

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 November 2007 (22.11.2007)

PCT

(10) International Publication Number
WO 2007/131953 A1

(51) International Patent Classification:

C07D 263/34 (2006.01) C07D 413/04 (2006.01)
C07D 263/48 (2006.01)

(21) International Application Number:

PCT/EP2007/054564

(22) International Filing Date: 11 May 2007 (11.05.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/799,674 12 May 2006 (12.05.2006) US

(71) Applicant (for all designated States except US): **AB SCIENCE** [FR/FR]; 3, avenue George V, F-75008 Paris (FR).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BENJAHAD, Abdellah** [FR/FR]; 55-57, rue Diderot Entrée 8, F-94500 Champigny Sur Marne (FR).

(74) Agent: **WARCOIN, AHNER, TEXIER, LE FORESTIER, CALLON DE LAMARCK, COLLIN, TETAZ-Cabinet Regimbeau**; 20, rue de Chazelles, F-75847 Paris Cedex 17 (FR).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

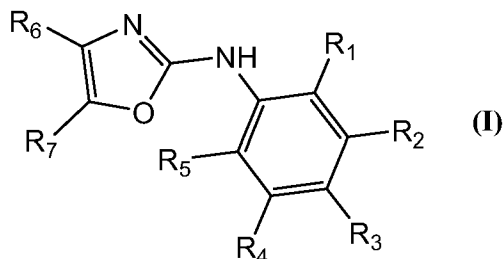
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A NEW PROCESS FOR THE SYNTHESIS OF 2-AMINOXAZOLE COMPOUNDS



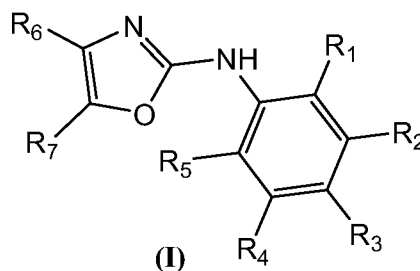
(57) Abstract: The present invention relates to a process for synthesizing in good yield substituted 2- aminoaryloxazole compounds of formula I which are useful as certain tyrosine kinase inhibitors and more particularly as c-kit, bcr-abl, Flt-3 and mutant forms thereof.

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A NEW PROCESS FOR THE SYNTHESIS OF 2-AMINOXAZOLE COMPOUNDS

- 5 The present invention relates to a process for synthesizing compounds having the formula (I) which are useful as certain tyrosine kinase inhibitors and more particularly as c-kit, bcr-abl, Flt-3 and mutant forms thereof. More specifically, it relates to the synthesis in good yield of substituted 2-aminoaryloxazole compounds of formula I wherein groups R1-R7, identical or different, are as described hereinafter.

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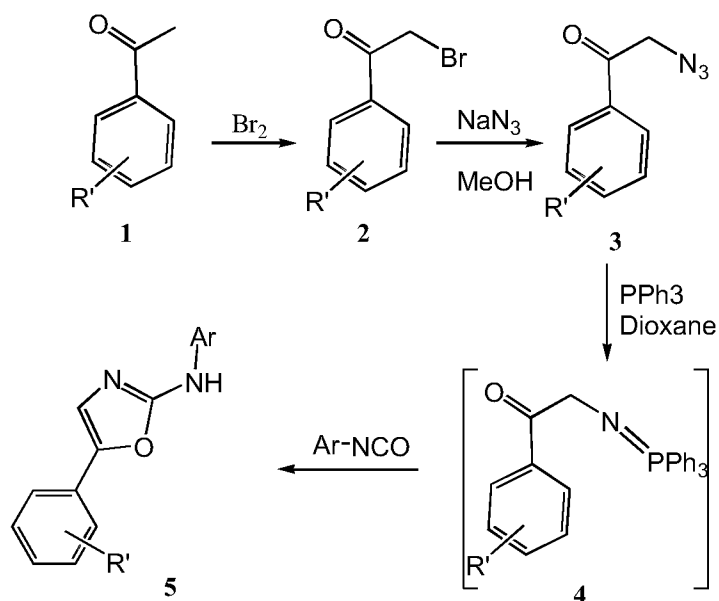
Background of the invention

- 15 We have recently found that compounds corresponding to substituted oxazole derivatives (WO2005040139) are potent and selective of certain tyrosine kinase inhibitors and more particularly of c-kit, bcr-abl, Flt-3 and mutant forms thereof. These compounds are good candidates for treating diseases such as autoimmune diseases, inflammatory diseases, cancers and mastocytosis. In view of the growing interest of such
- 20 compounds as candidate medicament, a process allowing high scale production is needed.

