

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

05 November 2020 (05.11.2020)



(10) International Publication Number

WO 2020/222158 A1

(51) International Patent Classification:

C07C 231/12 (2006.01) C07D 209/48 (2006.01)

C07C 237/06 (2006.01)

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(21) International Application Number:

PCT/IB2020/054081

(22) International Filing Date:

30 April 2020 (30.04.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

201921017216 30 April 2019 (30.04.2019) IN

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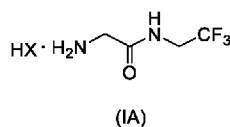
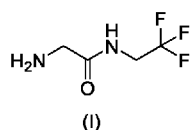
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS,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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

Published:

— with international search report (Art. 21(3))

(54) Title: PROCESS FOR THE PREPARATION OF 2-AMINO-N-(2,2,2-TRIFLUOROETHYL)-ACETAMIDE AND SALTS THEREOF



(57) Abstract: The present invention relates to an improved process for the preparation of 2-amino-N-(2,2,2-trifluoroethyl) acetamide of formula (I) and salts (IA) thereof, in an environment friendly and commercially viable manner in high yield and greater chemical purity.



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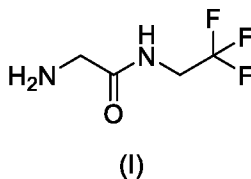
PROCESS FOR THE PREPARATION OF 2-AMINO-N-(2,2,2-TRIFLUOROETHYL)-ACETAMIDE AND SALTS THEREOF

RELATED APPLICATION

This application claims the benefit to Indian Provisional Application No. IN201921017216 filed on April 30, 2019, the contents of which are incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of 2-amino-N-(2,2,2-trifluoroethyl)-acetamide of formula (I) and salts thereof. The intermediate is a key starting material in preparing many active ingredients those are useful in pharmaceuticals and agrochemicals. The said process is environment friendly and commercially viable.



BACKGROUND OF THE INVENTION

The 2-amino-N-(2,2,2-trifluoroethyl)acetamide or salts thereof is a key intermediate in the field of pharmaceuticals and agrochemicals for preparing many active ingredients. The Japanese patent no. JP5652628B2(henceforth '628) disclosed a method for producing 2-amino-N-(2,2,2-trifluoroethyl) acetamide or a salt thereof in two steps i) by reacting chloroacetyl chloride with 2,2,2-trifluoroethylamine in presence of inorganic base such as sodium hydroxide, water ii) treating with aqueous ammonia in presence of methyl tert-butyl ether in an autoclave under pressure. The above reaction involves extensive reaction conditions and further leads to formation of dimer impurity N-(2,2,2-trifluoroethyl)-2-[[2,2,2-trifluoro-ethylcarbamoyl]-methyl]-amino}-acetamide. The dimer is resulting of sequential reaction of unreacted 2-chloro-N-(2,2,2-trifluoroethyl)

acetamide. It involves further purification there by reduces the yield and increases overall cost.

Alternatively, the '628 patent disclosed the preparation of 2-amino-N-(2,2,2-trifluoroethyl) acetamide using readily available reactant such as phthalylglycyl chloride. Phthalylglycyl chloride is either costly available reagent or involve expensive reaction steps with multiple purifications. Additionally, the process desires de protection to obtain 2-amino-N-(2,2,2-trifluoroethyl)acetamide. Therefore, the overall process set to become expensive and cumbersome in nature, which makes process non-applicable on commercial scale.

The Chinese patent application CN107353222A (henceforth '222) disclosed a method for preparation of 2-amino-N-(2,2,2-trifluoroethyl) acetamide or a salt thereof. The process involves expensive N-phthaloylglycine which reacts with 2,2,2-trifluoroethylamine hydrochloride in presence of coupling agent under basic condition followed by deprotection and purification. The '222 disclosed the preparation of 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-(2,2,2-trifluoroethyl)-acetamide using expensive N-phthaloylglycine, trifluoroethylamine hydrochloride in presence of 4-dimethylaminopyridine, dichloromethane and triethylamine, but it yields only 60%. Also '222 disclosed the preparation of 2-amino-N-(2,2,2-trifluoroethyl) acetamide by deprotection of 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-(2,2,2-trifluoroethyl)-acetamide in presence of ethanol, hydrazine hydrate and its salt in presence of hydrogen chloride gas and further converted into 2-amino-N-(2,2,2-trifluoroethyl) acetamide but it may contain dimer impurity.

Thus, the prior-art process has either failed to provide information of removal of dimer impurity or avoidance of the formation of dimer impurity in the preparation of pure 2-amino-N-(2,2,2-trifluoroethyl) acetamide and salts thereof.

To overcome the existing limitations the inventors of instant invention has developed a process for the preparation of 2-amino-N-(2,2,2-trifluoroethyl)

acetamide and salts thereof in cost effective and industrially convenient way in high yield and greater chemical purity.

