de celui-ci, où :

R est un alkyle ;
R^1 est un hydrogène, un alkyle, un aryle ou un hétéroaryle ; et
L est un halogène ou un sulfonate ;

où, dans chacune des définitions ci-dessus, « alkyle » désigne des restes dérivés d'alcanes monovalents à chaîne linéaire, ramifiés ou cycliques contenant 1 à 12 atomes de carbone, qui peuvent être substitués par jusqu'à quatre groupes substituants en tout point d'attachement,
qui comprend la réaction d'une cétone α-substituée ayant la formule II



II

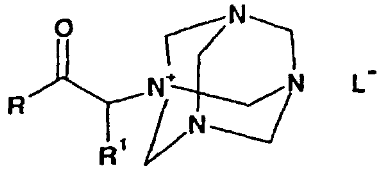
où :

R, R^1 et L sont tels que décrits ci-dessus ;
avec une alkylènetétramine cyclique dans un solvant ou un mélange de solvants approprié pour former le composé de formule III,

où le solvant ou le mélange de solvants comprend une cétone.

36. Procédé selon la revendication 35, dans lequel la cétone est l'acétone.

37. Procédé pour la préparation d'un composé ayant la formule III

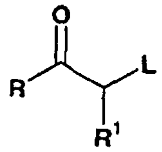


III

ou d'un sel de celui-ci, où :

R est le t-butyle ;
R^1 est un hydrogène, un alkyle, un aryle ou un hétéroaryle ; et
L est un halogène ou un sulfonate ;

où « alkyle » désigne des restes dérivés d'alcanes monovalents à chaîne linéaire, ramifiés ou cycliques contenant 1 à 12 atomes de carbone, qui peuvent être substitués par jusqu'à quatre groupes substituants en tout point d'attachement,
qui comprend la réaction d'une cétone α-substituée ayant la formule II



II

où :

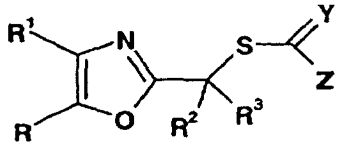
R, R^1 et L sont tels que décrits ci-dessus ;
avec une alkylènetétramine cyclique dans un solvant ou un mélange de solvants approprié pour former le composé de formule III.

38. Procédé selon la revendication 37, dans lequel la cétone α-substituée est une α-halogénopinacolone.

39. Procédé selon la revendication 38, dans lequel l'α-halogénopinacolone est l'α-bromopinacolone.

40. Procédé selon la revendication 35 ou la revendication 37, dans lequel l'alkylènetétramine cyclique est une hexaméthylènetétramine.

41. Procédé pour la préparation d'un composé ayant la formule IX

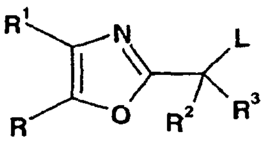


IX

ou d'un sel de celui-ci, où :

R est un alkyle, un aryle ou un hétéroaryle ;
R^1, R^2 et R^3 sont, chacun de façon indépendante, un hydrogène, un alkyle, un aryle ou un hétéroaryle ;
Y est O, S, NH, N-alkyle, N-aryle ou N-acyle ; et
Z est un hydrogène, un alkyle, un aryle, O-alkyle, O-aryle, S-alkyle, S-aryle, NH_2, N-alkyle, N-aryle ou N-acyle ;

où, dans chacune des définitions ci-dessus, « alkyle » désigne des restes dérivés d'alcanes monovalents à chaîne linéaire, ramifiés ou cycliques contenant 1 à 12 atomes de carbone, qui peuvent être substitués par jusqu'à quatre groupes substituants en tout point d'attachement,
qui comprend la réaction d'un dérivé 2-oxazolylalkyle de formule VII:



VII

où :

R, R^1, R^2 et R^3 sont tels que décrits ci-dessus ; et
L est un halogène ou un sulfonate ;
avec un réactif contenant du soufre dans un solvant ou un mélange de solvants approprié pour former un composé de formule IX.

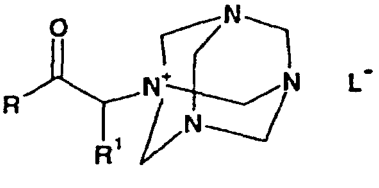
42. Procédé selon la revendication 41, dans lequel le réactif contenant du soufre est une thiourée N-substituée, une thiourée non-substituée, un thioacide ou un sel de celui-ci, ou un acide xanthique ou un sel de celui-ci.

43. Procédé selon la revendication 42, dans lequel le réactif contenant du soufre est la thiourée, l'acide thioacétique ou un sel de celui-ci, ou le sel de potassium de l'acide éthylxanthique.

44. Procédé selon la revendication 41, dans lequel le solvant est un hydrocarbure, un hydrocarbure halogéné, un éther, un ester, un amide, un alcool ou un mélange de ceux-ci.

45. Procédé selon la revendication 44, dans lequel le solvant est l'alcool et l'alcool est le méthanol ou l'éthanol.

46. Composé ayant la formule III



III

ou sel de celui-ci, où :

R est le t-butyle ;
R^1 est un hydrogène, un alkyle, un aryle ou un hétéroaryle ; et
L est un halogène ou un sulfonate ;

où « alkyle » désigne des restes dérivés d'alcanes monovalents à chaîne linéaire, ramifiés ou cycliques contenant 1 à 12 atomes de carbone, qui peuvent être substitués par jusqu'à quatre groupes substituants en tout point d'attachement,

47. Composé selon la revendication 46, dans lequel R^1 est un hydrogène.

48. Composé selon la revendication 47, dans lequel L est un halogène.

49. Composé selon la revendication 46, ce composé étant le bromure d'α-hexaméthylènetétraminopinacolone.