Several publications have described the synthesis of functionalized 2-aminoaryloxazole compounds. Examples include, Turchi, I. J. (Ed. Heterocyclic Compounds, J. Wiley and sons : N.Y., 1986); U. S. Patent US 2002/0143176A1 as well as publications by Froyen P. (Phosphorus, Sulfur and Silicon, 1991, vol 60 pp.81-84) and Murali Dhar, T. G. , et al. (Bioorganic & Medicinal Chemistry Letters, 2002, vol 12, pp. 3125-3128). However, and as summarized below, conventional methodologies have synthetic disadvantages

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concerning one or more of these characteristics: yield, scalability to multi-gram synthesis, highly reactive by- product formation, hazardous reaction conditions, impurity formation, number of synthetic steps, reaction conditions, and purifications. For example, the synthesis of 2-aminoaryloxazole **5** via Iminophosphorane **4** (Scheme 1) present two major disadvantages : a risk of explosions due to the presence of azide **3** (Murali Dhar, T. G. , et al. (Organic Letters, 2002, vol 4 (12), pp. 2091-2093)), and rapid decomposition under reaction conditions of 2-Azido Ketone **3**, when 5-aromatic moiety is highly functionalized. This decomposition adversely affects product recovery, and the reaction is characterized by numbers of byproducts and a yield that is too low to allow for its implementation in a scale-up process.



Scheme 1

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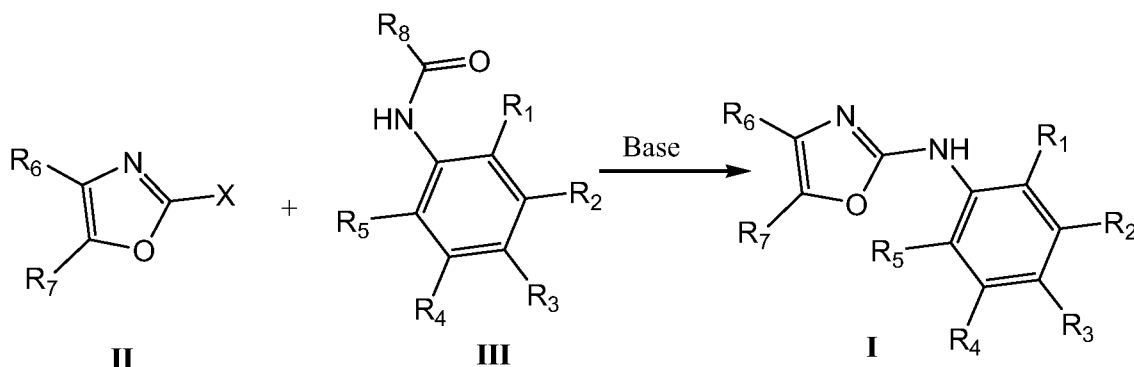
In contrast with conventional methodologies, the present invention provides a synthetic method that is characterized by at least one of the following features: good yields, with embodiments producing at least about 70% yield of the functionalized 2-aminooxazole derivative of interest; regioselectivity; purification by simple procedures, such as crystallization; and suitability for the production of multi-gram quantities of the products

of interest. A series of 2-aminooxazole derivatives are described herein. Also described are methods for preparing these derivatives, that are amenable to large-scale procedures.

The process according to the present invention presents the advantages of obtaining 5-
 5 fonctionnalisés oxazole in good yield such 5-carboxyl-oxazole or 5-cyano-oxazole.

