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(54) Title: AN IMPROVED PROCESS FOR PREPARATION OF RIVAROXABAN

(57) Abstract: The present invention relates to an improved process for the preparation of Rivaroxaban of formula (I) in high yield and purity. More particularly, the present invention is directed to an improved and greener process for preparation of Rivaroxaban employing isolated compound of formula (II) in high yield which substantially eliminates potential impurities.

AN IMPROVED PROCESS FOR PREPARATION OF RIVAROXABAN

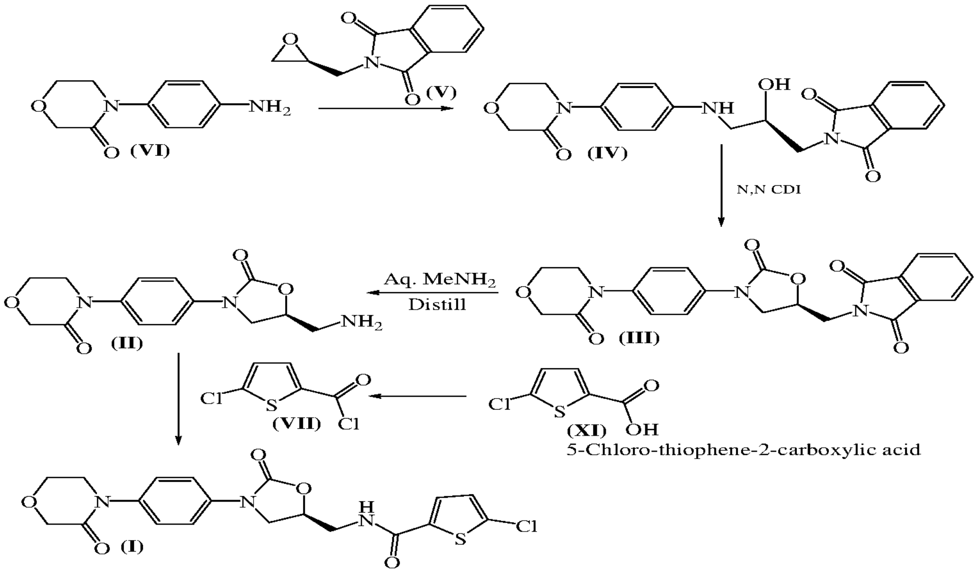
FIELD OF THE INVENTION

The present invention relates to an efficient process for the higher atom utilization than the prior art processes to the preparation of Rivaroxaban of formula (I) in high yields and purity. More particularly, the present invention is directed to an improved and greener process for preparation of Rivaroxaban employing isolated compound of formula (II) in high yields.

BACKGROUND OF THE INVENTION

Rivaroxaban, 5-chloro-N-({(5S)-2-oxo-3-[4-(3 -oxo-4-morpholinyl)phenyl] - 1 ,3 - oxazolidin-5-yl }methyl)-2-thiophenecarboxamide of Formula (I), acts as inhibitor of clotting factor Xa and can be employed as agent for the prophylaxis and/or treatment of thromboembolic disorders, in particular myocardial infarction, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transient ischaemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses.

WO2001/047919A1 discloses process for Rivaroxaban as represented below,



As represented above, the compound (II) is obtained by deprotection of compound (III) using aqueous methyl amine and is further forwarded to subsequent stage without isolation but as a concentrated oily mass obtained after distillation and degassing of the reaction mass.

The present inventors have observed that the said concentrated oily mass was contaminated with trapped unreacted amine, thereby resulting in formation of impurities in the subsequent stage leading to lower yields.

It is observed that compound (II) is highly soluble in water and partially or practically insoluble in most organic solvents like dichloromethane, ethyl acetate, toluene and others employed for conventional work-up, thereby making it difficult to isolate the compound (II) from the aqueous reaction mass by conventional work-up techniques to be known for an ordinary person skilled in the art.

In view of the above problems, it becomes difficult to isolate compound (II) in reactions involving phthalimide deprotection using aqueous amine, thereby compelling to forward the concentrate mass of compound (II) having excess amine to further stages resulting in further impurity formations and lower yields.

Forwarding compound (II) as concentrate mass without isolation results in final product with lower purity thereby requiring further tedious column chromatography, which is commercially not feasible for the compound of formula-I, which is the final product used for medicament.

Therefore it is desirable to isolate compound (II) free from excess unreacted amine coming from aqueous methyl amine.

Accordingly, it is desirable to identify an alternative base to aqueous methylamine for the step of deprotection of compound (III) to obtain compound (II) free from excess unreacted amine.

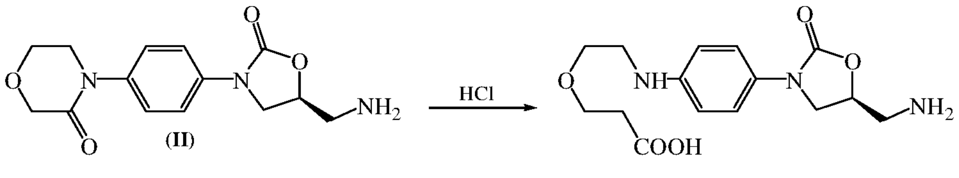
J. Med. Chem. **2005,** *48,* 5900-5908 discloses process similar to WO2001/047919A1 employing use of Aqueous Methyl Amine for preparation of compound (II), however it further suggests purification of (II) by employing tedious flash chromatography, which is commercially not feasible.

WO2013/121436 teaches a process for preparation of Rivaroxaban and intermediates thereof. It discloses in example 3, 4 and 5, deprotection of Phthalimide protected compound (compound III according to present invention) using Aqueous Methyl Amine, followed by treatment with conc. HCl to give its corresponding HCl salt of compound (II). This HCl salt is further used in the final stage to obtain Rivaroxaban.

