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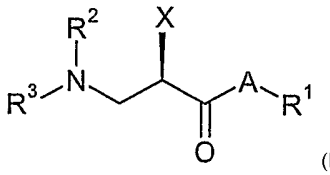
WO 2006/038872 A1

(54) Title: NEW PROCESS FOR THE PREPARATION OF PHOSPHINIC ACID



(I)

(57) Abstract: A new process for the synthesis of a compound of formula [Chemical formula should be inserted here. Please see paper copy] wherein A represents O or N; R¿1? represents a C?1#191-C?6#191 alkyl; R¿2? and R¿3? each independently represents C?1#191-C?10#191 alkyl, optionally substituted or interrupted by cyclic C?3#191-C?6#191 alkyl, cyclic C?3#191-C?6#191 heteroalkyl, aryl or heteroaryl; and X is selected from F, Cl, Br, or I, by a halogenation procedure comprising the consecutive sequence of following reactions: a) dienalkylation; b) formation of a leaving group on the alcohol function; and c) halogenation, is provided by the present invention as well as the compounds obtainable by the process.

NEW PROCESS FOR THE PREPARATION OF PHOSPHINIC ACID

Field of the invention

The present invention is directed to a new process for a regio- and stereoselective synthesis of α-halo-β-amino esters and α-halo-β-amino amides.

Background of the invention

Certain $GABA_B$-receptor agonists as well as methods of making said compounds are disclosed in WO 98/ 11885 A1 and in WO 01/ 42252 A1.

$GABA_B$ receptor agonists are being described as being of use in the treatment of central nervous system (CNS) disorders, such as muscle relaxation in spinal spasticity, cardiovascular disorders, asthma, gut motility disorders such as irritable bowel syndrome (IBS) and as prokinetic and anti-tussive agents. $GABA_B$ receptor agonists have also been disclosed as useful in the treatment of emesis (WO 96/11680, A2) and, as mentioned above, in the inhibition of transient lower oesophageal sphincter relaxations, TLOSR (WO 98/11885, A1).

EP 0356128, A1, describes the use of the specific compound (3-aminopropyl) methyl phosphinic acid, as a potent $GABA_B$ receptor agonist, in therapy. EP 0181833, A1, discloses substituted 3-aminopropyl phosphinic acids (or more correctly 3-aminopropyl phosphonous acids having very strong affinities towards $GABA_B$ receptor sites. EP 0399949, A1, discloses derivatives of (3-aminopropyl)methyl phosphinic acid that are described as potent $GABA_B$ receptor agonists. These compounds are stated to be useful as muscle relaxants. EP 0463969, A1, and FR 2722192, A, are both applications related to 4-aminobutanoic acid derivatives having different heterocyclic substituents at the β-carbon of the butyl chain.

Synthesis of α-halo-β-amino esters has been disclosed by Gani *et al.* (*J. Chem. Soc. Chem. Commun., 16, 1983, 898-900, Gani; Hitchcock, Young*). The synthesis described herein is a single step reaction performed by reaction between (N-dibenzyl)-(2-amino-3-hydroxy)-propionic acid and (diethylamino)sulphur trifluoride (a compound as hereinafter is called DAST). However, DAST is a thermally unstable compound and has risks when handed in bulk quantities.

Still a further fluorination procedure is described by Picq *et al.* (*Carbohydr. Res. 166, 1987, 309-313. Picq, Anker*). This fluorination reaction however included a different type of molecule.

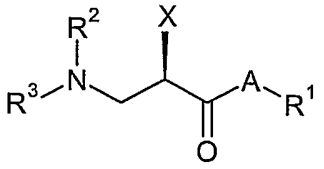
Description of the invention

The present invention provides a new process for large-scale halogenation i.e. for large-scale preparation of α-halo-β-amino esters or α-halo-β-amino amides. The reaction is a regioselective synthesis as well as a stereoselective synthesis of the α-halo-β-amino ester and α-halo-β-amino amide. The compound obtained by the process can be further processed to corresponding α-halo-β-amino acids.

One object of the present invention is to provide a process enabling the different reaction steps to be performed in a consecutive order, thus avoiding the time-consuming step of isolation, separation and filtration of the product after each reaction steps. This provides a more environmentally friendly process provided, as less amounts of, for example, solvents are needed for the process.