Description

The present invention relates to a process for the preparation of compounds of formula
 10 (I), comprising a condensation of compound of formula (II) and an acetamide derivative of formula (III), in very mild conditions which are in a solvent comprising a base:



Scheme 2

15 Wherein substituents R1 – R8 and X in are defined as follows:

R1, R2, R3, R4 and R5 each independently are selected from hydrogen, halogen (selected from F, Cl, Br or I), a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen
 20 (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, carboxyl, cyano, nitro, formyl, hydroxy, and CO-R, COO-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom,
 25 notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality.

R6 and R7 each independently are selected from:

i) hydrogen, a halogen (selected from F, Cl, Br or I), or

ii) an alkyl¹ group defined as a linear, branched or cycloalkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen (the latter optionally in the form of a pendant basic nitrogen functionality); as well as trifluoromethyl, carboxyl, cyano, nitro, formyl; as well as CO-R, COO-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality ; as well as a cycloalkyl or aryl¹ or heteroaryl¹ group optionally substituted by a pendant basic nitrogen functionality, or

(iii) an aryl¹ group defined as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as

- halogen(selected from I, F, Cl or Br);
- an alkyl¹ group;
- a cycloalkyl or aryl or group optionally substituted by a pendant basic nitrogen functionality;
- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, aryl, or

(iv) a heteroaryl¹ group defined as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl , triazolyl, tetrazolyl, indolyl, benzimidazole, quinolinyl group, which may additionally bear any combination, at any one ring position, of one or more substituents such as

- halogen (selected from F, Cl, Br or I);
- an alkyl¹ group;
- a cycloalkyl or aryl group optionally substituted by a pendant basic nitrogen functionality,

- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
 - NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or SO₂-R or SO₂NH-R
- 5 wherein R corresponds to hydrogen, alkyl¹, or
- (v) an O-aryl¹, or NH-aryl¹, or O-heteroaryl¹ or NH-heteroaryl¹ group
- (vi) trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality, or
- 10 (vi) NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹ or aryl.

R₈ is an alkyl, a cycloalkyl, an aryl or alkyloxy groups, said groups are substituted or not with a halogen atom as F, Cl, Br or I.

15

Substituent X is:

- i) halogen (selected from F, Cl, Br or I) or
- ii) SR, SO₂R, wherein R is alkyl, aryl, CF₃, F, CH₂CF₃ or
- iii) OR, OTs, OMs, OTf, wherein R is alkyl or aryl.

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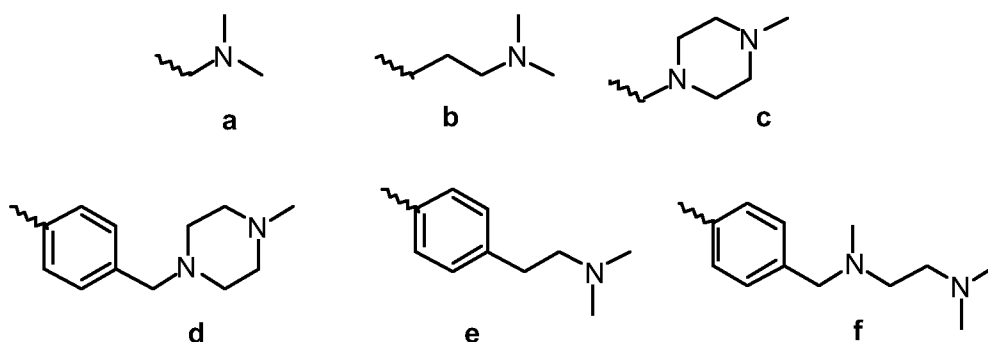
Unless stated otherwise, for the purpose of the present invention, the term “alkyl group” is intended to mean any linear or branched alkyl group having 1 to 10 carbon atoms, optionally substituted with a functional group, such as, but not limited to, methyl, ethyl or propyl. The term “cycloalkyl” preferably means a cycloalkyl group having 3 to 20

25 carbon atoms, such as, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl optionally substituted with a functional group. The term “alkyloxy group” is intended to mean any alkoxy group having 1 to 6 linear or branched carbon atoms, optionally substituted with a functional group, such as, but not limited to, OCH₃. The term “aryl group” is intended to mean one or more aromatic rings having 5 to 6 carbon atoms, which may be joined or

30 fused, optionally substituted with a functional group, such as, but not limited to, phenyl or pyridyl.