OBJECTIVES OF THE INVENTION

The main object of the present invention is to provide an improved process for the preparation of a compound of formula (I) and salts (IA) thereof, using key intermediate of formula(VI).

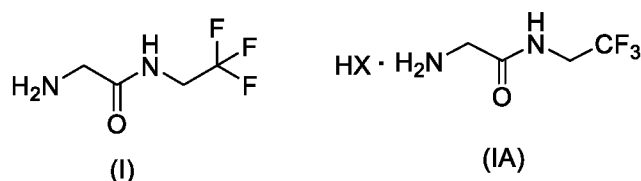
Another objective of the present invention is to provide an improved process for the preparation of a compound of formula (I) and salts (IA) thereof by avoiding the formation of dimer impurity (VIII).

Another objective of the present invention is to provide a process for preparation of compound of formula (I) and salts (IA) thereof by avoiding purification steps such as column chromatography or using limited number of purification steps achieve higher yield.

Yet another objective of the present invention is to provide an improved process for the preparation of Fluralaner by using compound of formula (I) or salts (IA) thereof which is obtained by a process of an instant invention as disclosed in JP 6032437B2.

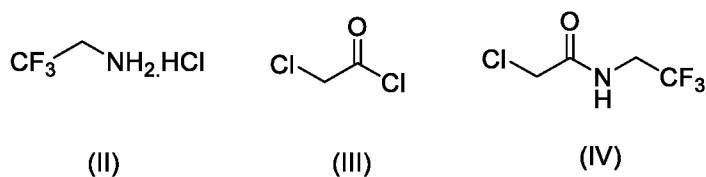
SUMMARY OF THE INVENTION

In one aspect of the present invention provides an improved process for the preparation of 2-amino-N-(2,2,2-trifluoroethyl) acetamide of formula (I) and salts (IA) thereof, which comprises the steps of:

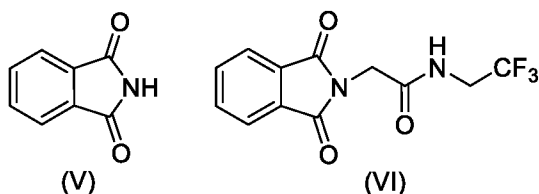


where X is Cl, Br, CF₃CO₂, CH₃SO₃, (SO₄)_{1/2} or (PO₄)_{1/3}

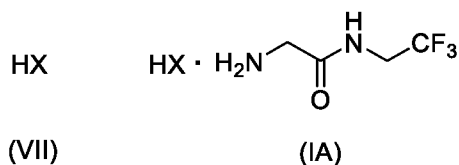
- a) reacting a compound of formula (II) with chloroacetyl chloride of formula (III) to obtain compound of formula (IV) in presence of base in a suitable solvent or mixture of solvents;



- b) reacting a compound of formula (IV) with compound of formula (V) to obtain compound of formula (VI) in presence of base, in a suitable solvent or mixture of solvents thereof, where the reaction avoids the formation of dimer impurity;

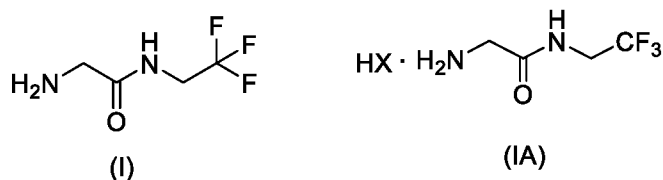


- c) converting a compound of formula (VI) in presence of base, in suitable organic solvent to obtain compound of formula (I); and
 d) converting compound of formula (I) using suitable acid of formula (VII) in suitable solvent or mixture of solvents to obtain corresponding acid addition salt of formula (IA).



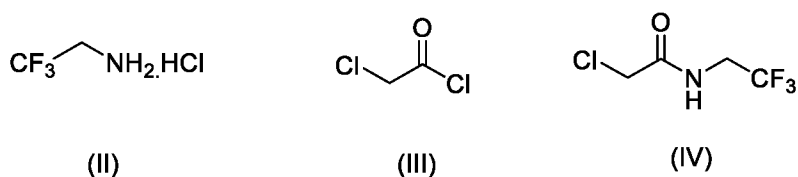
where X is Cl, Br, CF_3CO_2 , CH_3SO_3 , $(\text{SO}_4)_{1/2}$ or $(\text{PO}_4)_{1/3}$

In another aspect of the present invention provides an improved process for the preparation of 2-amino-N-(2,2,2-trifluoroethyl) acetamide of formula (I) and salts (IA) thereof, which comprises the steps of:

