The present invention provides a method of preparing 4-(4-aminophenyl)-3-morpholinone, including the step of reducing 4-(4-nitrophenyl)-3-morpholinone by reacting sodium hydrosulfite (Na2S2O4) with 4-(4-nitrophenyl)-3-morpholinone. This method is safe and economical because high-temperature and high-pressure hydrogen gas is not used, can easily produce 4-(4-aminophenyl)-3-morpholinone in large amounts because an expensive hydrogenation catalyst is not used, and is environmentally friendly because 4-(4-aminophenyl)-3-morpholinone can be crystallized in water after the reaction.
**Description**

**Title of Invention: NOVEL METHOD OF PREPARING 4-(4-AMINOPHENYL)-3-MORPHOLINONE**

**Technical Field**

[1] The present invention relates to a method of preparing 4-(4-aminophenyl)-3-morpholinone, including the step of reducing 4-(4-nitrophenyl)-3-morpholinone by reacting sodium hydrosulfite (Na$_2$S$_2$O$_4$) with 4-(4-nitrophenyl)-3-morpholinone. This method is safe and economically beneficial due to the absence of high-temperature and high-pressure, can allow the production of 4-(4-aminophenyl)-3-morpholinone on a mass scale because of the non-necessity of expensive hydrogenation catalysts, as well as being environmentally friendly thanks to the ability of 4-(4-aminophenyl)-3-morpholinone to be crystallized in water after the completion of the reaction. 4-(4-aminophenyl)-3-morpholinone has a structure represented by Formula I below:

[2] [Formula I]

[3]

[4]

**Background Art**

[5] Rivaroxaban, a kind of oxazolidinone derivative optimized to inhibit a free blood coagulation factor Xa and a blood coagulation factor Xa conjugated with a prothrombinase complex, serving as an oral anticoagulant, acts to prevent the production of thrombin itself. Rivaroxaban has useful applications in the prevention and treatment of various thromboembolic diseases, inter alia, deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, angina pectoris (AP), recurrence and restenosis of occlusive disease after angioplasty or coronary artery bypass surgery, stroke, transient ischemic attack, and peripheral arterial occlusive disease. Rivaroxaban has a structure represented by Formula II below:

[6] [Formula II]
A preparation method of rivaroxaban was first disclosed in PCT Patent Publication WO 2001/047919. In the method, 4-(4-aminophenyl)-3-morpholinone is used as a key intermediate of a synthesis of rivaroxaban. Specifically, rivaroxaban is synthesized in the method, as illustrated in the following Reaction Scheme I:

As shown in Reaction Scheme I, rivaroxaban is synthesized by coupling 4-(4-aminophenyl)-3-morpholinone (I) with 2-[(2S)-2-oxiranylmethyl]-1H-isoindole-1,3(2H)-dione (II), followed by introducing 5-chlorothiophene-2-carbonyl chloride (IV). That is, 4-(4-aminophenyl)-3-morpholinone (I) is disclosed to play as a key intermediate in the synthesis of rivaroxaban in this method.

The present inventors devise a novel method, distinct from prior art, of preparing 4-(4-aminophenyl)-3-morpholinone which is used as a key intermediate of the synthesis of rivaroxaban. The method of the present invention is characterized in that it is safe and economically beneficial because high-temperature and high-pressure hydrogen gas is not used, it can be easily applied to the mass production of 4-(4-aminophenyl)-3-morpholinone because an expensive hydrogenation catalyst is not needed, and it is environmentally friendly because 4-(4-aminophenyl)-3-morpholinone can be crystallized in water after the completion of the reaction.

A description given of conventional methods will be useful to manifest the characteristics of the method of preparing 4-(4-aminophenyl)-3-morpholinone according to
the present invention.

In PCT Patent Publication WO 2001/047919, 4-(4-aminophenyl)-3-morpholinone is prepared by reducing 4-(4-nitrophenyl)-3-morpholinone in the presence of a palladium catalyst under an atmosphere of the high-temperature and high-pressure hydrogen gas, as shown in Reaction Scheme II below:

[Reaction Scheme II]

Particularly, as shown in Reaction Scheme III, 4-(4-aminophenyl)-3-morpholinone (I) is prepared by reacting the starting material morpholin-3-one (VI) with 4-fluoronitrobenzene (VII) to synthesize 4-(4-nitrophenyl)-3-morpholinone (VIII) as an intermediate, followed by hydrogenating the intermediate in the presence of a palladium catalyst:

[Reaction Scheme III]

However, the step of hydrogenation requires a severe reaction condition, such as a hydrogen pressure of as high as 50 bars at 70°C for 8 hours. In spite of the severe reaction condition of high temperature and high pressure, this method only allows for a yield of no more than 37.6%, and thus is not economically efficient.