The term "functional group" means halogen atoms, hydroxy, cyano, amino, alkoxy groups as defined above, alkyl groups as defined above or a nitro group.

By "group bearing a pendant basic nitrogen functionality" it is meant herein a group comprising at least one nitrogen atom or amino group, such as represented for example by the structures **a** to **f** shown below, wherein the wavy line correspond to the point of attachment to core structure of formula **I**.



The process of the present invention is carried out in the presence of a suitable base. Suitable bases are organolithium bases (such as but not limited LDA, LiHMDS, *n*-BuLi, etc.) or metal hydride bases (such as NaH or KH).

The process of the present invention is carried out in a suitable solvent. Suitable solvents are aprotic non-basic solvents such as ethers (such as but not limited tetrahydrofuran, tetrahydropyran, diethyl ether, etc.) or amide (such as but not limited to dimethylformamide, dimethylacetamide, etc.) or halogenated hydrocarbons or mixtures thereof.

The process of the present invention is carried out under a temperature range of -40°C to 150°C , preferably between -20°C to 20°C .

The process of the present invention is carried out for a period of time in the range of 5 min. to 24 hours.

The process of the present invention can comprises purification step of the compound of formula (I). Generally, the reaction mixture was poured into water and the precipitate corresponding to the pure compound of formula (I), was collected by filtration. Thus, in one preferred embodiment, the above contemplated process further comprises a work-up using water to precipitate compounds of formula (I).

The invention is illustrated in the experimental details, which follow.

Examples of Compounds synthesis:

The present invention will be illustrated by the following examples, which will not limit the scope of the invention in any way.

General: All chemicals used were commercial reagent grade products. Solvents were of anhydrous commercial grade and were used without further purification. THF was freshly distilled under a stream of argon from sodium and benzophenone. The progress of the reactions was monitored by thin layer chromatography using precoated silica gel 60F 254, Merck TLC plates, which were visualized under UV light. Multiplicities in ¹H NMR spectra are indicated as singlet (s), broad singlet (br s), doublet (d), triplet (t), quadruplet (q), and multiplet (m) and the NMR spectrum were realized on a 300 MHz Bruker spectrometer.

Example 1

-Preparation of 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile

-Preparation of 4-Oxazol-5-yl-benzonitrile

To a solution of 4-Formyl-benzonitrile (5 g, 38.17 mmol) and tosylmethyl isocyanide (TosMIC) (from Aldrich, 8.33 g, 42 mmol) in MeOH (200 mL) was added K₂CO₃ (6.85 g, 49.62 mmol) and the mixture was stirred at reflux for 1h. The solvent was then evaporated and saturated aqueous NaHCO₃ was added. The resultant suspension was extracted with dichloromethane (3×100 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous MgSO₄ and concentrated to leave a yellow

solid. Trituration with heptane afforded a solid that was collected by filtration and dried under vacuum to give the title compound (6.3 g, 97%). m.p. = 140°C

^1H NMR (DMSO- d^6) δ = 7.91-7.98 (5H, m), 8.58 (1H, s).

-Preparation of 4-(2-Chloro-oxazol-5-yl)-benzonitrile

5 To a solution of 4-Oxazol-5-yl-benzonitrile (3 g, 17.65 mmol) in anhydrous THF (80 mL) at -78 °C under an argon atmosphere was slowly added a solution of LiHMDS (21.2 mL, 1 M in THF, 21.2 mmol). After 1h at -78 °C, solid hexachloroethane (6.275 g, 26.48 mmol) was added. The mixture was then stirred at -78 °C for 1h and allowed to slowly warm to room temperature and stir for 3 h. The reaction was diluted with
10 AcOEt/H₂O (50 mL/15 mL). The organic layer was washed with brine, dried with MgSO₄ and filtered. After removal of solvent the solid obtained was recrystallize from Hexane to give the title compound as a white solid (2.95 g, 82%). m.p. = 144°C

^1H NMR (DMSO- d^6) δ = 7.89 (d, J = 8.4, 2H); 7.97 (d, J = 8.4, 2H); 8.04 (s, 1H).