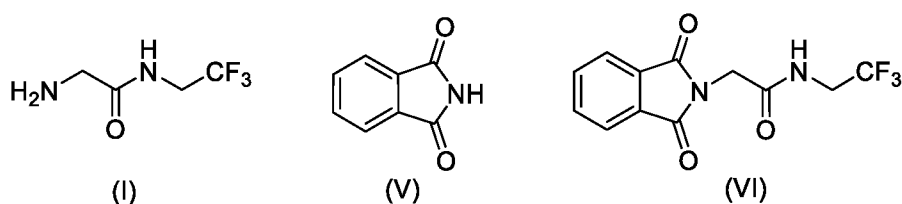


where X is Cl, Br, CF_3CO_2 , CH_3SO_3 , $(\text{SO}_4)_{1/2}$ or $(\text{PO}_4)_{1/3}$

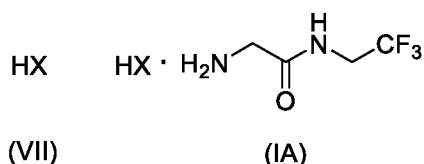
- a) obtaining compound of formula (IV) by reacting compound of formula (II) with chloroacetyl chloride of formula (III) in presence of base;



- b) obtaining a compound of formula (I) directly from compound of formula (IV) without an isolation of formula (VI); where, firstly, the compound of formula (IV) is reacted with compound of formula (V) in presence of base to obtain compound of formula (VI), where the reaction avoids the formation of dimer impurity; subsequently compound (VI) is reacted with base in solvent or mixture of solvents; and



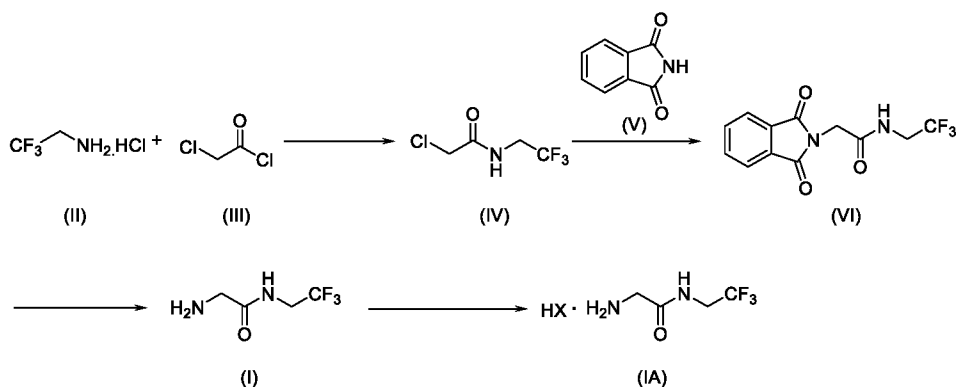
- c) converting compound of formula (I) using suitable acid of formula (VII) in presence of suitable solvent or mixture of solvents to obtain salt of formula (IA).



where X is Cl, Br, CF_3CO_2 , CH_3SO_3 , $(\text{SO}_4)_{1/2}$ or $(\text{PO}_4)_{1/3}$.

In another aspect of the present invention provides a process for the preparation of Fluralaner by using compound of formula (I) or salts (IA) thereof which is obtained by a process described herein, where a process for the preparation of Fluralaner is followed by a skilled person known in the art.

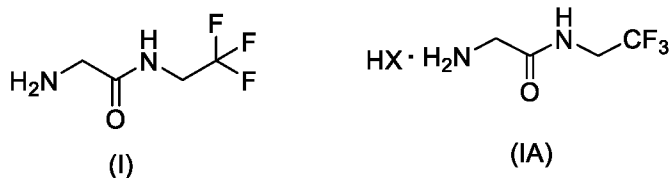
The above process is illustrated in the following general synthetic scheme:



DETAILED DESCRIPTION OF THE INVENTION

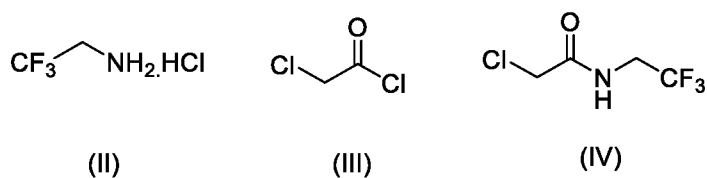
The present invention now will be described more fully hereinafter. As used herein, the terms "comprises," "comprising," "includes," "including," "has," "having," "contains" or "containing," or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a composition, a mixture, process, method, article, or apparatus that comprises a list of elements is not necessarily limited to only those elements but may include other elements not expressly listed or inherent to such composition, mixture, process, method, article, or apparatus. Further, unless expressly stated to the contrary, "or" refers to an inclusive or and not to an exclusive. As used in the specification, and in the appended claims, indefinite articles "a" and "an" preceding an element or component of the invention are intended to be nonrestrictive regarding the number of instances (i.e. occurrences) of the element or component. Therefore "a" or "an" should be read to include one or at least one, and the singular word form of the element or component also includes the plural unless the number is obviously meant to be singular indicates otherwise.

