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RESEARCH ARTICLE

An Improved Synthesis of (*S*)-5-chloro-*N*-{[2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]oxazolidin-5-yl]methyl} thiophene-2-carboxamide

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Abstract: A new and improved process has been developed for the oral anticoagulant rivaroxaban with 99.9% purity and 57.7% overall yield (three main steps). Formation and control of four observed impurities is described.

Keywords: Anticoagulant, Rivaroxaban, Synthesis, Impurity

Introduction

Rivaroxaban (**1**), chemically (Figure 1) known as 5-chloro-*N*-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide, is a novel, oral, selective direct inhibitor of factor Xa developed by Bayer Healthcare[1,2]. It has been approved by EMEA and FDA for the prevention of venous thromboembolism in adult patients after total hip replacement or total knee replacement surgery[3-6]. Rivaroxaban is available in the market under the brand name Xarelto® as 10mg tablets in Europe and US.

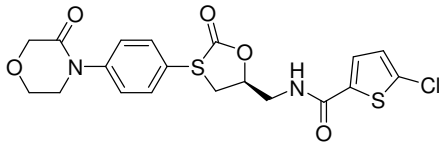


Figure 1. Structure of Rivaroxaban (**1**)

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-*d*6 using Brücker 500 MHz NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The LC-MS and mass spectrum was recorded on a Waters XEVO LC-MS spectrometer. The melting points were determined using the capillary method on a YRT-3 melting point

apparatus, which are uncorrected. HPLC analysis was performed on a Shimadazu SPD-15C instrument with a UV detector using Agilent TC-C18 (250 mm × 4.6 mm, 5 µm) column. Mobile phase A: 0.79 g of ammonium bicarbonate was dissolved in 1000 mL water and added 2.0 mL triethylamine, then adjusted the pH to 8.0 with formic acid. Mobile phase B: acetonitrile. Gradient: 0 min: 80% A, 20% B; 10 min: 80% A, 20% B; 18 min: 68% A, 32% B; 44 min: 34% A, 66% B; 50 min: 34% A, 66% B; 50.1 min: 80% A, 20% B; 60 min: 80% A, 20% B; UV detection at 250 nm; flow rate: 0.7 mL/min; Column oven temperature: 25 °C. The HPLC analysis data is reported in area % and is not adjusted to weight %. 4-(4-aminophenyl)morpholin-3-one (**4)** was provided from Optimus Drugs Ltd.

*Ethyl N-[4[(3-oxo-4-morpholinyl)phenyl]carbamate (**9**)*

4-(4-Aminophenyl)morpholin-3-one (1.23 kg, 6.40 mol) and K_2CO_3 (1.07 kg, 7.74 mol) were suspended in 6.75 L toluene and 2.05 L water at 0-5 ^oC. To the stirred suspension solution of ethyl chloroformate (0.91 kg, 8.39 mol) in 2.7 L toluene was slowly added at the same temperature and continued stirring for 3 h at room temperatue. Subsequently, the mixture was added 6.75 L water and stirred for 30 min. The precipitant was filtered and washed with 1.5 L water. The crude solid was slurried with ethyl acetate (6.75 L) for 2 h. The product was collected by filtration and dried under vacuum to give **9** as a white solid (1.49 kg, 88.1%) with % purity by HPLC. m. p. 190.3-193.1℃; ^1H NMR ($CDCl_3$) δ: 1.29 (3 H, m), 3.73 (2 H, m), 4.08 (2 H, m), 4.03 (2 H, m), 4.33 (2 H, s), 6.76 (1 H, s), 7.27 (2 H, d, *J*=9.0 Hz), 7.42 (2 H, d, *J*=8.0 Hz).