A further object of the present invention is to provide a process suitable for full-scale preparation with reactants that are easier and safety to handle, in comparison with DAST as this reactant is a thermally unstable compound.

The present invention, is a step-wise reaction for synthesising a compound of formula I:



I

wherein

A is O or N;

R^1 is a C_1- C_6 alkyl, optionally substituted by an aryl or a heteroaryl;

R^2 and R^3 are each and independently a C_1- C_{10} alkyl, optionally substituted or interrupted by an aryl or a heteroaryl; and

X is selected from F, Cl, Br, or I.

The reaction is a halogenation procedure comprising the consecutive sequence of following reactions:

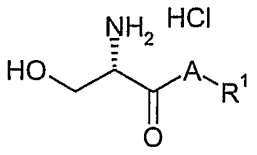
a) di-N-alkylation of α-amino-β-hydroxy-ester, or of α-halo-β-hydroxy-amide;

b) formation of a leaving group on the alcohol function; and

c) halogenation.

In one embodiment the reaction sequence comprises the following steps:

a) reacting compound of formula II



II

wherein

A represents O or N;

R^1 is as defined above;

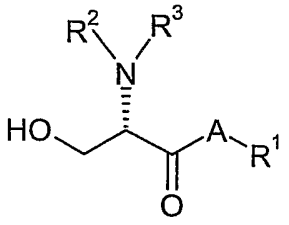
with R^2-Z or with R^3-Z, or a mixture thereof

wherein

R^2 and R^3 are each and independently C_1- C_{10} alkyl, optionally substituted by aryl, heteroaryl,

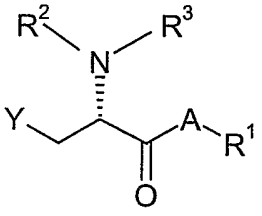
Z is selected from Cl, Br, I;

the reaction is hereinafter referred to "di-N-alkylation reaction", a reaction to provide a compound of formula III



III

Step b: transforming the alcohol to a leaving group Y, to give a compound of formula IV



IV

wherein

A represents O or N;

R^1 represents a C_1- C_6 alkyl, optionally substituted with aryl, heteroaryl;

R^2 and R^3 each independently represents C_1- C_{10} alkyl, optionally substituted by aryl, heteroaryl; and

Y represents the leaving group.

Step c: reacting compound of formula IV with a halogen source to give the compound of formula I. This compound is an intermediate in the process for synthesis of, for example alkyl phospinic acids.

The starting material to be used for the synthesis of compounds of formula I according to the process provided by the present invention are commercial available, for example from Sigma-Aldrich.

The term "C_1-C_{10} alkyl" as used throughout this specification includes linear, branched or cyclic C_1-C_{10} alkyl. Examples of C_1-C_{10} alkyl include, but are not limited to methyl, ethyl, propyl, n-propyl, isopropyl, cyclopropyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, cyclopentyl, hexyl and cyclohexyl.

The term "cyclic C_3-C_6 alkyl" as used throughout this specification means a cyclic alkyl having from 3 to 6 carbon atoms in the ring. Examples of cyclic C_3-C_6 alkyl are cyclic propyl, cyclic butyl, cyclic pentyl, and cyclic hexyl.

The term "cyclic C_3-C_6 heteroalkyl" as used throughout this specification means a cyclic alkyl which one or more of the from 3 to 6 in the ring are elements other than carbon, such as N, S and O.

The term "aryl" as used throughout this specification means an aromatic ring having from 6 to 10 carbon atoms, such as phenyl and naphtyl.

The term "heteroaryl" as used throughout this specification means an aromatic ring in which one or more of the from 5-10 atoms in the ring are elements other than carbon, such as N, S and O.

As used herein, the term "leaving group", denoted Y in the compound of formula IV, can be formed by reaction of III with a reagent suitable for the suitable for the present reaction which can be selected from a group consisting of mesylate ($-OSO_2CH_3$), tosylate - $OSO_2(C_6H_4)$ CH_3, triflate ($-OSO_2CF_3$), nosylate ($-OSO_2(C_6H_4)$ CH_3). These reagents are commercial available in their respectively chloride or/and anhydride form. The invention is not restricted to the leaving groups mentioned above.