One aspect of present invention provides an improved process for the preparation of 2-amino-N-(2,2,2-trifluoroethyl) acetamide of formula (I) and salts (IA) thereof which comprising the steps of:

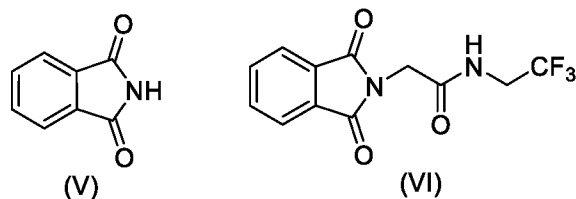


where X is Cl, Br, CF_3CO_2 , CH_3SO_3 , $(\text{SO}_4)_{1/2}$ or $(\text{PO}_4)_{1/3}$

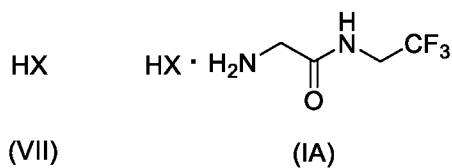
- a) reacting a compound of formula (II) with chloroacetyl chloride of formula (III) to obtain compound of formula (IV) in presence of base in a suitable solvent or mixture of solvents thereof;



- b) reacting a compound of formula (IV) with compound of formula (V) to obtain compound of formula (VI) in presence of base, in a suitable solvent or mixture of solvents thereof to avoid dimer impurity;

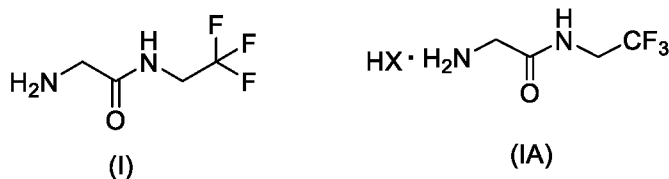


- c) converting a compound of formula (VI) with base in presence of suitable organic solvent to obtain compound of formula (I); and
 d) converting compound of formula (I) with suitable acid of formula (VII) in presence of suitable solvent or mixture of solvents to obtain salt of formula (IA).



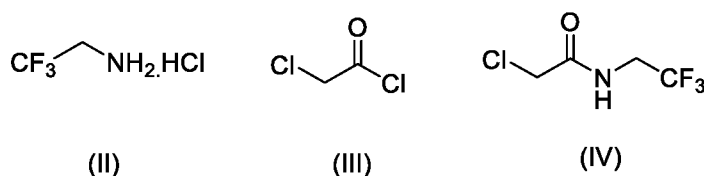
where X is Cl, Br, CF_3CO_2 , CH_3SO_3 , $(\text{SO}_4)_{1/2}$ or $(\text{PO}_4)_{1/3}$

In another aspect of present invention provides an improved process for the preparation of 2-amino-N-(2,2,2-trifluoroethyl) acetamide of formula (I) and salts (IA) thereof which comprises the steps of:

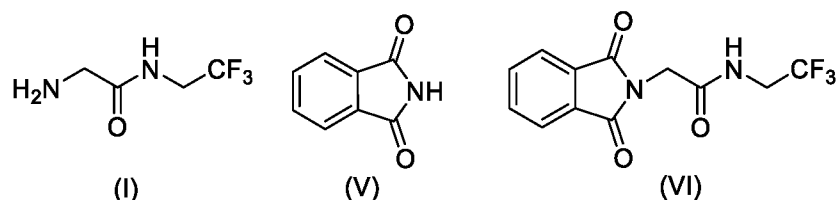


where X is Cl, Br, CF_3CO_2 , CH_3SO_3 , $(\text{SO}_4)_{1/2}$ or $(\text{PO}_4)_{1/3}$

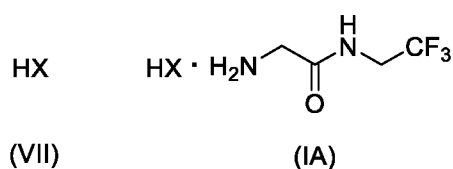
- a) obtaining compound of formula (IV) by reacting compound of formula (II) with chloroacetyl chloride formula (III) in presence of base and solvents;



- b) obtaining a compound of formula (I) directly from compound of formula (IV) without an isolation of formula (VI); where, firstly, the compound of formula (IV) is reacted with compound of formula (V) in presence of base to obtain compound of formula (VI), where the reaction avoids the formation of dimer impurity; subsequently compound (VI) is reacted with base in solvent or mixture of solvents; and



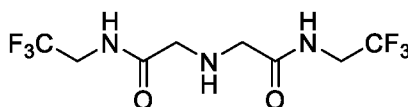
- d) converting compound of formula (I) using suitable acid of formula (VII) in presence of suitable solvent or mixture of solvents to obtain salt of formula (IA).



where X is Cl, Br, CF_3CO_2 , CH_3SO_3 , $(\text{SO}_4)_{1/2}$ or $(\text{PO}_4)_{1/3}$

In accordance with the objectives, wherein the present invention provides the process for preparation of 2-amino-N-(2,2,2-trifluoroethyl)acetamide of formula (I) and salts (IA) thereof which comprises the steps of reacting a compound 2,2,2-trifluoroethylamine hydrochloride of formula (II) with chloroacetyl chloride of formula (III) in presence of base and solvent(s) to obtain compound of formula (IV) followed by reacting with the compound of formula (V) in presence of base and solvent(s) to obtain a key intermediate compound of formula (VI) and further reacting the compound of formula (VI) with base, in presence of suitable solvents to obtain compound of formula (I) and converting the compound of formula (I) into its salt of formula (IA) with high yield, greater chemical purity in an economically and commercially viable manner.