*(s)-1-Chloro-3-[(4-chloro-E-benzylidene)-amino]-propan-2-ol (**10**)*

Compound **10** was synthesized from (s)-epichlorohydrin according to the reported procedure with minor modification[22]. To a solution of *p*-chlorobenzaldehyde (1.48 kg, 10.53 mol) in 6.0 L methanol was added 1.03 L aq. ammonia (28 wt%, mol) in one portion, the resulting mixture was stirred for 20 min at room temperature then (*s*)-epichlorohydrin (986.0 g, 15.27 mol) was charged in single portion. The reaction mixture was stirred for 12 h then heated to 40 ^oC and continued stirring for 2 h. After cooling to room temperature, 9.0 L water was added and methanol was evaporated under vacuum below 45 ℃. The precipitant was filtered and slurried with 5.0 L petroleum ether. The solid was filtered and then dissolved in 5.0 L dichlormethane. The organic phase was separated and dried with anhydrous Na_2SO_4. The filtrate containing compound **10** was used directly for the preparation of **3.HCl** without isolation.

*4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one hydrogen chloride (**3·HCl**)*

To a suspension of **10** (1.43 kg, 5.41 mol) in 2.25 L CH_2Cl_2, Lithium *t*-butoxide (1.17 kg, 10.42 mol) was added at 5-10 ℃ in three portions. After being stirred for 30 min at room temperature, the above solution containing compound **10** (~8.11 mol) was added over 30 min. The resulting solution was heated to reflux for 12 h then cooled to room temperature, 16.4 L ethanol was added and the pH of the solution was adjusted to 1.0-2.0 using concentrated HCl (1.6 L, mol). The reaction mixture was stirred for 1.5 h at room temperature, and then the solid was filtered and washed with ethanol (1.6×2 L). The filtrate was stored for the reuse of *p*-chlorobanzaldehyde. The wet solid was charged into ethanol (11.0 L), heated to reflux and stirred for 30 min. The resultant mixture was cooled to 25-30 ℃ and stirred for 60 min. The product was filtered, washed with ethanol (1.1×2 L) and dried at 45 ℃ under reduced pressure (400 mmHg) to afford 1.45 Kg (81.8%) of 3·HCl as an off-white solid.

The filtrate containing *p*-chlorobenzaldehyde was added into 25 L water, the organic phase was separated and washed with weter (2.5×2 L). After drying (Na_2S0_4) and evaporation of the solvent, the residue was distilled under reduced pressure to give g *p*-chlorobenzaldehyde (0.77 kg, 92-94 °C/10 torr), which could be reused for the synthesis of compound **10**.

*5-Chlorothiophene-2-carbonyl chloride (**8**)*

5-Chlorothiophene-2-carboxylic acid (0.75 kg, 4.61 mol) was suspended in 2.6 L toluene and heated to 80 ºC. Thionyl chloride (640 mL, 8.81 mol) was added dropwise over a period of 20 minutes at room temperature; the reaction mixture was heated to 120 ºC and stirred for 2 h at the same temperature. The reaction was monitored by TLC (charged one drop of reaction solution in 1 mL methanol) until gas evolution ceases. After removal of the excess thionyl chloride and toluene by evaporation under vacuum, the residue was dissolved in toluene (1.5 L) for the next step.

*Rivaroxaban (**1**)*

3·**HCl** (1.40 kg, 4.27 mol) was dissolved in 4.85 L water and filtered, to the filtrate 6.0 L toluene and Na_2CO_3 (0.56 kg, 5.28 mol) was added at room temperature. The mixture was cooled to 8 to 12 ºC, the above solution of **9** in toluene was then added, and the reaction mixture was stirred for 2 h at room temperature. After completion of reaction, 2.5 L acetone was added and the precipitated solid was filtered and washed with 2 mol/L aq. HCl (7.0 L). Wet solid was dried at 70 °C under reduced pressure (400 mmHg) to afford 1.76 kg of the crude product **1** with 99.0% purity by HPLC. The crude product was charged into acetic acid (7.8 L) and heated to reflux for 15 min. The clear solution was cooled to 15 °C and stirred for 2 h and the precipitated solid was filtered and washed with 1.5 L acetone. The wet solid was dried at 70 °C under reduced pressure (400 mmHg) to furnish 1.49 kg (80.0%) of the final product with 99.9% purity by HPLC.