-Preparation of 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzo-
15 *nitrile*

A solution of *N*-(5-Amino-2-methyl-phenyl)-acetamide (1.1 g, 6.7 mmol) in DMF (20 mL) was added to a suspension of NaH (402 mg, 10.05 mmol, 60% dispersion in mineral oil) in DMF (20 mL) at 0 °C under an atmosphere of argon. The mixture was stirred for 30 min. at room temperature and cooled to 0 °C. A solution of 4-(2-Chloro-
20 oxazol-5-yl)-benzonitrile (1.37 g, 6.7 mmol) in DMF (20 mL) was added dropwise to the mixture. After 30 min., at 0 °C, the reaction was poured into ice water (200 mL). The solid was collected by filtration, washed with water, and dried under vacuum to afford the title compound (1.45 g, 75%). m.p. = 228°C

^1H NMR (DMSO- d^6) δ = 2.14 (s, 3H); 4.91 (br s, 2H); 6.25 (dd, J = 7.8-1.9, 1H); 6.82
25 (d, J = 8.0, 1H) ; 7.01 (d, J = 2.4, 1H) ; 7.68 (m, 3H) ; 7.84 (d, J = 8.5, 2H) ; 9.22 (s, 1H).

30 **Example 2**

-Preparation of 4-[2-(2-Methyl-5-nitro-phenylamino)-oxazol-5-yl]-benzonitrile

The same procedure outlined above in the preparation of 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile was used. However *N*-(2-methyl-5-nitro-phenyl)-acetamide was used instead *N*-(5-Amino-2-methyl-phenyl)-acetamide. Yield = 83%. m.p. > 228°C.

- 5 ¹H NMR (DMSO-*d*⁶) δ = 2.45 (s, 3H); 7.50 (d, *J* = 8.4, 1H); 7.77 (d, *J* = 8.4, 2H) ; 7.85 (m, 2H) ; 7.94 (d, *J* = 8.4, 2H); 9.05 (d, *J* = 2.1, 1H) ; 9.97 (s, 1H).

Example 3

-Preparation of 4-[2-(6-Chloro-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile

- 10 The same procedure outlined above in the preparation 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile was used. However *N*-(6-chloro-2-methyl-phenyl)-acetamide was used instead *N*-(5-amino-2-methyl-phenyl)-acetamide. Yield = 89%.

- ¹H NMR (DMSO-*d*⁶) δ = 2.17 (s, 3H); 7.25 (m, 2H); 7.41 (d, *J* = 7.6, 1H); 7.61 (m, 3H)
15 ; 7.82 (d, *J* = 8.3, 2H); 9.70 (s, 1H).

Example 4

-Preparation of 4-[2-(3,5-Dimethoxy-phenylamino)-oxazol-5-yl]-benzonitrile

- The same procedure outlined above in the preparation of 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile was used. However *N*-(3,5-dimethoxyphenyl)-acetamide was used instead *N*-(5-amino-2-methyl-phenyl)-acetamide. Yield = 85%.

¹H NMR (CDCl₃) δ = 3.80 (s, 6H); 6.20 (s, 1H); 6.70 (s, 2H); 7.30 (s, 1H) ; 7.57 (d, *J* = 8.0, 2H); 7.64 (d, *J* = 8.0, 2H).

25 Example 5

-Preparation of 4-[2-(2,3-Dimethyl-phenylamino)-oxazol-5-yl]-benzonitrile

The same procedure outlined above in the preparation of 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile was used. However *N*-(2,3-dimethylphenyl)-acetamide was used instead *N*-(5-amino-2-methyl-phenyl)-acetamide. Yield = 91%.

- 30 ¹H NMR (CDCl₃) δ = 2.23 (s, 3H); 2.33 (s, 3H), 6.92 (d, *J* = 7.5, 1H); 7.16 (t, *J* = 7.5, 1H); 7.28 (s, 1H) ; 7.55 (d, *J* = 8.4, 2H); 7.67 (m, 3H).