In an embodiment of the present invention, wherein the use of easily available phthalimide compound (V) for the preparation of key intermediate compound formula (VI) which enhances reaction speed, thus makes process cost efficient; further the said reaction avoids the formation of dimer impurity of formula (VIII).



(VIII)

In another embodiment of the present invention, wherein the compound of formula (IV) of step (a) is obtained by reacting compound of formula (II) with compound of formula (III) in presence of suitable base in a suitable solvent(s) or mixture of solvents thereof.

In another embodiment of the present invention, wherein the compound of formula (VI) of step (b) is obtained by reacting compound of formula (IV) with compound of formula (V) in presence of suitable base(s) and suitable solvent(s) or mixture of solvents thereof.

In another embodiment of the present invention, wherein the compound of formula (I) of step (c) is obtained by reacting compound of formula (VI) with suitable base(s) in presence of suitable solvent(s) or mixture of solvent thereof.

In another embodiment of the present invention, wherein the base used in step (a), step (b) and step (c) is selected from organic or inorganic or combination thereof.

In another embodiment of the present invention, wherein the said base(s) of step (a), step (b) and step (c) is selected from the group consisting of sodium hydroxide (NaOH), potassium hydroxide (KOH), potassium carbonate (K_2CO_3), potassium bicarbonate ($KHCO_3$), sodium carbonate (Na_2CO_3), sodium bicarbonate ($NaHCO_3$), sodium hydride (NaH), potassium tert-butoxide (KtOBu), sodium methoxide (NaOMe), hydrazine hydrate ($NH_2NH_2.H_2O$), and ammonia (NH_3).

In another embodiment of the present invention, wherein the said base(s) of step (a) is selected from the group consisting of sodium hydroxide (NaOH), potassium hydroxide (KOH), potassium carbonate (K_2CO_3), potassium bicarbonate ($KHCO_3$), sodium carbonate (Na_2CO_3), and sodium bicarbonate ($NaHCO_3$).

In another embodiment of the present invention, wherein the said base(s) of step (b) is selected from the group consisting of sodium hydroxide (NaOH), potassium hydroxide (KOH), potassium carbonate (K_2CO_3), potassium bicarbonate ($KHCO_3$), sodium carbonate (Na_2CO_3), sodium bicarbonate ($NaHCO_3$), sodium hydride (NaH), potassium tert-butoxide (KtOBu), and sodium methoxide (NaOMe).

In another embodiment of the present invention, wherein the said base of step (c) is selected from hydrazine hydrate ($NH_2NH_2.H_2O$), aq. ammonia (NH_3), and alcoholic ammonia.

In another embodiment of the present invention, wherein the said base used for the conversion of compound (IV) to compound formula (VI) is selected from

sodium hydroxide (NaOH), potassium hydroxide (KOH), potassium carbonate (K_2CO_3), potassium bicarbonate ($KHCO_3$), sodium carbonate (Na_2CO_3), sodium bicarbonate ($NaHCO_3$), sodium hydride (NaH), potassium tert-butoxide (KtOBu), and sodium methoxide (NaOMe).

In another embodiment of the present invention, wherein the said base used for the conversion of compound (VI) to compound formula (I) is selected from hydrazine hydrate ($NH_2NH_2 \cdot H_2O$), aq. ammonia (NH_3), and alcoholic ammonia.

In another embodiment of the present invention, wherein the said solvent(s) used in step (a) is selected from group consisting of water, ketonic solvents, esters, halogenating solvents, ethereal solvents, and hydrocarbon solvent.

In another embodiment of the present invention, wherein the said solvent used in step (b) is selected from group consisting of alcoholic solvents, ketonic solvents, esters, halogenating solvents, ethereal solvents, hydrocarbon solvent, and polar aprotic solvent.

In another embodiment of the present invention, wherein the said solvent used in step (c) is selected from group consisting of water, alcoholic solvents, ketonic solvents and ester solvents.

In another embodiment of the present invention, wherein the said solvent used in step (b) and step (c) are alcoholic solvents such as methanol, ethanol, isopropanol, n-propanol and n-butanol.

In another embodiment of the present invention, wherein the said solvent used in step (a), step (b) and step (c) the ketonic solvents such as acetone, methyl isobutyl ketone, ethyl methyl ketone and n-butanone.

In another embodiment of the present invention, wherein the said solvent used in step (a), step (b) and step (c) the halogenating solvents such as ethylene dichloride, chloroform, and dichloromethane.