WO2005/068456 discloses improved process wherein compound (II) is purified by converting into corresponding hydrochloride salt by using hydrochloric acid thereby requiring additional steps involving salt formation and further salt breaking for use in further stages.

Another drawback of using hydrochloric acid is that it reacts with any excess unreacted methyl amine resulting in the formation of corresponding hydrochloride salt of methyl amine, which is difficult to separate from compound (II), leading to lower assay and yield variations.

Also employing acidic conditions may lead to morpholinone ring cleavage resulting in corresponding open-ring impurity in view of WO2007/036306 for synthesizing 2-aminoethoxyacetic acid derivatives as represented below,



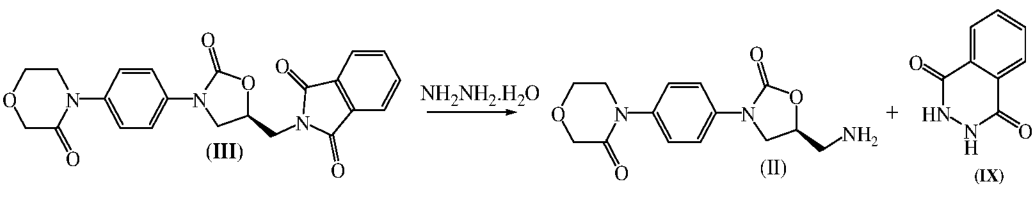
WO2014/155259 discloses process similar to as described in WO2001/047919A1 employing use of Aqueous Methyl Amine for preparation of compound (II) except that it further elaborates isolation of compound (II) employing tedious work-up involving extraction in Dichloromethane or Acetonitrile along followed by brine washings and further isolation from ethylacetate.

However work-up of compound (II) is not feasible at the industrial scale as it requires higher volumes of solvent given its solubility constraints. Compound (II) is only partially soluble in Dichloromethane and acetonitrile at ambient temperatures. Also compound of formula (II) has high solubility in water therefore making it difficult to perform conventional work-up by extraction.

WO2011/012321 entitled "Processes for crystallization of Rivaroxaban" teaches in example 32, step (f), the Synthesis of (S) -4- (4- (5- (aminomethyl) -2-oxooxazolidin-3-yl) phenyl) morpholin-3-one (Compound (II)) using methylamine (35% in ethanol) as a base and further isolating its hydrochloride salt which has several disadvantages as discussed above.

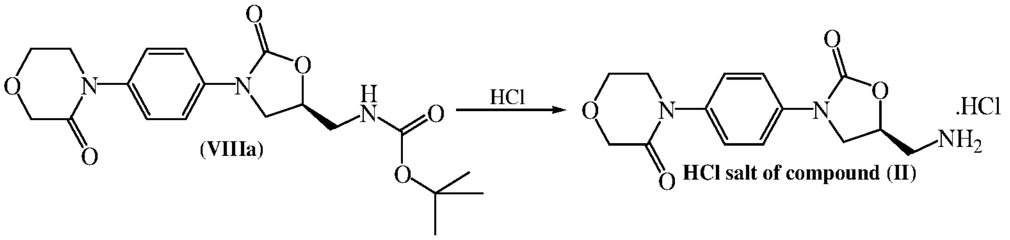
Thus there is a long felt need for improved process affording compound (II) free from excess unreacted amine, where it can be directly isolated without converting it into corresponding HCl salt.

WO2012/032533 discloses process for preparation of compound (II) employing use of Hydrazine Hydrate as represented below,



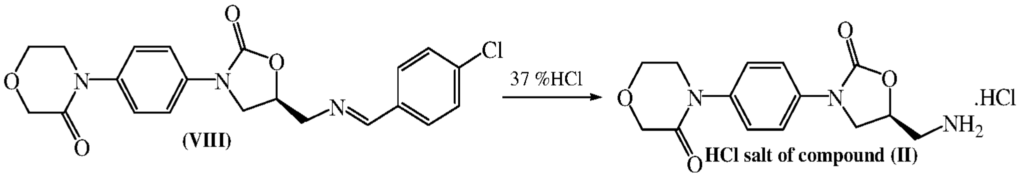
However, the process involves formation of Compound (IX) as side product which separates out as a bulky precipitate, the handling of which requires large amounts of solvents and equipments. The high price of hydrazine is also an impact to its economical use. Moreover, Hydrazine Hydrate is a well known genetoxic substance thereby requiring stringent controls for the same in final product and hence, not a preferred choice of reagent.

WO2012/171246 and **WO2013/120465** discloses deprotection of compound of formula (VIIIa) and (VIII) using Hydrochloric Acid as represented below to give corresponding hydrochloride salt of compound of formula (II):



(VIIIa)

HCl salt of compound (II)



(VIII)

HCl salt of compound (II)

However employing acidic conditions is not advisable as discussed above.

In view of the problems occurred in above methods, there remains a need for more efficient and industrially scalable process for the preparation of Rivaroxaban employing isolated compound (II) free from excess amine, in higher yield which overcomes the drawbacks as disclosed in the prior art.

The present inventors have studied various parameters for isolation of the compound (II) and surprisingly found that ensuring a non-aqueous reaction conditions during phthalimide deprotection of compound (III) afforded isolation of compound (II) free from excess unreacted amine in higher yields.

This effect can be related to better reaction conditions employing the use of non-aqueous amine thereby avoiding the disadvantages of aqueous amine as outlined below.

1. Use of aqueous amine renders it difficult to strip out excess unreacted methyl amine from the reaction mass completely and it further reacts in subsequent stages resulting in the impurities formation and lower yields in subsequent stage.
2. The compound (II) is highly soluble in water and partially or practically insoluble in most organic solvents like dichloromethane, ethyl acetate, toluene and others employed for conventional work-up, thereby making it difficult to isolate the compound (II) from the aqueous reaction mass by conventional work-up techniques.