Example 6***-Preparation of 2-(5-Amino-2-methyl-phenylamino)-oxazole-5-carboxylic acid methyl ester***

5 To a solution of glyoxylic acid ethyl ester (50% w/w in toluene) (4 mL, 2 mmol) and Tosmic (3.86 g, 2 mmol) in MeOH (60 mL) was added K₂CO₃ (5.6 g, 4 mmol) and the mixture was stirred at reflux for 7h. The solvent was then evaporated and 100 mL of water was added. This solution was saturated with sodium chloride and extracted with diethyl ether. The organic layer was washed with brine, dried (MgSO₄) filtered and
10 concentrated to give 1.58 g (60%) of oxazole-5-carboxylic acid methyl ester as white solid. m.p. = 35-50°C.

To a solution of oxazole-5-carboxylic acid methyl ester (1.4 g, 11 mmol) in anhydrous THF (50 mL) at -40 °C under an argon atmosphere was slowly added a solution of LiHMDS (13.3 mL, 1 M in THF). After 1h at -40 °C, solid hexachloroethane (3.91 g,
15 16.5 mmol) was added. The mixture was then allowed to slowly warm to room temperature and stir for 16 h. The reaction was diluted with AcOEt/H₂O (30 mL/10 mL). The organic layer was washed with brine, dried with MgSO₄ and filtered. After removal of solvent the residue was silica gel column chromatographed (CH₂Cl₂/Cyclohexane : 1/1) to give 1.1 g of 2-chloro-oxazole-5-carboxylic acid methyl
20 ester (62%) as a white solid. m.p. = 35-50°C.

A solution of *N*-(5-Amino-2-methyl-phenyl)-acetamide (0.51 g, 3.1 mmol) in THF (12 mL) was added to a suspension of NaH (186 mg, 4.65 mmol, 60% dispersion in mineral oil) in THF (12 mL) at 0 °C under an atmosphere of argon. The mixture was stirred for 30 min. at room temperature and cooled to 0 °C. A solution of 2-chloro-oxazole-5-
25 carboxylic acid methyl ester (0.5 g, 3.1 mmol) in THF (12 mL) was added dropwise to the mixture. After 30 min., at 0 °C, the reaction was poured into ice water (30 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried (MgSO₄) and filtered. After removal of solvent the residue was silica gel column chromatographed (CH₂Cl₂/Ethanol : 99/1) to give 0.54 g of 2-(5-Amino-2-methyl-phenylamino)-oxazole-
30 5-carboxylic acid methyl ester (71%) as a Colorless sirup.

^1H NMR (CDCl_3) δ = 2.10 (s, 3H); 3.64 (br s, 2H), 3.82 (s, 3H), 6.30 (dd, J = 8.0-2.3, 1H); 6.82 (br s, 1H) ; 6.87 (d, J = 8.0, 1H); 7.39 (d, J = 2.4, 1H); 7.55 (s, 1H).

Example 7

5 ***-Preparation of 5-(2-chloropyridin-4-yl)-N-(5-(ethoxymethyl)-2-methylphenyl)oxazol-2-amine***

A solution of *N*-(5-(ethoxymethyl)-2-methylphenyl)ethanamide (344 mg, 1.66 mmol) in DMF (5 mL) was added to a suspension of NaH (133 mg, 3.32 mmol, 60% dispersion in mineral oil) in DMF (5 mL) at 0 °C under an atmosphere of argon. The mixture was stirred for 1h at room temperature and cooled to 0 °C. A solution of 2-chloro-5-(2-chloropyridin-4-yl)oxazole (357 mg, 1.66 mmol) in DMF (5 mL) was added dropwise to the mixture. After 1h at 0 °C, the reaction was poured into ice water (20 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried (MgSO_4) and filtered. After removal of solvent the residue was silica gel column chromatographed (CH₂Cl₂/Ethanol : 98/2) to give 474 mg of 5-(2-chloropyridin-4-yl)-*N*-(5-(ethoxymethyl)-2-methylphenyl) oxazol-2-amine (83%) as a beige solide.

^1H NMR ($\text{DMSO}-d_6$) δ = 1.15 (t, J = 7.0, 3H); 2.27 (s, 3H); 1.48 (q, J = 7.0, 2H); 4.42 (s, 2H); 6.99 (d, J = 7.6, 1H); 7.19 (d, J = 7.7, 1H); 7.46 (d, J = 5.3, 1H); 7.58 (s, 1H) ; 7.73 (s, 1H) ; 7.89 (s, 1H) ; 7.37 (d, J = 5.3, 1H); 9.64 (s, 1H).