In another embodiment of the present invention, wherein the said solvent used in step (b) and step (c) esters used such as ethyl acetate, n-propyl acetate and isopropyl acetate.

In another embodiment of the present invention, wherein the said solvent used in step (b) is polar aprotic solvents used such as dimethyl formamide, acetonitrile, dimethyl sulfoxide, and dimethyl acetamide.

In another embodiment of the present invention, wherein the compound of formula (IA) of step (d) is obtained by reacting compound of formula (I) with an acid in presence of solvent(s) or mixture of solvent.

In another embodiment of the present invention wherein the said acid of step (d) is selected from group consisting of hydrochloric acid, hydrobromic acid, trifluoroacetic acid, sulfuric acid, methane sulfonic acid and phosphoric acid.

In another embodiment of the present invention wherein the said acid of step (d) is dissolved in alcoholic solvents such as methanol, ethanol, propanol isopropanol and the like or mixture of solvent(s) thereof.

In another embodiment of the present invention, the reaction step (a), step (b) is carried out at temperature 20°C to 40°C, the step (b) is carried out at temperature 20°C to 145°C and step (c) and step (d) is carried out at temperature 20°C to 100°C.

In another embodiment of the present invention, wherein the preparation of a compound of formula (I) and salts (IA) thereof is performed in an *in-situ* manner.

In still another embodiment of the present invention wherein the one or more steps from (a) to (d) of the instant invention is performed in *in-situ* manner.

In another embodiment of the present invention, wherein all the crude compound may be used as such or may be purified by distillation or crystallization or any other purification technique well understood by those skilled in the art.

The compound 2-amino-N-(2,2,2-trifluoroethyl) acetamide of formula (I) and salts (IA) thereof obtained by the process described herein is further used for the preparation of Fluralaner.

The invention is further illustrated by the following examples, which should not be construed to limit the scope of the invention in anyway.

EXPERIMENTAL

Example 1: Preparation of 2-chloro-N-(2,2,2-trifluoroethyl) acetamide (IV)

The potassium carbonate (244.76g, 1.2eq), water (1000mL) and dichloromethane (1000mL) were charged into a round bottom flask and stirred. The reaction mixture was cooled to about 0°C to 10°C and 2,2,2-trifluoroethylamine hydrochloride (200g, 1.0eq) was added and stirred, then chloroacetyl chloride (250g, 1.5eq.) was added to the reaction mixture and stirred for about 10 minutes. The reaction mixture was heated to 20°C to 30°C, maintained for about 2-3 hours and two layers were separated. The aqueous layer was extracted with dichloromethane (400 mL). The obtained organic layer was washed with saturated sodium bicarbonate solution (200 mL), followed by water (600 mL). The organic layer was concentrated under vacuum at about 40°C to 45°C to obtain a residue, which was taken in heptane (600 mL) and stirred for 1-2 hours. The obtained solid was collected by filtration, washed, and dried in a vacuum oven at 45°C to 50° C for about 4-5 hours to obtain the compound IV (226.0g, 87.2% yield, HPLC purity: 99.88%). **¹H NMR (DMSO-*d*₆):** 8.88-8.91 (tr, 1H), 4.16 (s, 2H), 3.90-3.99 (m, 2H). **LCMS:** 175-2; **IR (cm⁻¹):** 3332, 3020, 1685, 1569, 1274, 1164;

Example 2: 2-phthaloyl-N-(2,2,2-trifluoroethyl) acetamide (VI)

The phthalimide (37.71g, 0.9eq) and dimethyl formamide (350mL) were charged into a round bottom flask and stirred. Sodium methoxide (18.46g, 1.2eq.) was

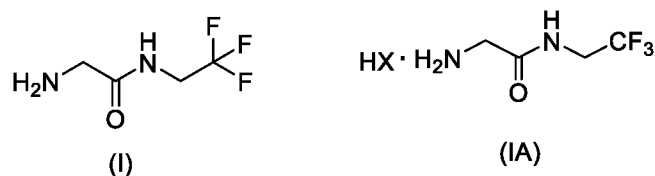
added to reaction mixture and heated to about 40°C to 45°C and maintained for about 2-3 hours. The reaction mixture was cooled to about 20°C to 30°C. To the reaction mixture, the compound (IV) (50g, 1.0eq.) was added and maintained for about 10-12 hours. The solvent was concentrated under vacuum at about 50°C to 55° C to obtain a residue, which was taken in water (350 mL) and stirred for 1-2 hours. The obtained solid was collected by filtration, washed with water (150 mL) to obtain crude compound, which was purified in methanol (350 mL) to obtain compound 2-phthaloyl-N-(2,2,2-trifluoroethyl) acetamide (VI, 272g, 69.9% yield, HPLC purity 99.71%). ¹H NMR (DMSO-d₆): 8.93-8.96 (tr, 1H), 7.90-7.94 (m, 2H), 7.86-7.90 (m, 2H), 4.27 (s, 2H), 3.89-3.98 ppm (m, 2H). LCMS: 287+1; IR (cm⁻¹): 3478, 3301, 1775, 1682, 1569, 1419, 1153;