PCT Patent Publication WO 2005/026135 discloses a reductive reaction of 4-(4-nitrophenyl)-3-morpholinone (VIII) in the presence of a hydrogenation catalyst in ethanol, as shown in Reaction Scheme IV. Particularly, 4-(4-aminophenyl)-3-morpholinone (I) is synthesized by hydrogenating 4-(4-nitrophenyl)-3-morpholinone (VIII) at a temperature of 40 ~ 120°C and a pressure of 2 ~ 10 bars for about 1 hour. This method has a yield of 93%.

[Reaction Scheme IV]
For all the above reactions, however, this method is also disadvantageous in that it requires a reaction condition of the high temperature and high pressure as before, it has difficulty in preparing 4-(4-aminophenyl)-3-morpholinone unless a hydrogenation reactor is used, and it must use an expensive hydrogenation catalyst. Such a hydrogenation reaction of the high temperature and high pressure is not safe because of a danger of explosion. These disadvantages restrict an industrially useful large-scale reaction.

As described above, the above-mentioned conventional technologies were problematic in that they did not allow for the production of 4-(4-aminophenyl)-3-morpholinone without danger of explosion. Additionally, economical efficiency, feasibility of mass production, and environmental safety were not possible. Therefore, there has been a need for a method of preparing 4-(4-aminophenyl)-3-morpholinone that is safe and economically beneficial because neither high-temperature nor high-pressure hydrogen gas is used, and is cheaper than that of the use of a hydrogenation catalyst, thereby feasibly allowing for mass scale production, in addition to being environmentally friendly.

Disclosure of Invention

Technical Problem

An object of the present invention is to provide a method of preparing 4-(4-aminophenyl)-3-morpholinone, which is safe and economically beneficial because neither high-temperature nor high-pressure hydrogen gas is used, and is cheaper than the use of a hydrogenation catalyst, thereby feasibly allowing for mass scale production, in addition to being environmentally friendly thanks to ability to crystallize 4-(4-aminophenyl)-3-morpholinone in water after the completion of the reaction. Through the method of the present invention in which a nitro-reduction reaction is stably conducted on mass scale, revaroxaban can be synthesized safely, economically beneficially, and environmentally friendly.

Solution to Problem

In order to accomplish the above object, an aspect of the present invention provides a novel method of preparing 4-(4-aminophenyl)-3-morpholinone. The method includes the reduction after 4-(4-nitrophenyl)-3-morpholinone reacts with sodium hydrosulfite.
Advantageous Effects of Invention

The method of preparing 4-(4-aminophenyl)-3-morpholinone according to the present invention is economical because a hydrogenation catalyst is not used, and is safe because hydrogen gas is not used, thus excluding a high-pressure reaction. Thus, in this method, a large-scale nitro-reduction reaction can be stably conducted. Further, this method is economical and environmentally friendly because 4-(4-aminophenyl)-3-morpholinone is crystallized in water immediately after the reaction is finished. Therefore, this method is more economical in terms of equipment extension and production cost, and is safe and environmentally friendly in the process of preparing 4-(4-aminophenyl)-3-morpholinone and rivaroxaban.

Mode for the Invention

The present invention addresses a method of preparing 4-(4-aminophenyl)-3-morpholinone, including the steps of: a) adding 4-(4-nitrophenyl)-3-morpholinone in a solvent to prepare a solution; and b) reacting sodium hydrosulfite with the solution. As used herein, the "solvent" may be a single solvent or mixed solvent, and, specifically, may include a solvent first used in completing a reaction, and any solvent used subsequently.

The method may further include the step of b2) stirring the solution after the addition of sodium hydrosulfite. When the solution is stirred, the starting material may remain unreacted. The reason is because the reaction has not yet been completed. In this case, the reaction can be completed by adding another solvent to the reaction solution and then stirring this solution.

The solvent may be at least one selected from the group consisting of water, aliphatic alcohol, tetrahydrofuran, acetone, acetonitrile, dioxane, dimethylsulfoxide, acetic acid, dimethylformamide, N-methylpyrrolidinone, and dimethylacetamide. The aliphatic alcohol may be methanol or ethanol.

Preferably, the solvent may be at least one selected from among water, methanol, ethanol, and tetrahydrofuran. More preferable is purified water.