In the backdrop of above problems, it becomes difficult to isolate compound (II) in reactions involving phthalimide deprotection using aqueous amine, thereby compelling to forward the concentrate mass of compound (II) having excess amine to further stages resulting in further impurities formations and lower yields.

As the deprotection reaction involves formation of multiple impurities, which are difficult to control and carried further to the final stage. To obtain the product in required purity, either purification by preparative HPLC or multiple crystallizations are warranted. This affects the yield and extra operational steps are required to obtain the final compound leaving the process non suitable for industrial production.

Thus there is a need for developing an efficient process for preparing Rivaroxaban overcoming the problems as reported in the prior art.

The present inventors have studied the process conditions for deprotection and found that treating compound (III) with non-aqueous amine according to the present invention ensures better reaction control effecting reduced impurity formation and affords compound (II) in high yields, which when used further in subsequent stage affords Rivaroxaban of formula (I) in high yields and purity. Further the process is also industrially feasible due to the non-usage of hazardous or genotoxic reagents and fewer isolation steps.

The present inventors have found an efficient process for synthesis of Rivaroxaban in higher yields and purity by ensuring non-aqueous reaction conditions employing use of non-aqueous amine during phthalimide deprotection reaction thereby controlling the formation of impurities and affording isolated higher yields of compound (II), which on further reaction gives Rivaroxaban of formula (I) in very good yields and purity making process inventive, novel and industrially applicable.

OBJECTS OF THE INVENTION:

It is an object of the present invention to provide an improved process for the preparation of Rivaroxaban in higher yields and purity.

It is another object of the present invention to provide an improved process for the preparation of Rivaroxaban in higher yields and purity employing isolation of compound (II), in higher yields, free from excess unreacted amine, wherein the use of HCl to convert compound (II) to its hydrochloride salt is avoided, thereby formation of impurity arising due to opening of morpholinone ring is avoided.

It is another object of the present invention to provide an improved process for the preparation compound (II), in higher yields, free from excess unreacted amine and by using non-aqueous amine.

It is yet another object of the present invention to provide an improved process for the preparation compound (II) in higher yields by using non-aqueous amine wherein no work-up/purification of reaction mass is required.

It is yet another object of the present invention to provide an improved process for preparation of Rivaroxaban in higher yields and purity employing use of non-aqueous amine in an organic solvent or mixtures thereof for preparation of compound (II).

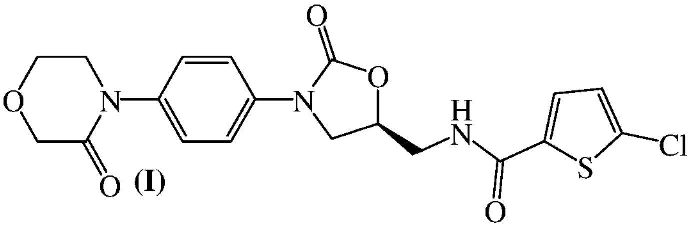
It is yet another object of the present invention to provide an improved process for preparation of Rivaroxaban in higher yields and purity employing use of amine in gaseous form for preparation of compound (II).

It is yet another object of the present invention to provide an improved process for preparation of Rivaroxaban in higher yields and purity employing fewer purifications and unit operations.

It is further object of the present invention to provide an improved process for preparation of Rivaroxaban in higher yields and purity which is feasible at commercial scale.

SUMMARY OF THE INVENTION

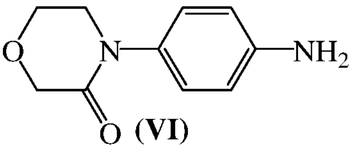
According to an aspect of the present invention there is provided an improved process for the preparation of Rivaroxaban of formula (I),



(I)

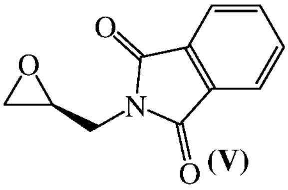
comprising the steps of:

a) reacting a compound of formula (VI)

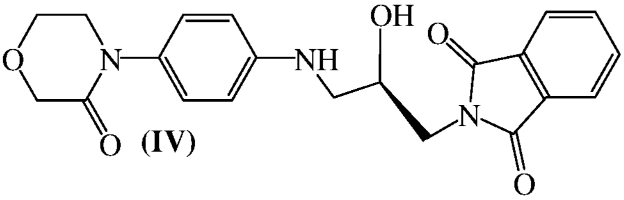


(VI)

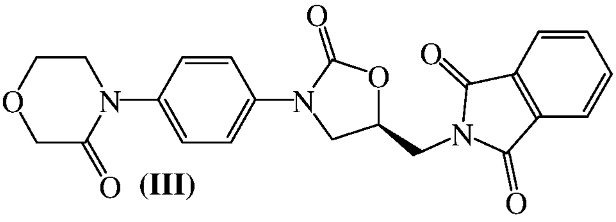
with a compound of formula (V)


(V)

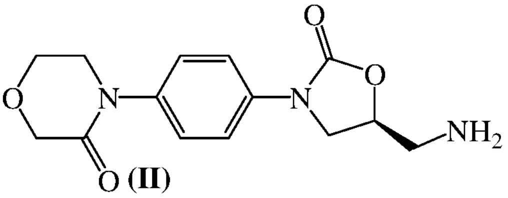
in suitable solvent to obtain compound of formula (IV);


(IV)

b) cyclising the compound of formula (IV) with a phosgene equivalent in suitable solvent to give compound of formula (III);

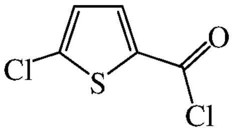

(III)

c) deprotecting the compound of formula (III) to obtain a compound of formula (II);


(II)

characterized in using non aqueous amine in suitable solvent to obtain a compound of formula (II) which is further isolated and optionally purified;

d) reacting the compound of formula (II) with a compound of formula (VII)