Example 8

20 ***-Preparation of 5-(3,5-dichloropyridin-4-yl)-N-(5-(ethoxymethyl)-2-methylphenyl)oxazol-2-amine***

The same procedure outlined above in the preparation of 5-(2-chloropyridin-4-yl)-*N*-(5-(ethoxymethyl)-2-methylphenyl) oxazol-2-amine was used. However 2-chloro-5-(3,5-dichloropyridin-4-yl)oxazole was used instead 2-chloro-5-(2-chloropyridin-4-yl)oxazole. Yield = 81%.

^1H NMR ($\text{DMSO}-d_6$) δ = 1.14 (t, J = 7.0, 3H); 2.27 (s, 3H); 1.47 (q, J = 7.0, 2H); 4.41 (s, 2H); 6.99 (d, J = 7.7, 1H); 7.19 (d, J = 7.6, 1H); 7.64 (s, 1H); 7.66 (s, 1H); 8.70 (s, 2H); 9.68 (s, 1H).

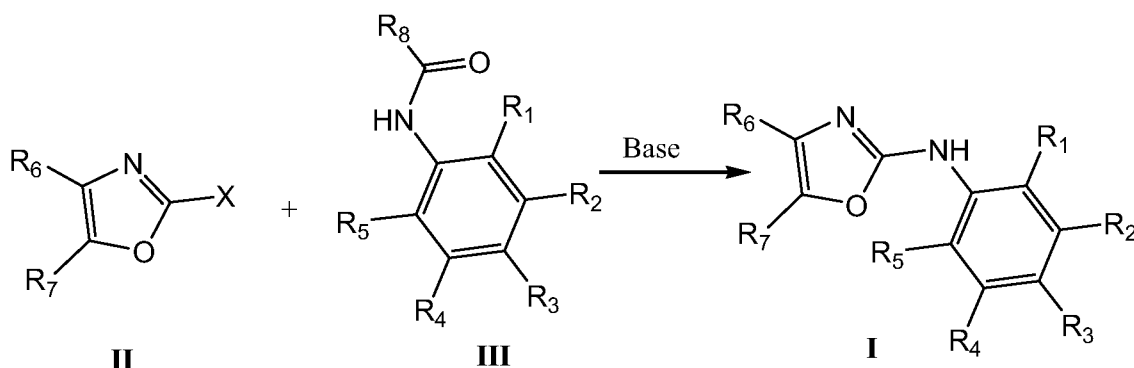
Example 9***-Preparation of 4-(2-(5-amino-2-methylphenylamino)-4-chlorooxazol-5-yl)-2,6-dimethylbenzonitrile***

The same procedure outlined above in the preparation of 4-[2-(5-Amino-2-methyl-phenylamino)-oxazol-5-yl]-benzonitrile was used. However 4-(2,4-dichlorooxazol-5-yl)-2,6-dimethylbenzonitrile was used instead 4-(2-Chloro-oxazol-5-yl)-benzonitrile. Yield = 74%.

^1H NMR ($\text{DMSO}-d^6$) δ = 2.10 (s, 3H); 2.50 (s, 6H), 5.08 (br s, 2H); 6.32 (dd, J = 7.9-1.7, 1H); 6.87 (d, J = 8.0, 1H) ; 6.88 (s, 1H) ; 7.51 (s, 2H) ; 9.58 (s, 1H).

CLAIMS

1. A process for the preparation of compounds of formula (I), comprising a condensation of a compound of formula (II) and an amide derivative of formula (III), in a solvent comprising a base:



Wherein

- R1, R2, R3, R4 and R5 each independently are selected from hydrogen, halogen (selected from F, Cl, Br or I), a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality; as well as trifluoromethyl, C₁₋₆alkyloxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, carboxyl, cyano, nitro, formyl, hydroxy, and CO-R, COO-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing from 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality.