Further, in the step b), sodium hydrosulfite may be added to the solution, and then heated to about 40°C to about 80°C, preferably, about 50°C to about 70°C.

This method may be performed at normal pressure.

The sodium hydrosulfite may be used in an amount of 1 to 5 molar equivalents, based on one molar equivalent of 4-(4-nitrophenyl)-3-morpholinone, and preferably in an amount of 3 to 3.5 molar equivalents.

The method may further include the steps of:
c) adding an acid into the reaction solution;
d) adding a base into the acid-added reaction solution to adjust a pH thereof; and
e) cooling the pH-adjusted reaction solution to obtain crystals.

The step c) may further include heating the reaction solution prior to the adding of the acid after the completion of the reaction. In this case, the reaction solution may be preferably heated to about 45°C to about 75°C.

When the acid is not added as in the step c), a portion of sodium hydrosulfite may still remain undecomposed, and thus may be present in the reaction product during crystallization.

The acid may be hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, carbonic acid, boric acid, formic acid, acetic acid, propionic acid, lactic acid, butyric acid, isobutyric acid, trifluoroacetic acid, malic acid, maleic acid, malonic acid, fumaric acid, succinic acid, monoamido succinate, glutamic acid, tartaric acid, oxalic acid, citric acid, glycolic acid, glucuronic acid, ascorbic acid, benzoic acid, phthalic acid, salicylic acid, anthranilic acid, dichloroacetic acid, aminoxyacetic acid, benzensulfonic acid, 4-toluenesulfonic acid, methanesulfonic acid or an aqueous solution thereof, with preference for hydrochloric acid or an aqueous solution thereof. More preferable is an aqueous hydrochloric acid solution of about 20% (w/w) to about 35% (w/w). Most preferably, the acid may be an aqueous hydrochloric acid solution of about 25% (w/w).

The completion of the reaction, and the degree of progress of the reaction may be determined by thin layer chromatography (TLC), and specifically, by analyzing the relative intensity of starting materials, by-products and reaction products appearing on TLC when monitoring the reaction solution using an UV lamp after developing the reaction solution on the TLC.

The step d) may include cooling the reaction solution prior to the adding of a base after the adding of the acid. In this case, the reaction solution may be cooled to room temperature, preferably, about 23°C.

The base may be sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, calcium hydroxide, magnesium hydroxide, sodium methoxide, sodium ethoxide, potassium t-butoxide, tetrabutylammonium hydroxide, benzytrimethylammonium hydroxide, potassium carbonate, sodium carbonate, calcium carbonate, sodium hydrogen carbonate (sodium bicarbonate), potassium hydrogen carbonate (potassium bicarbonate) or an aqueous solution thereof, with preference for sodium hydroxide or an aqueous solution thereof. More preferable is a 20% (w/w) to 40% (w/w) aqueous sodium hydroxide solution. Most preferably, the base may be a 30% (w/w) aqueous sodium hydroxide solution.

The pH of the reaction solution may be adjusted to 10 or less, preferably 5 to 10,
more preferably 9 to 10, and most preferably about 9.

[55] The pH-adjusted reaction solution may be cooled to about -5 to about 10°C.

[56] The step e) may include stirring the pH-adjusted reaction solution prior to the crystallization of the pH-adjusted reaction solution after the cooling thereof. In this case, the pH-adjusted reaction solution may be preferably stirred for 4 hours or more. The pH-adjusted reaction solution may be more preferably stirred for about 4 hours.

[57] The method may further include the step of d2) distilling the pH-adjusted reaction solution, between step d) and step e).

[58] The pH-adjusted reaction solution may be distilled under a reduced pressure of about 30 to about 50 mmHg, preferably about 40 mmHg.

[59] The distillation under reduced pressure may be performed until the pH-adjusted reaction solution remains in an amount of 8 to 15 ml/g based on 4-(4-nitrophenyl)-3-morpholinone as a starting material.

[60] The method may further include the steps of:

f) filtering and washing the obtained crystals; and

[62] g) drying the washed crystals.

[63] The method may further include the steps of:

[64] f2) adding a solvent to the washed crystals and then cooling the crystal-containing solution to obtain the crystals; and

[65] f3) filtering and washing the obtained crystals, between step f) and step g).

[66] The solvent added to the washed crystals may be at least one selected from the group consisting of water, methanol, ethanol, tetrahydrofuran, acetone, acetonitrile, dioxane, dimethylsulfoxide, acetic acid, dimethylformamide, N-methylpyrrolidinone, and dimethylacetamide. Preferably, the solvent may be at least one selected from among water, methanol, ethanol, and tetrahydrofuran. More preferable is purified water.