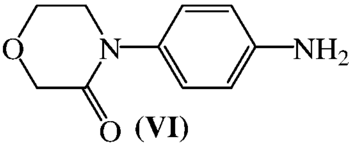
(VII)

in presence of suitable base in suitable solvent to obtain Rivaroxaban of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

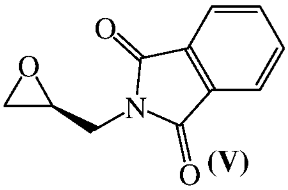
The present invention relates to an improved process for synthesis of Rivaroxaban in high yields and purity. The present invention provides a process for the preparation of Rivaroxaban of formula (I) comprising the steps of:

a) reacting a compound of formula (VI)



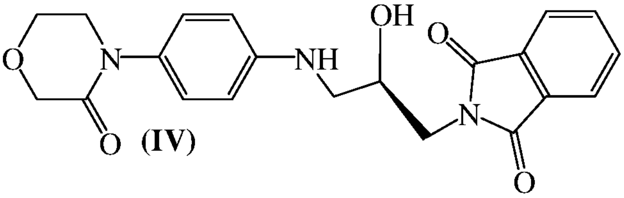
(VI)

with a compound of formula (V)



(V)

in suitable solvent to obtain compound of formula (IV)

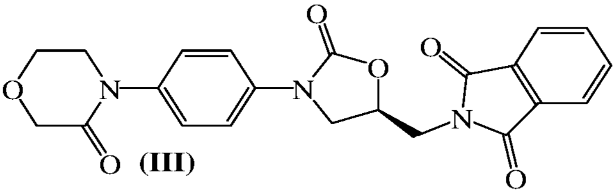

(IV)

The reaction in step a) may be preferably carried out at temperatures ranging from about but not limiting to 60°C to 70°C as reported in the prior art.

In one embodiment of the present invention in accordance with this aspect, after the reaction is completed the reaction mass is filtered to obtain compound (IV).

Suitable solvent used for step a), is selected from a group of solvents comprising alcohols such as methanol, ethanol, n-propanol, 2-propanol, tert-butanol, n-butanol; water or mixtures thereof.

b) cyclising the compound of formula (IV) with a phosgene equivalent, preferably N,N-carbonyldiimidazole in suitable solvent to give compound of formula (III)

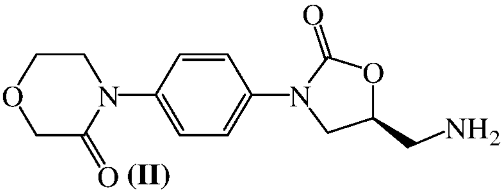

(III)

The cyclisation reaction in step b) may be preferably carried out at temperatures ranging from about but not limiting 105°C to 115°C as reported in the prior art.

Suitable solvent used for step b), is selected from group of solvents comprising hydrocarbon such as toluene, xylene etc.

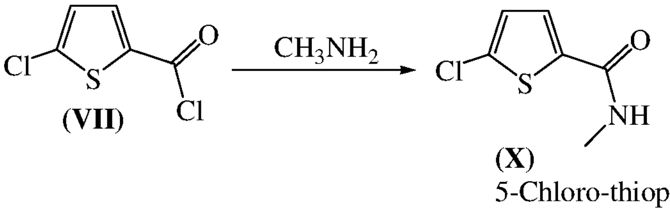
In one embodiment of the present invention in accordance with this aspect, after the reaction is completed the reaction mass is quenched by adding methanol followed by filtration of reaction mass to obtain compound (III).

c) deprotecting the compound of formula (III) by using non aqueous amine in the suitable solvent to obtain a compound of formula (II), isolating and optionally purifying compound of formula (II);


(II)

The present inventors have studied the reaction profile of deprotection reaction employing use of aqueous methyl amine and established the side reactions as represented below because of excess unreacted methyl amine, leading to formation of impurities and lower yields in final stage.

Side reaction due to excess unreacted methyl amine:

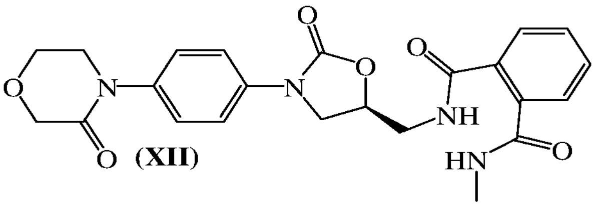

(VII) **(X)**

5-Chloro-thiophene-2-carboxylic acid methylamide

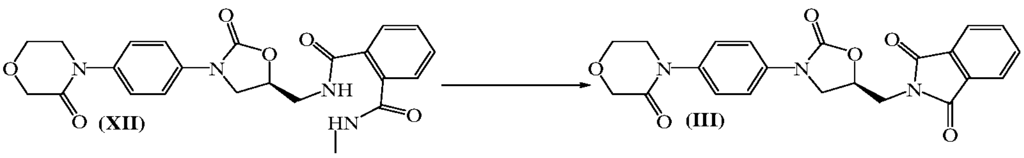
As represented in above reaction excess unreacted amine results in the formation compound (X) in substantial amounts thereby resulting in lower yields and purity.

It is observed that Rivaroxaban obtained by using compound (II) from aqueous methyl amine is contaminated with compound (X) broadly ranging from minimum 5% to 10% area % as analysed by HPLC with RRT at 0.74 with respect to compound (I), depending upon the amount of excess amine trapped in compound (II) oily mass obtained after deprotection reaction using aqueous methyl amine.

Further after extensive study of the reaction profile for deprotection of compound of formula (III), present inventors have found that using aqueous methyl amine affords compound (II) contaminated with compound of formula (XII) ranging from 3.0% to 8.0% which is carried forward to final stage affording Rivaroxaban contaminated with compound of formula (XII) ranging from 6.0% to 9.0%, thereby requiring multiple purifications to obtain Rivaroxaban passing in ICH limits and thus rendering process unsuitable for industrial purposes.