^{1}H NMR (DMSO) δ: 3.61 (2 H, t, *J*=5.4 Hz), 3.71 (2 H, t, *J*=5.4 Hz), 3.85 (1 H, m), 3.97 (2 H, t, *J*= 4. 5 Hz), 4.19 (3 H, t, *J*=7. 5 Hz), 4.84 (1 H, m), 7.19 (1 H, d, *J*=4.2Hz), 7.40 (2 H, d, *J*=9.0 Hz), 7.57 (2 H, t, *J*=9.0 Hz), 7.69 (1 H, d, *J*= 4.19 Hz), 8.96 (1 H, t, *J*=5.7 Hz).

Many methods have been reported to date for the synthesis of rivaroxaban[7-12]. Most of them share the use of 5-*s*-hydroxymethyl oxazolidione **2** or 5-*s*-aminomethyl oxazolidione (**3**) as key intermediate. However 5-*s*-hydroxymethyl group must be activated as sulfonate then displaced with excess ammonia in sealed vessel[13] or substituted with potential explosive NaN_3 then hydrogenated[14,15] to generate the corresponding aminomethyl group of rivaroxaban. So more efforts have been made on the synthesis of 5-*s*-aminomethyl oxazolidione **3** as key intermediate (Figure 2).

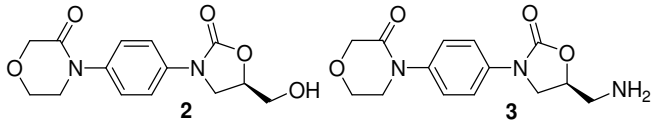
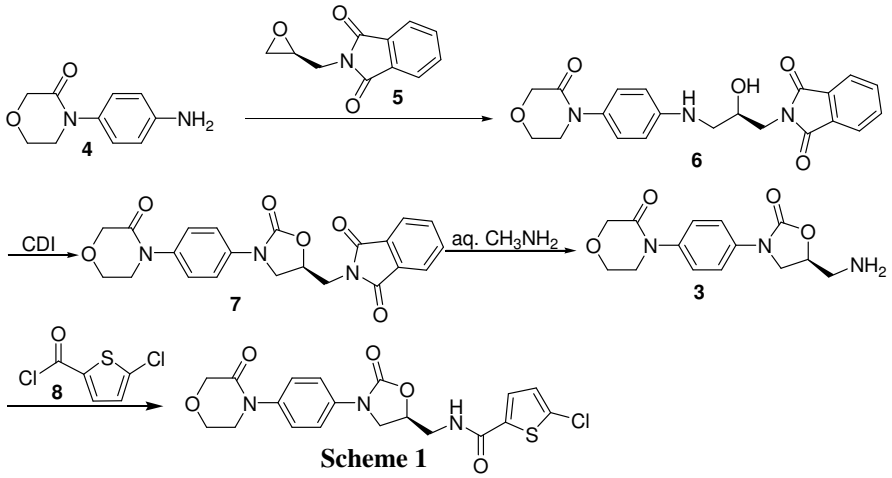


Figure 2. Structure of 5-*s*-hydroxymethyl oxazolidione (**2**) and 5-*s*-aminomethyl oxazolidione (**3**)