[67] The cooling of the crystal-containing solution may be performed at about -5 to about 10°C.

[68] The washing of the crystals may be performed by at least one solvent selected from the group consisting of water, methanol, ethanol, tetrahydrofuran, acetone, acetonitrile, dioxane, dimethylsulfoxide, acetic acid, dimethylformamide, N-methylpyrrolidinone, and dimethylacetamide. Preferably, the washing of the crystals may be performed by at least one selected from among water, methanol, ethanol, and tetrahydrofuran. More preferably, the washing of the crystals may be performed by purified water.

[69] The drying of the washed crystals may be performed drying under vacuum or reduced pressure.

[70] When the drying of the washed crystals is performed under reduced pressure, it may be performed at a pressure of about 60 mmHg.

[71] The drying of the washed crystals may be performed at about 30°C to about 50°C,
preferably, about 40°C.

Through this method, 4-(4-aminophenyl)-3-morpholinone can be obtained as an almost white solid at a high purity and a high yield.

In the method of the present invention, commercially available starting materials and reagents can be purchased and used.

Hereinafter, the present invention will be described in more detail with reference to the following Examples and Comparative Examples. However, these Examples and Comparative Examples are set forth only to illustrate the present invention, and the scope of the present invention is not limited thereto.

In the following Examples, 4-(4-nitrophenyl)-3-morpholinone (VIII) was purchased from Chem Express Haoyuan Corporation in China and used as it was, without further purification. Further, sodium hydrosulfite, ferrous sulfate heptahydrate, acetic acid, ferric chloride, ammonium formate and hydrazine monohydrate were purchased from Daejung Chemical Industry Co., Ltd.; iron phthalocyanine from TCI Corp.; reduced iron powder, diisopropylethylamine, diethylchlorophosphite, palladium on active carbon (10%), and calcium chloride from Aldrich Corp.. All these reagents were used as they were, without further purification. WiseVen (Wisd) was used as a vacuum dryer.

**Example 1** Synthesis of 4-(4-aminophenyl)-3-morpholinone 1

A solution of 10g of 4-(4-nitrophenyl)-3-morpholinone in 75 mL of purified water was stirred at 23°C for 30 min. Then, 25.85g of sodium hydrosulfite was added to the solution, heated to 50°C and then stirred for 2.5 hours. After completion of the reaction, the reaction mixture was heated to 70°C, and dropwise added with 45.5 mL of a 25%(w/w) aqueous hydrochloric acid solution for 3 hours. Thereafter, the reaction mixture was cooled to 23°C, and adjusted to a pH of 9-10 by dropwise adding a 30% (w/w) aqueous sodium hydroxide solution thereto. Then, the resulting solution was distilled under a reduced pressure of 40 mmHg to a volume of 80 mL. Then, the remaining solution was subjected to crystallization while stirring for 4 hours at 3~5°C. The crystals thus formed were filtered and then washed with 30 mL of purified water at 5°C. Finally, the resulting crystals were dried in a vacuum at 40°C for 6 hours to obtain 8.04 g (93%) of the title compound as a white solid.

Melting point: 171°C

**Example 2** Synthesis of 4-(4-aminophenyl)-3-morpholinone 2

A solution of 2.2g of 4-(4-nitrophenyl)-3-morpholinone in 34 mL of methanol was
stirred at 23°C for 30 min. Then, 5.75g of sodium hydrosulfite was added to
the solution, heated to 50°C and then stirred for 3 hours. Then, the resulting solution was
added with 34 mL of water, and further stirred at 50°C for 2 hours to complete a
reaction. After completion of the reaction, the reaction mixture was heated to 70°C,
dropwise added with 10 mL of a 25%(w/w) aqueous hydrochloric acid solution, and
then stirred for 1 hour. Thereafter, the reaction mixture was cooled to room tem-
perature, and adjusted to a pH of 9-10 by dropwise adding a 30% (w/w) aqueous
sodium hydroxide solution thereto. Then, the resulting solution was distilled under a
reduced pressure of 40 mmHg to a volume of 18 mL. Then, the remaining solution was
subjected to crystallization while stirring at 0°C for 3 hours. The crystals thus formed
were filtered and then washed with 10 mL of purified water. Then, the washed crystals
were introduced into 15 mL of water, and then suspended and stirred at 0°C for 1 hour.
Then, the crystals were filtered, and then washed with 5 mL of purified water at about
5°C. Finally, the washed crystals were dried under a reduced pressure of 60 mmHg for
2 hours to 1.73 g (90%) of the title compound as a white solid.