(XII)

Furthermore, when compound of formula (XII) is subjected to the reaction conditions for obtaining Rivaroxaban of high quality, it gets converted into compound of formula (III) as represented below.


(XII) (III)

It is observed that purifying Rivaroxaban contaminated with compound of formula (III) is a difficult task as it requires multiple purifications to bring compound of formula (III) to below 0.10% as per ICH requirement.

The present inventors have found that Rivaroxaban obtained using compound of formula (II) prepared from aqueous methyl amine is contaminated with compound of formula (III) arising due to above disclosed reasons.

Thus it becomes crucial to control impurity of formula (XII) during deprotection reaction to avoid its further conversion into compound of formula (III) during the reaction conditions for the preparation of Rivaroxaban.

The present inventors have studied the reaction parameters for deprotecting compound of formula (III) and found that when non-aqueous reaction conditions are employed using non-aqueous methyl amine the formation of compound of formula (XII) was controlled to below 0.50% thereby affording Rivaroxaban substantially free of compound of formula (XII) with limits well below to that required by ICH guidelines and further avoiding multiple purifications.

Further, as the compound of formula (XII) is controlled well below 0.50% during the deprotection stage using non-aqueous amine, the Rivaroxaban so obtained further is substantially free of compound of formula (III), which is resulted due to conversion of compound of formula (XII) into compound of formula (III) during reaction conditions of converting compound (II) to final compound (I) thereby resulting in significantly higher yields, fewer unit operations and reduced process time making process highly cost effective and suitable for industrial purposes, where the effective atom consumption is also lowered.

It is also observed that compound of formula (X) in Rivaroxaban, was controlled to below 0.10% as analysed by HPLC, thereby resulting in significant higher yields and purity. This improvement in purity profile of Rivaroxaban is attributed to the use of compound (II) obtained according to the present invention for preparing Rivaroxaban.

A comparative data for purity profile of Rivaroxaban as obtained by using compound of formula (II) prepared by employing use of aqueous and non-aqueous amine for deprotection is tabulated below:

Rivaroxaban purity profile		
Compound of formula (II)	**Compound X**	**Compound XII**
Aqueous Methyl Amine	8.24%	5.12%
Non-Aqueous Methyl Amine	0.10%	0.40%

As evident from the above table the Rivaroxaban prepared from compound (II) obtained by using non-aqueous amine has a better purity profile in comparison to Rivaroxaban prepared from compound (II) obtained by using aqueous amine.

The deprotection reaction in step c) may preferably be carried out at temperatures ranging from about but not limiting to 20°C to 90°C, preferably 35°C to 75°C, more preferably 45°C to 55°C.

Suitable solvent used for step c), is selected from group of solvents comprising alcohols such as methanol, ethanol, n-propanol, isopropanol, tert-butanol, n-butanol or mixture thereof. Preferred solvent is methanol.

In one embodiment of the present invention the solvent used for step c) is the mixture of methanol and isopropanol.

Non-Aqueous amine used in step c), may be selected from methyl amine, ethyl amine, n-propyl amine and the likes. Preferably the non-aqueous amine is methyl amine.

In an embodiment according to this aspect of the present invention the non- aqueous amine is methanolic methyl amine.

In an embodiment according to this aspect of the present invention the non-aqueous amine is methanolic methyl amine dissolved in isopropanol.

In an embodiment according to this of the present invention the non-aqueous amine is gaseous methyl amine.

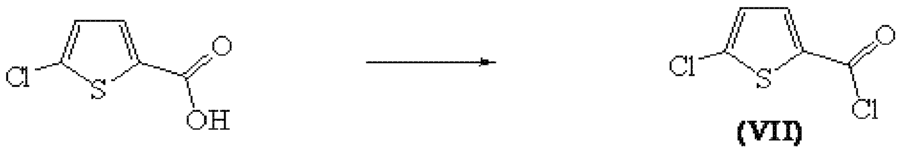
In an embodiment according to this aspect of the present invention the gaseous methyl amine is purged into the reaction mass of organic solvent.

Preferably the organic solvent is an alcohol and more preferably the alcohol is isopropanol.

In an embodiment according to this of the present invention the amine is gaseous methyl amine purged in isopropanol.

In an embodiment according to this of the present invention, after the deprotection reaction complies, the reaction mass is filtered to obtain compound (II) as solid.

In one embodiment of the present invention there is provided a process for preparation of compound (VII) from 5-Chloro-thiophene-2-carbioxylic acid (XI).

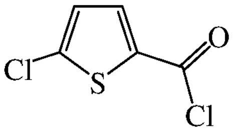


(VII)

5-Chloro-thiophene-2-carboxylic acid

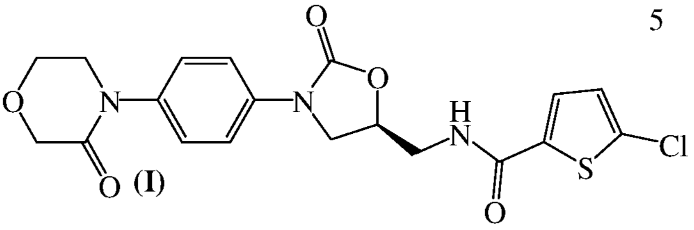
In further embodiment of the present invention, after the deprotection reaction complies, the reaction mass may be partially or completely concentrated and compound (II) isolated by filtration from suitable solvent, preferably methyl tert butyl ether.

d) reacting the compound (II) with a compound of formula (VII)



(VII)

in presence of suitable base in suitable solvent to obtain Rivaroxaban of formula (I)



(I)

wherein suitable base is an inorganic or organic base.

The reaction in step d) may preferably be carried out at temperatures ranging from about but not limiting -5°C to 50°C, preferably -5°C to 15°C, more preferably 0°C to 5°C.