As used herein the term "halogene source" denotes any compound abel to donate a halide, such compounds can be selected from the group comprising potassium halide, tetraalkyl ammoniumhalide or pyridine hydrohalide. The halide used is selected from fluoride, chloride, bromide, and iodide. Non-limiting examples of halogene source are triethyl amine trihydrofluoride, potassium fluoride, tetrabutyl ammoniumfluoride, pyridine hydrofluoride, triethyl amine hydrochloride, trimethyl amine hydrochloride, potassium chloride, tetrabutyl ammoniumchloride, and pyridine hydrochloride. However, the group of halogenating agents is not restricted to these mentioned.

Suitable solvent for the reaction sequence is selected from the group comprising toluene, methyl *iso*-butylketone, ethylacetate, acetonitrile, or an equivalent solvent, or mixture thereof.

The reaction is performed as stepwise reaction wherein the different step follows in a consecutive order, thus, without isolation of the intermediates.

One object of the present invention is to provide a process for the production of α-halo-β-amino esters with high enantioselective excess. The process of the invention can be stereoselective and more than 98 % enantiomeric excess (%ee) can be achieved. Also when production on larger scale, i.e. of volumes equal or larger than 50 l, high enantiomeric excess is achieved. The stereoselectivity of the reaction can be obtained by specific selection of reactants, for example by coupling a sterically hindered group such as benzyl-group to enantiomerically pure (>99 %ee) methyl-(2-amino-3-hydroxy)-propionic acid.

A further object of the invention is to provide a process for the production of a compound of formula I wherein X represents fluorine or chlorine and R_1 represents methyl.

The procedure is regioselective, it is possible to provide the desired isomer in a ratio of 15-20:1.

The process according to the present invention provides a good yield, i.e. 80 % or higher and reduced production time when performed on larger scale.

The compound of formula I may be further processed, even without isolation, for example, by reduction of the ester functionality forming the corresponding alcohol. This reaction is suitable performed by sodium borohydride using polyethylene glycol 400 (PEG) as solvent (Santaniello, Ferraboschi, Fiecchi, Grisenti, Manzocchi, J.Org. Chem. 1987, 52, pp. 671-4). Surprisingly it was found that the reaction proceeded to completion by using toluene (or tetrahydrofuran) as solvent with as little as 10 % (v/v) PEG present. This also enabled an easy extractive work-up procedure with water. By adding PEG slowly to the mixture of sodium borohydride and (methyl(*2R*)-3-(dibenzylamino)-2-fluoropropanate), dissolved in toluene, severe foaming during the reaction could be avoided. Hence, an effective and practical protocol for the reduction of an ester-functionality was developed, suitable also for large-scale production.

The examples below will further illustrate the reaction sequence of the invention. These examples are not intended to limit the scope if the invention as defined hereinabove or as claimed below.

EXAMPLES:

Example 1:

Step 1: Di-N-alkylation

943 g $NaHCO_3$ (11.2 mol, 4.5 eq.) and 841 g benzylbromide (4.86 mol, 2 eq.) were dispensed in 2.8 L acetonitrile/water 5:2 mixture and heated to 50 °C. 400 g of L-Serine-methylester x HCl (2.54 mol, 1.02 eq) was added slowly. The reaction mixture was heated over night (13 hours) and then cooled to 18 °C. HPLC showed 96 % conversion to methyl N,N dibenzylserinate. The inorganic salts were filtered off and washed with 500 mL toluene. 1L toluene and 500 mL water were added to the filtrate, the layers were separated after 15 minutes stirring (two clear phases).

1.5 L water was charged to the organic layer, stirred and separated. 320 g NaCl had to be charged to get separation of the layers. The organic layer was dried by distillation (T(jacket)=30°C, 0.08 bar). Approximately 1L was distilled off and 1.5L toluene was added.

Water content: <0.1 % (w/v)

Acetonitrile (GC): 0.1 % (w/w)

Step 2: Transforming of alcohol to a leaving group – mesylation

The reaction mixture was cooled to 6° C. 280 g triethyl amine (2.74 mol, 1.1 eq) was charged followed by slow addition (1h 15 min) of 318 g mesyl chloride (2.74 mol, 1.1 eq) diluted in 200 mL toluene. The addition was exothermic, temperature was raised to 15 °C. +99 % conversion was achieved after 35 minutes (HPLC). 2L water was charged at 10 °C followed by 150 g Na_2CO_3 (s) and 300 mL toluene.