<Example 3> Synthesis of 4-(4-aminophenyl)-3-morpholinone 3
A solution of 2.2g of 4-(4-nitrophenyl)-3-morpholinone in 34 mL of ethanol was
stirred at 23°C for 30 min. Then, 5.75g of sodium hydrosulfite was added to the
solution, heated to 50°C and then stirred for 3 hours. Then, the resulting solution was
added with 34 mL of water, and further stirred at 50°C for 2 hours to complete a
reaction. After completion of the reaction, the reaction mixture was heated to 70°C,
dropwise added with 10 mL of a 25%(w/w) aqueous hydrochloric acid solution, and
then stirred for 1 hour. Thereafter, the reaction mixture was cooled to 23°C, and
adjusted to a pH of 9-10 by dropwise adding a 30% (w/w) aqueous sodium hydroxide
solution thereto. Then, the resulting solution was distilled under a reduced pressure of
40 mmHg to a volume of 18 mL. Then, the remaining solution was subjected to crys-
tallization while stirring at 0°C for 3 hours. The crystals thus formed were filtered and
then washed with 10 mL of purified water. Then, the washed crystals were introduced
into 15 mL of water, and then suspended and stirred at 0°C for 1 hour. Then, the
crystals were filtered, and then washed with 5 mL of purified water at about 5°C.
Finally, the washed crystals were dried under a reduced pressure of 60 mmHg for 2
hours to 1.63 g (85%) of the title compound as a white solid.

<Example 4> Synthesis of 4-(4-aminophenyl)-3-morpholinone 4
A solution of 2.2g of 4-(4-nitrophenyl)-3-morpholinone in 34 mL of tetrahydrofuran
was stirred at room temperature for 10 min. Then, 5.75g of sodium hydrosulfite was added to the solution, heated to 50°C and then stirred for 17 hours (starting material was not reacted to remain as before).

Then, the resulting solution was added with 34 mL of water, and further stirred at 50°C for 3 hours to complete a reaction. After completion of the reaction, the reaction mixture was dropwise added with 10 mL of a 25% (w/w) aqueous hydrochloric acid solution, and then stirred at 50°C for 1 hour. Thereafter, the reaction mixture was cooled to 23°C, and adjusted to a pH of 9-10 by dropwise adding a 30% (w/w) aqueous sodium hydroxide solution thereto. Then, the resulting solution was distilled under a reduced pressure of 40 mmHg to a volume of 30 mL. Then, the this solution was subjected to crystallization while stirring at 23°C for 2.5 hours and then further stirring 5 ~ 10°C for 1 hour. The crystals thus formed were filtered and then washed with 10 mL of purified water at about 5°C. Finally, the washed crystals were dried under a reduced pressure of 60 mmHg for 2 hours to 1.21 g (63%) of the title compound as a white solid.

Melting point: 171°C

<Example 5> Synthesis of 4-(4-aminophenyl)-3-morpholinone 5

A solution of 2.2g of 4-(4-nitrophenyl)-3-morpholinone in 34 mL of methanol was stirred at 23°C for 30 min. Then, 5.75g of sodium hydrosulfite was added to the solution, heated to 50°C and then stirred for 48 hours. After completion of the reaction, the reaction mixture was dropwise added with 34 mL of water and 10 mL of a 25% (w/w) aqueous hydrochloric acid solution, and then stirred at 50°C for 1 hour. Thereafter, the reaction mixture was cooled to 23°C, and adjusted to a pH of 9-10 by dropwise adding a 30% (w/w) aqueous sodium hydroxide solution thereto. Then, the resulting solution was distilled under a reduced pressure of 40 mmHg to a volume of 30 mL. Then, the remaining solution was subjected to crystallization while stirring 5 ~ 10°C for 2 hours. The crystals thus formed were filtered and then washed with 10 mL of purified water at 5°C. Finally, the washed crystals were dried under a reduced pressure of 60 mmHg for 2 hours to 1.16 g (60%) of the title compound as a white solid (60%).