The synthesis of rivaroxaban via 4-[4-[5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl] phenyl]-morpholin-3-one was originally reported[2] in WO0147919, the synthetic route shown in Scheme 1, Initially (R)-2-(2-hydroxy-3-{[4-(3-oxomorpholin-4-yl) phenyl)amino]-1*H*-isoindole-1,3-(2*H*)-dione (**6**) is obtained by reaction between 4-(4-amino-phenyl)morpholin-3-one (**4**) and (s)-2-[2-oxiranylmethyl]-1*H*-isoindole -1,3-(2*H*)-dione (**5**) in an ethanol/water mixture, then compound **6** reacted with *N, N*-carbonylimidazole (CDI) in

the presence of a catalytic amount of DMAP using THF as solvent to get compound 2-[[(5S)-2-Oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1, 3-oxazolidin-5-yl] methyl]-1H-isoindole-1, 3(2H)-dione (**7**), then phthalimide protective group of **7** is removed by reaction with aq. CH_3NH_2 to give 5-*s*-aminomethyl oxazolidione (**3**), which was acylated with 5-chlorothiophene-2-carbonyl chloride (**8**) using pyridine as solvent and acid scavenger to afford rivaroxaban (**1**) with HPLC purity of 100% after column chromatography purification. Berwe[16] and Mali[17] *et al.,* disclosed some optimization of reaction conditions described in the WO 0147919 to make this process suitable for scale-up in a commercial plant. Unfortunely the difficulty in reuse of the phthalimide protecting group after hydrazinolysis or aminolysis enable this process less green and cheap. Several other routes have been reported on the synthesis of 5-(*s*)-aminomethyl oxazolidione (**3**), however, there are several drawbacks associated with the process described in these reported patents and papers. These drawbacks include the use of tedious chromatography for purification[18], use of potential explosive[19] or inflambe reagent during the reaction[20] and low yield of the intermediate and final product[21]. Therefore there is a need for improved process of rivaroxaban for industrial application.