The water layer was removed and the organic layer was washed with 1.5 L water and 50 g Na_2CO_3 (s). The water layer was removed and the organic layer dried by distillation

((T(jacket)=25 °C, 0.06 bar). Approximately 200mL (from 4L to 3.8 L) solvent was distilled off and 500 mL toluene was charged.
Water content: <0.1 % (w/v)

Step 3 Halogenation – fluorination
410g triethylamin trihydrofluoride (2.49 mol, 1.0 eq.) was charged to the reaction mixture, which then was heated to 89 °C. After 2.5 h 99 % conversion (HPLC) was achieved and the reaction-mixture was cooled to 20 °C and stirred over night. 1 L water was charged and pH was adjusted with NH_4OH, concentrated (390 mL) to pH 10. The layers were separated and the organic layer washed twice with 1.5 L water.

A 50 mL sample was removed from the 4 L reaction mixture and concentrated to a brownish oil, 8.84 g(98.0 % ee (HPLC); purity (GC) 86 % methyl (*2R*)-3-(dibenzylamino)-2-fluoropropanate, (5 % fluor regioisomer and 4.4 % toluene).

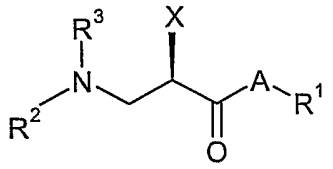
Yield 83 %.

Example 2

1.0g N,N-dibenzylserinate (3.3 mmol, 1.0 eq) was dissolved in 8 mL methyl isobutyl ketone. To the clear solution 0.291 mL mesyl chloride (3.7 mmol, 1.1 eq) was charged followed by 0.515 mL triethyl amine (3.7 mmol, 1.1 eq) yielding a thick slurry, which was diluted with 3 mL methyl isobutyl ketone. The reaction mixture was heated to 110°C and stirred for one hour. After cooling to ambient temperature the reaction mixture was washed two times with 7 mL Water. The water layers were discarded and the organic layer filtrated through sodium sulphate followed by concentration under vacuum yielding methyl (2R)-3-(dibenzylamino)-2-chloropropanate as an oil. Purity 92.7 area% (GC).

CLAIMS

1. A process for preparing a compound of formula I



I

wherein

A is O, N

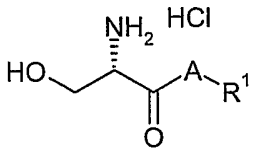
R^1 is C_1- C_6 alkyl;

R^2 and R^3 are each and independently C_1-C_{10} alkyl, optionally substituted or interrupted by aryl, cyclic C_3-C_6 alkyl, cyclic C_3-C_6 heteroalkyl, aryl or heteroaryl;

X is selected from F, Cl, Br, or I;

comprising the following steps:

step 1: reacting a compound of formula II



II

wherein

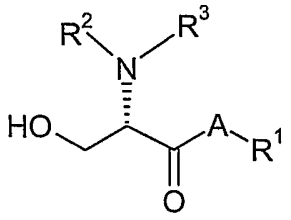
A and R^1 are defined as above;

with a mixture of R^2 –Z and R^3-Z;

wherein R^2 and R^3 are as defined above,

Z represents Cl, Br, I;

to provide a compound of formula III

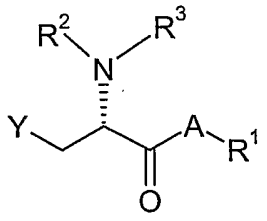


III

wherein

A, R^1 ,R^2 and R^3 are as defined above;

step 2: formation of a leaving group Y, a compound of formula IV



IV

wherein

A, R^1, R^2 and R^3 are as defined above; and

Y represents a leaving group;

step 3: reacting a compound of formula IV with a halogen source providing a compound of formula I.