Melting point: 171°C

<Comparative Example 1> Synthesis of 4-(4-aminophenyl)-3-morpholinone 6

2.22 g of 4-(4-nitrophenyl)-3-morpholinone was added to a mixed solvent of 11.1 mL of purified water and 11.1 mL of ethanol, and stirred to complete dissolution of the solid. To this solution were added 28.4 mg of iron phthalocyanine and 13.9 mg of ferrous sulfate heptahydrate, followed by stirring at 23°C for 30 minutes. Then, the
resulting solution was added with 1 g of hydrazine monohydrate, and stirred under reflux at 76 ~ 78°C for 6 hours. Subsequently, the solution was cooled to 23°C, and then stirred for 61 hours (reaction proceeded to 80%, as monitored by TLC). Thereafter, the reaction mixture was filtered with a celite pad, and washed with 40 mL of a mixed solvent of ethanol and water (l:l(volume: volume)). Then, excess ethanol was distilled under a reduced pressure of 40 mmHg until the volume of the reaction mixture was reduced to 18 mL. Then, the this solution was subjected to crystallization while stirring for 3 hours at 0°C. Then, the crystals thus formed were filtered, and washed with 10 mL of purified water. Afterwards, the obtained crystals were introduced into 15 mL of water, and then suspended by stirring at 0°C for 1 hour. Again, the crystals were filtered, and then washed with 5 mL of purified water at about 5°C. Finally, the washed crystals were dried under a reduced pressure of 60 mmHg for 2 hours to obtain 807 mg (42%) of the title compound as a light brown solid.

[102] Melting point: 171 °C

[103]

<Comparative Example 2> Synthesis of 4-(4-aminophenyl)-3-morpholinone 7

[104] 2.22 g of 4-(4-nitrophenyl)-3-morpholinone, 1.675 g of reduced iron powder and 1.47 g of calcium chloride were added to 44.4 mL of ethanol, and then stirred at 23°C for 30 min. This solution was added with 2.22 ml of purified water, and stirred 60 ~ 70°C for 24 hours (reaction proceeded to 50%, as monitored by TLC). Thereafter, the reaction mixture was filtered with a celite pad, and washed with 40 mL of a mixed solvent of ethanol and water (l:l(volume: volume)). Then, excess ethanol was distilled under a reduced pressure of 40 mmHg until the volume of the reaction mixture was reduced to 18 mL. Then, this solution was stirred at 0°C for 3 hours (crystals were not formed). Again, the resulting solution was distilled under reduced pressure, and then residues were purified by a column using ethyl acetate as a mobile phase to obtain 577 mg (30%) of a light brown solid.

[106] Melting point: 171 °C

[107]

<Comparative Example 3> Synthesis of 4-(4-aminophenyl)-3-morpholinone 8

[108] 2.22 g of 4-(4-nitrophenyl)-3-morpholinone was added to 66.6 mL of anhydrous ethanol, and then stirred at 23°C for 30 min. This solution was added with 4.44 mL of acetic acid, and stirred under reflux at 80°C for 30 min. Then, this solution was added with 4.12 g of reduced iron powder and 324 mg of ferric chloride, and then stirred for 8 hours and 30 minutes (reaction proceeded to 95% or more, as monitored by TLC as monitored by TLC). Thereafter, the reaction mixture was cooled to 23°C, filtered with a celite pad, and washed with 40 mL of a mixed solvent of ethanol and water (l:l(volume: volume)). Then, excess ethanol was distilled under a reduced pressure of
40 mmHg until the volume of the reaction mixture was reduced to 18 mL. Then, this solution was stirred at 0°C for 3 hours (crystals were not formed). Again, the resulting solution was distilled under reduced pressure, and then residues were purified by a column using ethyl acetate as a mobile phase to obtain 1.057 g (55%) of a light brown solid.

Melting point: 171 °C

<Comparative Example 4> Synthesis of 4-(4-aminophenyl)-3-morpholinone 9

2.22 g of 4-(4-nitrophenyl)-3-morpholinone was added to 40 mL of methanol, and then stirred at 23°C for 30 min. Then, this solution sequentially was added with 480 mg of palladium on active carbon (10%) and 3.15 g of ammonium formate, and then stirred at 23°C for 6 hours (reaction was completed, as monitored by TLC). Thereafter, the reaction mixture was filtered with a celite pad 545, and then concentrated under a reduced pressure of 40 mmHg. Then, the residues were added with 18 mL of purified water, and subjected to crystallization while stirring for 3 hours at 0°C. Then, the crystals thus formed were filtered, and washed with 10 mL of purified water. Afterwards, the washed crystals were dried under a reduced pressure of 60 mmHg for 2 hours to obtain 650 mg (34%) of the title compound as a white solid.