Suitable solvent used for step d) is selected from group of solvents comprising of but not limited to hydrocarbon such as toluene, xylene; halogenated hydrocarbons such as methylene dichloride; ketones such as acetone; esters such as ethyl acetate; alcohols such as methanol, ethanol, n-propanol; ethers such as diethyl ether, di-isopropyl ether, tetrahydrofuran, water or mixtures thereof.

Suitable base used in step d) is selected from organic or inorganic base. The organic base may be selected from a group comprising of but not limited to diisopropyl ethylamine, diethylamine, triethylamine or mixtures thereof. The inorganic base may be selected from the group consisting of carbonates such as sodium carbonate, potassium carbonate; bicarbonates such as sodium bicarbonate, potassium bicarbonate or mixtures thereof.

In an embodiment according to this aspect of the invention, after the reaction complies, water is added to the reaction mass followed by filtration to isolate compound of formula (I), which is optionally recrystallised either from acetic acid or from Dimethyl sulphoxide and Methanol mixture to give pure compound of formula (I).

Thus present invention provides an efficient process for synthesis of Rivaroxaban in higher yields and purity by ensuring non-aqueous reaction conditions employing use of non-aqueous amine during phthalimide deprotection reaction thereby controlling the formation of impurities specifically compound (X) and compound (XII) affording isolated compound (II) in higher yields, which on further reaction gives Rivaroxaban of formula (I) in higher yields and purity.

All the referenced patents and applications are incorporated herein by reference in their entirety. Furthermore, where a definition or use of a term in a reference, which is incorporated by reference herein, is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

EXAMPLES

The following examples are used to illustrate the invention, but are not intended to limit the invention in any way.

Example (I): Preparation of Formula (IV)

To a 2 litre 4 neck RBF, charge Methanol (1500 ml), 4-(4-aminophenyl)-3-morpholinone Compound (VI), (100 gms), (S)-Glycidyl Phthalimide Compound (V), (127 gms). Reflux the reaction mass for 24 hrs. Cool the reaction mass at 25-30°C and filter. Wash the residue with Methanol (50 ml). Dry the solid at 45-50°C under vacuum.

Dry Wt: 180 gms (Theoretical yield: 87.50%); Purity: 98.20%

Example (II): Preparation of Formula (III)

To a 2 litre 4 Neck RBF, charge Toluene (830 ml), Compound (IV) (100 gms). Stirr the reaction mass and cool to 10-15°C. Charge N,N-carbonyl-diimidazole (82 gms). Reflux the reaction mass at 105-110°C for 2 hrs. Cool the reaction mass to 55-60°C and charge methanol (170 ml). Cool the reaction mass further to 25-30°C and filter. Wash the residue with Methanol (50 gms). Dry the solid under vacuum.

Dry Wt: 100 gms (Theoretical yield: 93.80%); Purity: 99.78%

Example III): Preparation of Formula (II) using Methanolic methyl amine in Isopropanol.

To a 2000 ml 4 neck RBF, charge Isopropanol (1000 ml), Methyl amine 33% solution in methanol (1000 ml) and 100 gms compound (III). Stirr the reaction mass at 55-60°C for 5 hrs. Cool the reaction mass at 25-30°C and stirr for 1 hr. Filter the reaction mass and wash with Isopropanol (50 ml). Dry the solid at 45-50°C under vacuum.

Dry Wt: 55 gms (Theoretical yield: 79.60%); Purity: 97.70%

Example IV): Preparation of Formula (II) using gaseous methyl amine.

To a 2000 ml 4 neck RBF, charge Isopropanol (1000 ml) and 100 gms compound (III). Purge the reaction mass with Methyl amine gas at 25-30°C for 2 hrs and then at 50-55°C for 5 hrs. Cool the reaction mass at 25-30°C and stirr for 1 hr. Filter the reaction mass and wash with Isopropanol (50 ml). Dry the solid at 45-50°C under vacuum.

Dry Wt: 90 gms; Purity: 90.40%

Example V): Preparation of Formula (II) using methanolic methyl amine.

To a 500 ml 4 neck RBF, charge Methyl amine 33% solution in methanol (250 ml) and 100 gms compound (III). Stir the reaction at 50-55°C for 2 hrs. Concentrate the reaction mass under vacuum and strip out with MTBE (100 ml*2). Charge 600 ml MTBE to the reaction mass and stirr for 2 hrs. Filter the reaction mass and wash with MTBE (50 ml). Dry the solid at 45-50°C under vacuum.

Dry Wt: 95 gms; Purity: 90.70%

Example (VI): Preparation of Formula (I) using organic base.

To a 500 ml 4 neck RBF, charge 250 ml toluene under nitrogen, 5-chloro-thiophene-2-carboxylic acid (XI) (67 gms). Heat the reaction mass to 75-80°C. Charge Thionyl chloride (122 ml) to the reaction mass and stirr at same temperature for 2 hrs. Cool the reaction mass to 50-55°C and concentrate the reaction mass under vacuum. Strip out excess thionyl chloride with toluene (100 ml). Charge Dichloromethane (250 ml) to reaction mass to obtain solution of compound (VII), which is gradually added at 0-5°C to a pre-cooled solution of compound (II) (100 gms), Dichloromethane (700 ml) and Diisopropyl ethyl amine (50 ml). Stirr the reaction mass for 30 mins at same temperature followed by stirring at 25-30°C for 30 mins. Cool the reaction mass and stir at 10-15°C for 30 mins followed by stirring at 25-30°C for 30 mins. Filtered the solid and dried under vacuum at 45-50°C for 5 hrs.