R6 and R7 each independently are selected from:

- i) hydrogen, a halogen (selected from F, Cl, Br or I), or
- ii) an alkyl¹ group defined as a linear, branched or cycloalkyl group containing from 1 to 10 carbon atoms and optionally substituted with one or more heteroatoms such as halogen (selected from F, Cl, Br or I), oxygen, and nitrogen (the latter optionally in the form of a pendant basic nitrogen functionality); as well as trifluoromethyl, carboxyl,

cyano, nitro, formyl; as well as CO-R, COO-R, SO₂-R, and SO₂NH-R wherein R is a linear or branched alkyl group containing 1 to 10 carbon atoms and optionally substituted with at least one heteroatom, notably a halogen (selected from F, Cl, Br or I), oxygen, and nitrogen, the latter optionally in the form of a pendant basic nitrogen functionality ; as well as a cycloalkyl or aryl¹ or heteroaryl¹ group optionally substituted by a pendant basic nitrogen functionality, or

(iii) an aryl¹ group defined as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as

- halogen(selected from I, F, Cl or Br);
- an alkyl¹ group;
- a cycloalkyl or aryl or group optionally substituted by a pendant basic nitrogen functionality;
- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, aryl, or

(iv) a heteroaryl¹ group defined as a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl , triazolyl, tetrazolyl, indolyl, benzimidazole, quinolinyl group, which may additionally bear any combination, at any one ring position, of one or more substituents such as

- halogen (selected from F, Cl, Br or I);
- an alkyl¹ group;
- a cycloalkyl or aryl group optionally substituted by a pendant basic nitrogen functionality,
- trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality;
- NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or SO₂-R or SO₂NH-R wherein R corresponds to hydrogen, alkyl¹, or

(v) an O-aryl¹, or NH-aryl¹, or O-heteroaryl¹ or NH-heteroaryl¹ group

(vi) trifluoromethyl, O-alkyl¹, carboxyl, cyano, nitro, formyl, hydroxy, NH-alkyl¹, N(alkyl¹)(alkyl¹), and amino, the latter nitrogen substituents optionally in the form of a basic nitrogen functionality, or

(vi) NHSO₂-R or NHSO₂NH-R or CO-R or COO-R or SO₂-R or SO₂NH-R wherein R
5 corresponds to hydrogen, alkyl¹ or aryl;

R₈ is an alkyl, a cycloalkyl, an aryl or alkyloxy groups, said groups are substituted or not with a halogen atom as F, Cl, Br or I;

10 and wherein substituent X is:

i) halogen (selected from F, Cl, Br or I) or

ii) SR, SO₂R, wherein R is alkyl, aryl, CF₃, F, CH₂CF₃ or

iii) OR, OTs, OMs, OTf, wherein R is alkyl or aryl.

15 2. A process according to claim 1, which is carried out in a presence of a suitable base. Suitable bases are organolithium bases (such as but not limited LDA, LiHMDS, *n*-BuLi, etc.) or metal hydride bases (such as NaH or KH).

20 3. A process according to claims 1, which is carried out in a suitable solvent. Suitable solvents are aprotic non-basic solvents such as ethers (such as but not limited tetrahydrofuran, tetrahydropyran, diethyl ether, etc.) or amide (such as but not limited to dimethylformamide, dimethylacetamide, etc.) or halogenated hydrocarbons or mixtures thereof.

25 4. A process according to claim 1, which is carried out under a temperature range of -40° to 150° C, preferably between -20° C to 20° C.

5. A process according to claim 1, further comprising a work-up using water to precipitate compounds of formula (I).

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/054564

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D263/34 C07D263/48 C07D413/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/228031 A1 (BILODEAU M T ET AL) 13 October 2005 (2005-10-13) the whole document, particularly pages 25 and 26	1
A	NODIFF E A ET AL: "Synthesis of phenothiazines. III. Derivatives of hydroxy- and mercaptophenothiazines" JOURNAL OF ORGANIC CHEMISTRY, vol. 25, no. 1, January 1960 (1960-01), pages 60-65, XP002444426 the whole document, particularly page 61	1



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- * & * document member of the same patent family

Date of the actual completion of the international search

26 July 2007

Date of mailing of the international search report

07/08/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Allard, Michel

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/054564

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005228031	A1	13-10-2005	NONE