Melting point: 171 °C

Comparative Example 5> Synthesis of 4-(4-aminophenyl)-3-morpholinone 10

5 g of 4-(4-nitrophenyl)-3-morpholinone was added to 100 mL of chloroform, and then stirred at 23°C for 30 min under a nitrogen atmosphere. This solution was sequentially added with 11.75 mL of diisopropylethylamine and 9.7 mL of diethylchlorophosphite, and then stirred at 23°C for 12 hours. This solution was sequentially added with 80 mL of methanol and then 80 mL of acetyl chloride at 0°C for 1 hour, and stirred at 50°C for 6 hours (reaction proceeded to 5% or less, as monitored by TLC). Thereafter, the reaction mixture was cooled to room temperature, filtered with a celite pad, and then washed with 40 mL of a mixed solvent of ethanol and water (1: 1(v/volume: volume)). Then, excess ethanol was distilled under a reduced pressure of 40 mmHg until the volume of the reaction mixture was reduced to 18 mL. Then, this solution was stirred at 0°C for 3 hours (crystals were not formed). Again, the resulting solution was distilled under reduced pressure, and then residues were purified by a column using ethyl acetate as a mobile phase to obtain 58 mg (3%) of a white solid.

Melting point: 171 °C

<Comparative Example 6> Synthesis of 4-(4-aminophenyl)-3-morpholinone 11

5 g of 4-(4-nitrophenyl)-3-morpholinone was added to 100 mL of isopropyl alcohol,
and then stirred at 23°C for 30 min. This solution was added with 1 g of active carbon having a pH of 3 ~ 5, and stirred under reflux at 90°C for 30 min. Then, this solution was added with 2.72 mL of hydrazine monohydrate for 30 minutes, and then stirred at 90 °C for 12 hours (reaction proceeded to 30%, as monitored by TLC). Thereafter, the reaction mixture was cooled to 23°C, filtered with a celite pad, and then washed with 40 mL of a mixed solvent of ethanol and water (1: 1 (volume: volume)). Then, excess ethanol was distilled under a reduced pressure of 40 mmHg until the volume of the reaction mixture was reduced to 18 mL. Then, this solution was stirred at 0°C for 3 hours (crystals were not formed). Again, the resulting solution was distilled under reduced pressure, and then residues were purified by a column using ethyl acetate as a mobile phase to obtain 28 mg (15%) of a white solid.

[122] Melting point: 171 °C

[123]

[124] The results of nitro-reduction reactions of Examples 1 to 5 and Comparative Examples 1 to 6 are given in Table 1 below.

[125] [Table 1]
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Reaction progress</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>sodium hydrosulfite</td>
<td>purified water</td>
<td>About 99% based on TLC</td>
<td>93%</td>
</tr>
<tr>
<td>2</td>
<td>sodium hydrosulfite</td>
<td>water/methanol</td>
<td>About 99% based on TLC</td>
<td>90%</td>
</tr>
<tr>
<td>3</td>
<td>sodium hydrosulfite</td>
<td>water/ethanol</td>
<td>About 99% based on TLC</td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td>sodium hydrosulfite</td>
<td>water/tetrahydrofuran</td>
<td>About 99% based on TLC</td>
<td>63%</td>
</tr>
<tr>
<td>5</td>
<td>sodium hydrosulfite</td>
<td>methanol</td>
<td>About 90% based on TLC</td>
<td>60%</td>
</tr>
<tr>
<td>C.</td>
<td>iron phthalocyanine, ferrous</td>
<td>purified water/ethanol</td>
<td>80% based on TLC</td>
<td>42%</td>
</tr>
<tr>
<td>1</td>
<td>sulfate heptahydrate, hydrazine</td>
<td>monohydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td>reduced iron powder, calcium</td>
<td>ethanol, purified water</td>
<td>50% based on TLC</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>chloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td>acetic acid, reduced iron powder,</td>
<td>anhydrous ethanol</td>
<td>95% or more based on TLC</td>
<td>55%</td>
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<td>3</td>
<td>ferric chloride</td>
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<td>C.</td>
<td>Palladium on active carbon</td>
<td>methanol</td>
<td>99% based on TLC</td>
<td>34%</td>
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<tr>
<td>4</td>
<td>(10%), ammonium formate</td>
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<td>C.</td>
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<td>chloroform</td>
<td>5% or less based on TLC</td>
<td>3%</td>
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<td>chlorophosphite</td>
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<td>C.</td>
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<td>isopropyl alcohol</td>
<td>30% based on TLC</td>
<td>15%</td>
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The result of nitro-reduction reaction of Comparative Example 3 is the best among those of nitro-reductions under an iron catalyst, but is problematic in that it is difficult to remove iron oxides, to obtain pure 4-(4-aminophenyl)-3-morpholinone, and thus the synthesis method of 4-(4-aminophenyl)-3-morpholinone of Comparative Example 3 is not suitable as an industrial synthesis method.