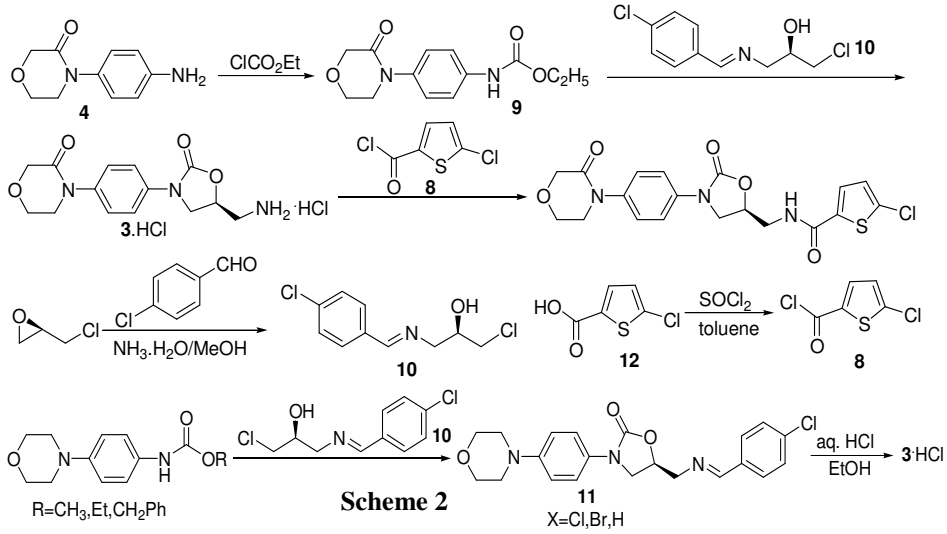


Scheme 1

Results and Discussion

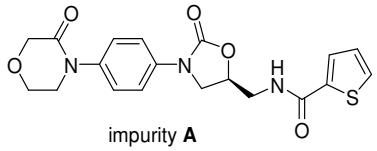
The structure of oxazolidinone is a magic medicinal feature in many medicines including linezolide, rivaroxaban and cethromycin. Inspired by the process to linezolide[22], a similar protocol was taken to building the oxazolidinone moiety. 4-(4-Aminophenyl)morpholin-3-one (**4**) was reacted with ethyl chloroformate in a mixture of toluene and water using K_2CO_3 as acid scavenger to afford carbamate (**9**). Carbamate (**9**) has poor solubility in water and toluene which lead to ready isolation through filtration. As reported that 4-chlorohydrin imine analogue was highly crystalline[23] and choosed in the oxazolidione formation, then the cyclization of carbamate (**9**) with chlorohydrin imine (**10**) proceeded in refluxing CH_2Cl_2 in the presence of lithium *t*-butoxide. The reaction could be complete within 12 h without the formation of significant impurities, however, isolation and purification of the desired imine coumpound 4-[4-[(5S)-5-[[[(4-Chlorophenyl) methylene] amino] methyl]-2-oxo-3-oxazolidinyl] phenyl]-3-morpholine (**11**) were problematic as it is prone to cleave to **3** during the work-ups. To overcome this problem, the isolation of imine **11** from the reaction mixture was not carried out immediately when the reaction finished. Reaction mass was acidified to pH 2–3 using a solution of HCl and ethanol to precipitate **3.HCl**.

As we expected the aminomethyl oxazolidione HCl salt was precipitated from the reaction mixture which was filtrated and dried for the next step. It was noteworthy to mention that the reaction using benzyl carbamate and methyl carbamate gave the required product with 28% and 75% yields, respectively.



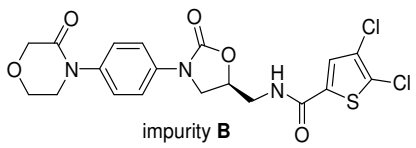
Scheme 2

The compound 4-[4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl]-morpholin-3-one HCl (**3.HCl)** was dissolved in water then subjected to acylation with 5-chlorothiophene-2-carbonyl chloride (prepared from 5-chlorothiophene-2-carbonylic acid **12**) in toluene using Na_2CO_3 as acid binding agent according to the literature method, rivaroxaban (**1**) was precipitated out with a good yield but failed to eliminate dichloro impurity **A** and deschloro impurity **B** after recrystallization (Figure 3). It is obvious that these two impuritie are derived from the raw material 5-chloro-furan-2-carboxylic acid, in which unreacted and excess chlorination byproducts may be present. To our delight the source of these two impurities could be further controlled in starting material by choosing reliable supplier.



impurity **A**

N-[[(5S)-2-Oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-5-oxazolidinyl]methyl]-2-thiophenecarboxamide

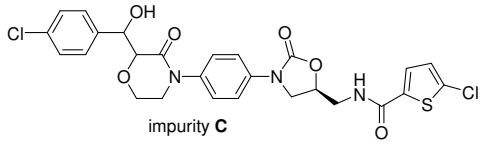


impurity **B**

4,5-Dichloro-*N*-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]-2-thiophenecarboxamide

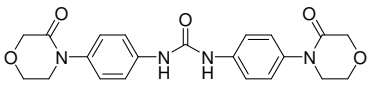
Figure 3. Structure of impurities A & B

The synthetic route shown in Scheme 2 has been used to manufacture several batches of the API rivaroxaban. The HPLC analysis rivaroxaban API indicated the presence of two new impurities at 0.15 and 0.05 area % in several batches of rivaroxaban, identified as 'impurity **C**' and 'impurity **D**' (Figure 4). Further work demonstrated that these two impurities were difficult to purge during the final recrystallization and suggested that upstream control would be important. Impurity **C** and **D** had been isolated from the mother liquor by silica gel column chromatography, and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and ESI HRMS.



impurity **C**

4,5-Dichloro-*N*-[[4- chloro benzyl alchol-(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]-2-thiophenecarboxamide