Example (VII): Purification of Formula (I)

To a 500 ml 4 neck RBF, Charge formula (I) (80 gms), acetic acid (480 ml) at 110-115°C to obtained a clear solution. Charcoalised at same temperature with 4.0 gms charcoal for 5-10 mins followed by celite filtration. The filtrate is partially concentrated under vacuum at 110-115°C till approximately 3 volumes remain. Cool the reaction mass to 25-30°C and maintain for 30 mins. Further cool the reaction mass to 16-18°C and maintain for 2 hrs. Filter the solid and wash with Acetic Acid (40 ml), Water (40 ml), followed by Acetone (40 ml). Dry the solid under vacuum at 45-50°C.

Example (VIII): Preparation of Formula (I) using inorganic base and compound (II) obtained using gaseous methyl amine.

Part A: Preparation of compound (II)

To a 2000 ml 4 neck RBF, charge Isopropanol (1000 ml) and 100 gms compound (III). Purge the reaction mass with Methyl amine gas at 25-30°C for 2 hrs and then at 50-55°C for 5 hrs. Cool the reaction mass at 25-30°C and stirr for 1 hr. Filter the reaction mass and wash with Isopropanol (50 ml). Dry the solid at 45-50°C under vacuum. Dry Wt: 90 gms.

Part B: Preparation of compound (VII)

To a 500 ml 4 neck RBF, charge (270 ml) toluene under nitrogen, 5-chloro-thiophene-2-carboxylic acid (XI) (75 gms). Charge Thionyl chloride (137 ml) to the reaction mass. Heat the reaction mass to 75-80°C and stirr at same temperature for 5 hrs. Cool the reaction mass to 50-55°C and concentrate the reaction mass under vacuum. Strip out excess thionyl chloride with toluene (90 ml) and dilute the reaction mass with (90 ml) acetone to obtain the title compound.

Part C: Preparation of compound (I)

To a 5 lit 4 neck RBF, charge Acetone (225 ml), Water (45 ml) and Compound (II) (90 gms) and 10% Aqueous sodium carbonate solution (360 ml) and stirr the reaction mass at 5-10°C. Gradually charge a solution of compound (VII) as obtained in Part B and stirr the reaction mass at 50-55°C for 3 hrs. Filter the reaction mass at 25-30°C and wash with water (180 ml) and acetone (180 ml). Dry the solid at 40-45°C under vaccum.

Dry wt: 85 gms. (Theoretical yield: 82.20% from compound III); Purity: 98.67%)

Part D: Purification of compound (I)

To a 500 ml 4 neck RBF, Charge formula (I) (85 gms), acetic acid (480 ml) at 110-115°C to obtained a clear solution. Charcoalised at same temperature with 4.0 gms charcoal for 5-10 mins followed by celite filtration. Cool the filtrate to 25-30°C and maintain for 30 mins. Further cool the reaction mass to 25-30°C and maintain for 2 hrs. Filter the solid and wash with Acetic Acid (40 ml), Water (40 ml), followed by Acetone (40 ml). Dry the solid under vacuum at 45-50°C.

Dry wt: 73 gms. (Theoretical yield: 70.60% from compound III); Purity: 99.86%)

Example (IX): Preparation of Formula (I) using inorganic base and compound (II) obtained using Methanolic methyl amine in isopropanol.

Part A: Preparation of compound (II)

To a 50 lit. 4 neck RBF, charge Isopropanol (18.2 lit.) and 1.82 Kg. compound (III). Charge (18.2 lit.) Methanolic Methyl amine and stirr the reaction mass at 55-60°C for 2 hrs and then at 65-70°C for 3 hrs. Cool the reaction mass at 25-30°C and stirr for 1 hr. Filter the reaction mass and wash with (8:2) Methanol: Isopropanol mixture (3.64 lit.). Dry the solid at 45-50°C under vacuum.

Dry Wt: 1.0 kg. Theoretical Yield: (79.60% from compound III); Purity: 99.12%)

Part B: Preparation of compound (VII)

To a 10 lit. 4 neck RBF, charge (3.0 lit.) toluene under nitrogen, 5-chloro-thiophene-2-carboxylic acid (XI) (0.68 Kg.). Heat the reaction mass to 75-80°C. Charge Thionyl chloride (1.25 lit.) to the reaction mass and stirr at same temperature for 5 hrs. Cool the reaction mass to 50-55°C and concentrate the reaction mass under vacuum. Strip out excess thionyl chloride with toluene (3.0 lit.) and dilute the reaction mass with (1.0 lit.) acetone to obtain the title compound.

Part C: Preparation of compound (I)

To a 5 lit 4 neck RBF, charge Acetone (2.5 lit.), Water (0.5 lit.) and Compound (II) (1.0 Kg.) and 10% Aqueous sodium carbonate solution (4.0 lit.) and stirr the reaction mass at 5-10°C. Gradually charge a solution of compound (VII) as obtained in Part B and stirr the reaction masss at 50-55°C for 3 hrs. Filter the reaction mass at 25-30°C and wash with water (2.0 lit.) and acetone (2.0 lit.).

Dry the solid at 40-45°C under vacuum.

Dry wt: 1.30 Kg. (Theoretical yield: 69.0% from compound III); Purity: 99.0%)

Part D: Purification of compound (I)

To a 500 ml 4 neck RBF, Charge formula (I) (1.30 Kg.), acetic acid (6.50 lit.) at 110-115°C to obtained a clear solution. Charcoalised at same temperature with 0.065 Kg charcoal for 5-

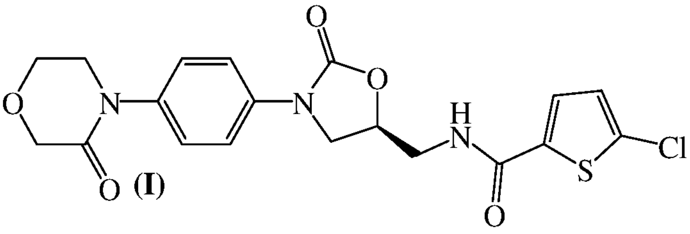
10 mins followed by celite filtration. Cool the filtrate to 25-30°C and maintain for 30 mins. Further cool the reaction mass to 25-30°C and maintain for 2 hrs. Filter the solid and wash with Acetone (1.30 lit.) followed by water (1.30 lit.). Dry the soild under vacuum at 45-50°C. Dry wt: 1.10 Kg. (Theoretical yield: 58.40% from compound (III)); Purity: 99.86%)

Comparative data of yield and purity of the final product Rivaroxaban against prior art cited in the table.