The nitro-reduction reaction of Comparative Example 4 is a nitro-reduction reaction under a palladium catalyst. The synthesis method of 4-(4-aminophenyl)-3-morpholinone of Comparative Example 4 is advantageous in that a reaction is completely performed and hydrogen gas is not used, but is problematic in that an excessive amount of harmful ammonia gas is discharged, so the safety of
workers is threatened and environmental pollution is caused, thereby restricting the mass production of 4-(4-aminophenyl)-3-morpholinone. Further, the synthesis method of 4-(4-aminophenyl)-3-morpholinone of Comparative Example 4 is problematic in that it is difficult to obtain pure 4-(4-aminophenyl)-3-morpholinone.

In contrast, the synthesis methods of 4-(4-aminophenyl)-3-morpholinone of Examples 1 to 5 are advantageous in that very cheap sodium hydrosulfite and water (an environmentally friendly solvent) or a water-containing mixed solvent are used, so a crystallization process is performed without complicated appliances and complicated processes, and in that pure 4-(4-aminophenyl)-3-morpholinone can be obtained in the state of white solids.

Although the preferred embodiment of the present invention have been disclosed for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

Industrial Applicability

The method of preparing 4-(4-aminophenyl)-3-morpholinone according to the present invention is economical because a hydrogenation catalyst is not used, and is safe because hydrogen gas is not used to exclude a high-pressure reaction. Thus, in this method, a large-scale nitro-reduction reaction can be stably conducted. Further, this method is economical and environmentally friendly because 4-(4-aminophenyl)-3-morpholinone is crystallized in water immediately after the reaction is finished. Therefore, this method is more economical in terms of equipment extension and production cost, and is safe and environmentally friendly in the process of preparing 4-(4-aminophenyl)-3-morpholinone and rivaroxaban.
Claims

[Claim 1] A method of preparing 4-(4-aminophenyl)-3-morpholinone, comprising the steps of:
   a) adding 4-(4-nitrophenyl)-3-morpholinone in a solvent to prepare a solution; and
   b) reacting sodium hydrosulfite with the solution.

[Claim 2] The method of claim 1, wherein the solvent is at least one selected from the group consisting of water, aliphatic alcohol, tetrahydrofuran, acetone, acetonitrile, dioxane, dimethylsulfoxide, acetic acid, dimethylformamide, N-methylpyrrolidinone, and dimethylacetamide.

[Claim 3] The method of claim 2, wherein the aliphatic alcohol is methanol or ethanol.

[Claim 4] The method of any one of claims 1 to 3, wherein the step b) is carried out by adding sodium hydrosulfite to the solution, and then heating the solution to 40°C to 80°C.

[Claim 5] The method of claim 1, further comprising the steps of:
   c) adding an acid into the reaction solution;
   d) adjusting a pH of the reaction solution with a base; and
   e) cooling the pH-adjusted reaction solution to obtain crystals.

[Claim 6] The method of claim 5, wherein the acid is hydrochloric acid.

[Claim 7] The method of claim 5, wherein the base is sodium hydroxide.

[Claim 8] The method of claim 5, wherein the pH is adjusted to 9 to 10.

[Claim 9] The method of claim 5, wherein the pH-adjusted reaction solution is cooled to -5 to 10°C.

[Claim 10] The method of claim 5, further comprising the step of d2) distilling the pH-adjusted reaction solution, between the step d) and the step e).

[Claim 11] The method of claim 10, wherein the pH-adjusted reaction solution is distilled under reduced pressure of 30 to 50 mmHg.
A. CLASSIFICATION OF SUBJECT MATTER
C07D 265/32(2006.01)i, A61K 31/5375(2006.01)i, A61P 9/00(2006.01)i, A61P 7/02(2006.01)i

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 265/32; A61K 31/5375; A61P 9/00; A61P 7/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: Sodium hydrosulfite, Rivaroxaban, 4-(4-aminophenyl)-3-morpholine, 4-(4-nitrophenyl)-3-morpholine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>IN 274/CHE/2011 (BABU, H.S. et al.) 16 November 2012 See abstract, experiment IV and claims 1 - 5.</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
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  "&" document member of the same patent family

Date of the actual completion of the international search
30 July 2014 (30.07.2014)

Date of mailing of the international search report
30 July 2014 (30.07.2014)

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