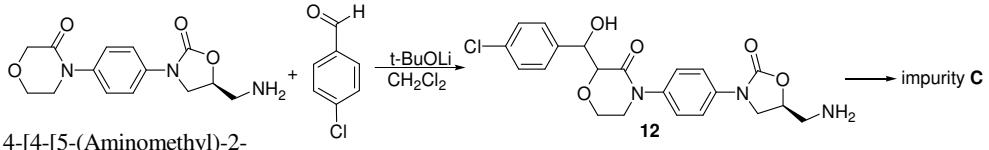


impurity **D**

N,N'-bis[4-(3-oxo-4-morpholinyl) phenyl]-urea

Figure 4. Structure of impurities C & D

The impurity **C** was believed to arise from related impurities in the intermediate **3**.**HCl**. It is generally believed that there are small amounts of *p*-chlorobenzaldehyde in chlorohydrin imine **10**, where the carbonyl group could be attacked by lithium salt of 4-aryl- 3-morpholinone in the cyclization step to give 2-(1-hydroxyalkyl)-3-morpholinone (**12**). Similar nucleophilic attack of aldehyde by 3-morpholinone lithium salt[24] to form penultimate impurity **C** has been noted in the literature report. After the amidation of **12** with 5-chlorothiophene-2-carbonyl chloride to give the impurity **C** as shown in synthetic scheme **3**, the impurity **C** was found to be present at levels greater than 0.15% in the final product. Unfortunately, removal of *p*-chlorobenzaldehyde from the intermediate by slurry wash or recrystallization proved difficult. To our delight, impurity precursors **12** could be removed efficiently after the crude aminomethyloxazolidione **3**.HCl was slurried with ethanol. Proposed formation of impurity **C** during the synthesis of rivaroxaban.

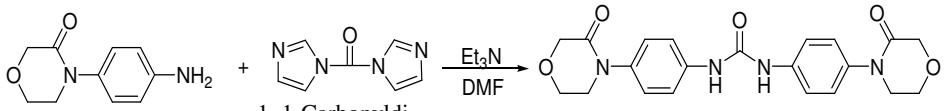


4-[4-[5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl] phenyl]-morpholin-3-one

4-Chloro-benzaldehyde

Scheme 3

The structure of impurity **D** as N,N'-bis[4-(3-oxo-4-morpholinyl)phenyl]-urea was also confirmed by synthesis as shown in scheme **4,** the impurity **D** was easily synthesized from 4-(4-aminophenyl)morpholin-3-one **4** with CDI and matched unambiguously with the fractionated sample of the impurity by ^{1}H NMR and HPLC retention time.



4-(4-Aminophenyl)-3-morpholinone

1, 1-Carbonyldi-imidazole

N,N'-bis[4-(3-oxo-4-morpholinyl)phenyl]urea

Scheme 4

It is obvious that this impurity is generated during the carbamate formation of **9**. The formation of impurity **D** is possible by the aminolysis of carbamate with 4-(4-aminophenyl)morpholin-3-one under the given conditions. It was found that the use of organic base for example Et_3N and pyridine in CH_2Cl_2 increased the formation of this impurity drastically. When the reaction was carried out in a mixture of toluene and water using inorganic base for example Na_2CO_3 and K_2CO_3 as acid scavenger, the content of this impurity could be minimized to 0.5%. This impurity can not be efficiently eliminated by recrystallization in the carbamation and the next cyclization step due to its high crystallizability. Fortunately, this impurity was almost insoluble in water, so we can remove it by filtration from 3.HCl solution in water before the next amidation step.

Conclusion

We have developed a convenient synthesis of rivaroxaban, three steps from 4-(4-aminophenyl)morpholin-3-one with one additional step to prepare chiral intermediate chlorohydrin **10**. Four observed impurities of rivaroxaban were characterized by NMR and MS, the origins of formation impurities **A–D** during the preparation of rivaroxaban were also mapped out. In addition, the method to lower the concentrations of these impurities to levels accepted by ICH is proposed. All the synthesized products were characterized by IR, NMR and Mass spectroscopic data and their melting points were compared with authentic samples.

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