Example 3: 2-amino-N-(2,2,2-trifluoroethyl) acetamide hydrochloride (IA)

The compound (VI, 50g, 1.0eq), isopropyl alcohol (1500mL) and hydrazine hydrate (33.19g, 3.0eq) were charged into a round bottom flask and stirred. The Reaction mixture was heated to about 75°C to 80°C and maintained for about 5-6 hours. The reaction mixture was cooled to about 20°C to 30°C, filtered the solid and washed with isopropyl alcohol (150mL). The filtrate was concentrated under vacuum at about 50°C to 60°C to obtain a residue, which was taken in ethyl acetate (1000mL) and cooled to 0°C to 10° C stirred for 1-2 hours. Filtered the solid and washed with ethyl acetate. The isopropyl alcohol in hydrochloride (IPA.HCl, 50ml) was added to filtrate and stirred for 1-2 hours. The obtained solid was collected by filtration, washed with ethyl acetate (150mL) to obtain the title compound (2-amino-N-(2,2,2-trifluoroethyl) acetamide hydrochloride (IA) (28.86g, 85.96% yield, HPLC purity 98.85%, dimer impurity content: not detected). ¹H NMR (DMSO-d₆): 9.24-9.28 (tr, 1H), 8.31 (s, 3H), 3.95-4.03 (m, 2H), 3.62-3.66 (qt, 2H); Mass: 156+1; IR (cm⁻¹): 3307, 2990, 1692, 1579, 1168; DSC: 291.55°C.

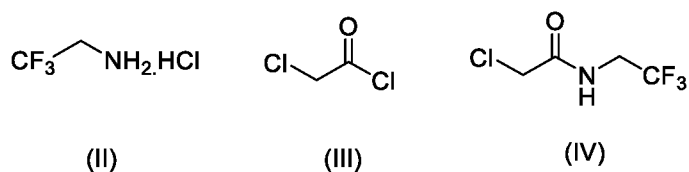
CLAIM:

1. An improved process for the preparation of 2-amino-N-(2,2,2-trifluoroethyl)acetamide of formula (I) and salts (IA) thereof which comprises the steps of:

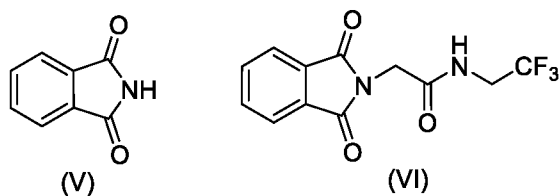


where X is Cl, Br, CF_3CO_2 , CH_3SO_3 , $(\text{SO}_4)_{1/2}$ or $(\text{PO}_4)_{1/3}$

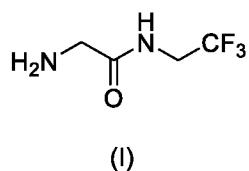
a) reacting a compound of formula (II) with chloroacetyl chloride of formula (III) to obtain compound of formula (IV) in presence of base in a solvent or mixture of solvents;



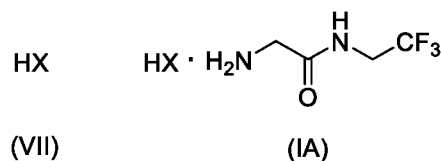
b) reacting a compound of formula (IV) with compound of formula (V) to obtain compound of formula (VI) in presence of base, in a solvent or mixture of solvents, where the reaction avoids the formation of dimer impurity;



c) converting a compound of formula (VI) in presence of base, in a solvent or mixture of solvents to obtain compound of formula (I); and

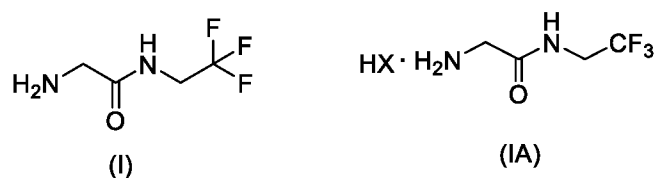


- d) converting compound of formula (I) using an acid of formula (VII) in presence of a solvent or mixture of solvents to obtain salt of formula (IA).

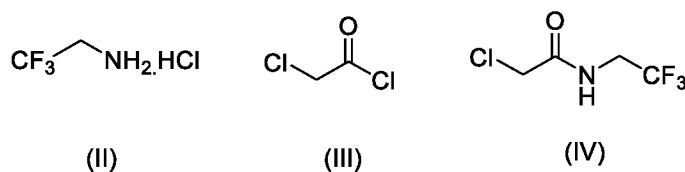


where X is Cl, Br, CF_3CO_2 , CH_3SO_3 , $(\text{SO}_4)_{1/2}$ or $(\text{PO}_4)_{1/3}$.