Compound (I) Rivaroxaban		
	Yield	Purity
Rivaroxaban obtained through compound of Formula II obtained by employing aqueous methylamine. **(Present invention)**	Yield obtained from compound III to Rivaroxaban **82.20%** (Example VIII)	**98.67%** (Example VIII)
Rivaroxaban obtained through compound of Formula II obtained by employing non-aqueous methylamine and isolated as hydrochloride salt of Formula II. **(WO2013/121436)**	Yield calculated from compound III to Rivaroxaban (Example 6 and Example 8 of WO2013/121436) **69.67%**	**99%**
	Yield calculated from compound III to Rivaroxaban (Example 6 and Example 9 of WO2013/121436) **65.16%**	**99.7%**

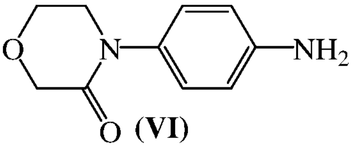
CLAIMS

1. A process for the preparation of Rivaroxaban of formula (I),

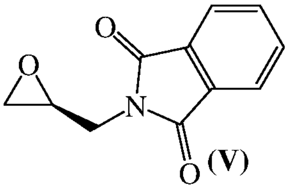

(I)

comprising the steps of:

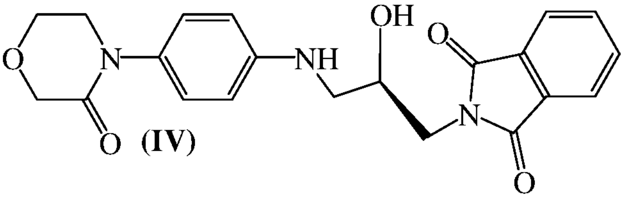
a) reacting a compound of formula (VI)


(VI)

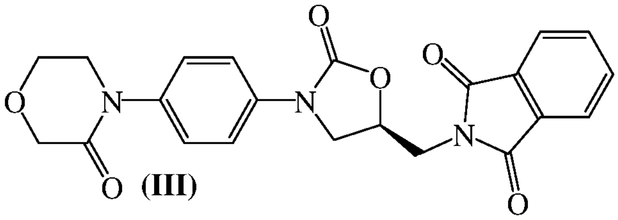
with a compound of formula (V)


(V)

in suitable solvent to obtain compound of formula (IV);

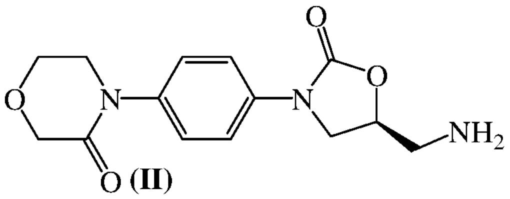

(IV)

b) cyclising the compound of formula (IV) with a phosgene equivalent in suitable solvent to give compound of formula (III);



(III)

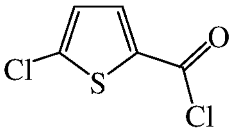
c) deprotecting the compound of formula (III) to obtain a compound of formula (II);



(II)

characterized in using non aqueous amine in suitable solvent to obtain a compound of formula (II), which is further isolated and optionally purified;

d) reacting the compound of formula (II) with a compound of formula (VII)



(VII)

in presence of suitable base in suitable solvent to obtain Rivaroxaban of formula (I).

2. The process for the preparation of Rivaroxaban of formula (I) according to claim 1, wherein the non aqueous amine in step c) is gaseous methyl amine.

3. The process for the preparation of Rivaroxaban of formula (I) according to claim 1, wherein the non aqueous amine in step c) is methyl amine dissolved in a suitable organic solvent.
4. The process for the preparation of Rivaroxaban of formula (I) according to claim 1, wherein the suitable solvent in step c) is selected from the group consisting of alcohols such as methanol, ethanol, n-propanol, isopropanol, tert-butanol, n-butanol or mixtures thereof.
5. The process for the preparation of Rivaroxaban of formula (I) according to claim 3, wherein the suitable solvent is methanol.
6. The process for the preparation of Rivaroxaban of formula (I) according to claim 3, wherein the suitable solvent is mixture of methanol and isopropanol.
7. The process for the preparation of Rivaroxaban of formula (I) according to claim 1, wherein after the completion of the reaction in step (c), the compound (II) is isolated as solid.
8. The process for the preparation of Rivaroxaban of formula (I) according to claim 1, wherein after the completion of the reaction in step (c), the reaction mass is partially or completely concentrated and compound (II) is isolated from a suitable solvent.
9. The process for the preparation of Rivaroxaban of formula (I) according to claim 8, wherein the suitable solvent is methyl tertiary butyl ether.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/053346

A. CLASSIFICATION OF SUBJECT MATTER
C07D413/14 Version=2016.01

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)

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)

Patseer, 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.
Y	WO2010124385A1 (Apotex Pharmachem Inc) 4-11-2010(4 November 2010); Pages 54-71 claims 1-51	1-9
Y	EP2855465A1 (Ranbaxy Laboratories Limited) 8-04-2015 (8 April 2015); Pages 11-14 Claims 1-13	1-9

☐ 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 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
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Date of the actual completion of the international search 02-08-2016	Date of mailing of the international search report 02-08-2016
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Latika Dawara Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IB2016/053346

Citation	Pub.Date	Family	Pub.Date
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