2. A process according to claim 1 wherein a compound of formula I

wherein

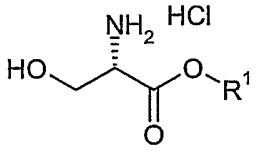
A is O

R^2 and R^3 are each and independently benzyl; and,

X is selected from F, or Cl;

is provided by

step 1: reacting a compound of formula II



II

wherein R^1 is as defined above;

with R^2-Z and R^3-Z

wherein

R^2 and R^3 are both benzyl; and

Z is selected from Cl, Br, or I;

to provide a compound of formula III

wherein

A, R^1, R^2, and R^3 are as defined above;

step 2: formation of a leaving group, providing a compound of formula II

wherein

A, R^1, R^2, and R^3 are as defined above; and

Y represents a leaving group;

step 3: reacting a compound of formula IV with a halogen source to provide a compound of formula I.

3. A process according to claim 1 or 2, whereby the leaving group Y is selected from the group comprising mesylat, tosylate, triflate, and nosylate

4. A process according to claim 3, whereby Y is mesylate.

5. A process according to claims 1 to 4, whereby X is F.

6. A process according to claim 1, whereby the fluorinating procedure is performed in consecutive order without isolation of the intermediates formed during the process.

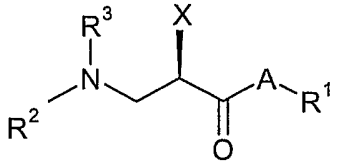
7. A process according to claims 1 to 6, whereby the halogene source is triethyl amine trihydrohalide, potassium halide, tetrabutyl ammoniumhalide or pyridine hydrohalide.

8. A process according to claims 7, whereby the halogene source is triethylamine trihydrofluoride.

9. A process according to claims 1 to 8, whereby the solvent used during the process is selected from toluene, methyl iso-butylketone, ethylacetate, acetonitrile, or mixture therof.

10. A process according to claim 9, whereby the solvent is toluene.

11. A compound of formula I



I

wherein

A is O, N;

R^1 is a C_1-C_6 alkyl;

R^2 and R^3 are each independently C_1- C_{10} alkyl, optionally substituted or interrupted by cyclic C_3- C_6 alkyl, cyclic C_3- C_6 heteroalkyl, aryl or heteroaryl; and

X is selected from F, or Cl;

obtainable by the process according to any of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/001472

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
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)

IPC: C07C

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Somekh, Lila et al, "Facile Stereospecific Synthesis of alpha-Fluoro-Beta-amino Acids", J. Am. Chem. Soc., 1982, vol. 104, page 836 - page 5837, page 7471 - 7472; conclusion --	1-10
Y	Takamatsu, Satoshi, et al, "9-(2,3-Dideoxy-2-fluoro-Beta-D-threo-pentofuranosyl)adenine (FddA) via a Purine 3´-Deoxynucleoside", J. Org. Chem., 2001, vol. 66, page 7469 - page 7477, abstract --	1-10

[X] Further documents are listed in the continuation of Box C. [X] 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 application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December 2005	20 -12- 2005
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/Els Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/001472

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 2004:859374, Simonsson, Roger: "Synthesis of 14C-labelled AZD-3355"; & Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the International Symposium, 8th, Boston, MA, United States, June 1-5, 2003 (2004), Meeting Date 2003, 33-36 --	11
A	Gani, David et al, "Stereochemistry of the Metabolism of the DNA Base Thymine and the Drug 5-Fluorouracil", J. Chem. Soc., Chem. Commun, 1983, page 898 - page 900 --	1-10
A	Pankiewicz, Krzysztof W., "A Synthesis of 9-(2-Deoxy-2-fluoro-Beta-D-arabinofuranosyl)adenine and Hypoxanthine. An Effect of C3'-Endo to C2'-Endo Conformational Shift on the Reaction Course of 2'-Hydroxyl Group with DAST1", J. Org. Chem., 1992, vol. 57, page 553 - page 559, scheme 1 --	1-10
A	EP 1052265 A1 (AJINOMOTO CO., INC.), 15 November 2000 (15.11.2000), pages 7-8 --	1-10

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International application No.
PCT/SE2005/001472

INTERNATIONAL PATENT CLASSIFICATION (IPC):

C07C 209/54 (2006.01)
C07C 229/20 (2006.01)

EP	1052265	A1	15/11/2000	CA	2318277 A	05/08/1999
				JP	51009195 Y	11/03/1976
				JP	11217396 A	10/08/1999
				WO	9938879 A	05/08/1999