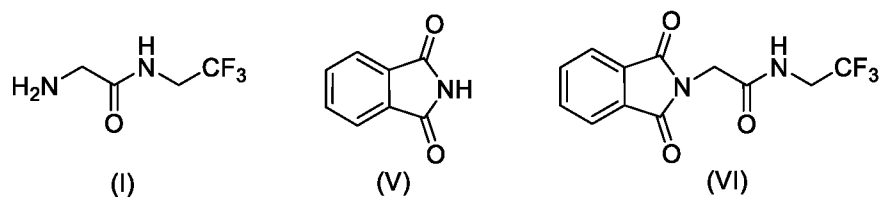
2. An improved process for the preparation of 2-amino-N-(2,2,2-trifluoroethyl)acetamide of formula (I) and salts (IA) which comprises the steps of:



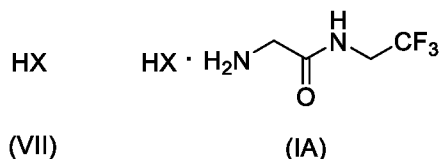
- a) reacting a compound of formula (II) with chloroacetyl chloride(III) to obtain compound of formula (IV) in presence of base;



- b) obtaining a compound of formula (I) directly from compound of formula (IV) without an isolation of formula (VI); where, firstly, the compound of formula (IV) is reacted with compound of formula (V) in presence of base to obtain compound of formula (VI) where the reaction avoids the formation of dimer impurity; subsequently compound (VI) is reacted with base in solvent or mixture of solvents;



- c) converting compound of formula (I) using suitable acid of formula (VII) in presence of suitable solvent or mixture of solvents to obtain salt of formula (IA).



where X is Cl, Br, CF_3CO_2 , CH_3SO_3 , $(\text{SO}_4)_{1/2}$ or $(\text{PO}_4)_{1/3}$.

3. The process as claimed in claim 1 and 2, wherein the base used is organic or inorganic base.
4. The process as claimed in claim 1 and 2, wherein base is selected from sodium hydroxide (NaOH), potassium hydroxide (KOH), potassium carbonate (K_2CO_3), potassium bicarbonate (KHCO_3), sodium carbonate (Na_2CO_3), sodium bicarbonate (NaHCO_3), sodium hydride (NaH), potassium tert-butoxide (KtOBu), sodium methoxide (NaOMe), hydrazine hydrate ($\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$), and ammonia (NH_3).
5. The process as claimed in claim 1 and 2, wherein the said solvent used in step (a) is selected from water, acetone, methyl isobutyl ketone, ethyl methyl ketone, n-butanone; ethylene dichloride, chloroform, and dichloromethane or mixture of solvents.
6. The process as claimed in claim 1 and 2, wherein the said solvent used in step (b) and (c) is selected from methanol, ethanol, isopropanol, n-propanol, n-butanol; acetone, methyl isobutyl ketone, ethyl methyl ketone, n-butanone; ethyl acetate, n-propyl acetate, isopropyl acetate; ethylene dichloride, chloroform, dichloromethane; dimethyl formamide, acetonitrile, dimethyl sulfoxide, and dimethyl acetamide or mixture of solvents..

7. The process as claimed in claim 1 and 2, wherein the said solvent used for preparation of salts of formula (IA) is selected from methanol, ethanol, isopropanol, n-propanol, n-butanol or mixture of solvents.
8. The process as claimed in claim 1 and 2, wherein the said acid is selected from group consisting of hydrochloric acid, hydrobromic acid, trifluoroacetic acid, sulfuric acid, methane sulfonic acid and phosphoric acid.
9. The process as claimed in claim 1 and 2, where one or more step from (a) to (d) of the process is performed in *in-situ* manner.
10. A process for the preparation of Fluralaner by using compound of formula (I) or salts thereof which is obtained by a process described herein.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2020/054081

A. CLASSIFICATION OF SUBJECT MATTER C07C231/12, C07C237/06, C07D209/48 Version=2020.01		
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) C07C, 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 practicable, search terms used) TotalPatent One, IPO Internal Database		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN107353222A (JINGMEN PHARMACEUTICAL INDUSTRY TECH INSTITUTE) 17 November 2017 (17-11-2017) page 1, abstract	1-10
A	WO2012047543A1 (E.I. DU PONT DE NEMOURS AND COMPANY) 12 April 2012 (12-04-2012) abstract, Page 1, para 5	1-10
A	CN102358725B (CHONGQING PORTON FINE CHEMICALS CO LTD) 14 August 2013 (14-08-2013) (page 1, abstract, claim 1)	1-10
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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 "D" document cited by the applicant in the international application "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 14-08-2020		Date of mailing of the international search report 14-08-2020
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14, Dwarka, New Delhi-110075 Facsimile No.		Authorized officer Srikanta Karmakar Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2020/054081

Citation	Pub.Date	Family	Pub.Date
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