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AN IMPROVED AND PRACTICAL SYNTHESIS OF RIVAROXABAN

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Abstract – Herein we report the development of an improved and practical synthesis of rivaroxaban, an oral anticoagulant drug as a factor Xa inhibitor. The synthesis of rivaroxaban was accomplished by five steps with a total yield of 68.5% on the 220 g scale with a purity of ≥ 99% (single impurity ≤ 0.10%). The epoxy ring-opening reaction was significantly improved with the addition of the magnesium salt. Then, a plausible mechanism was proposed according to our experimental results. Three process-related impurities were identified and controlled by process optimization. The optimized synthesis is expected to offer the technical support for large scale production.

Rivaroxaban **21** (Figure 1) is an anticoagulant and orally active direct factor Xa (FXA) inhibitor developed by Bayer. It is widely used for the treatment and prevention of various thromboembolic diseases, mainly

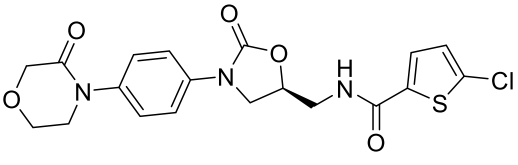
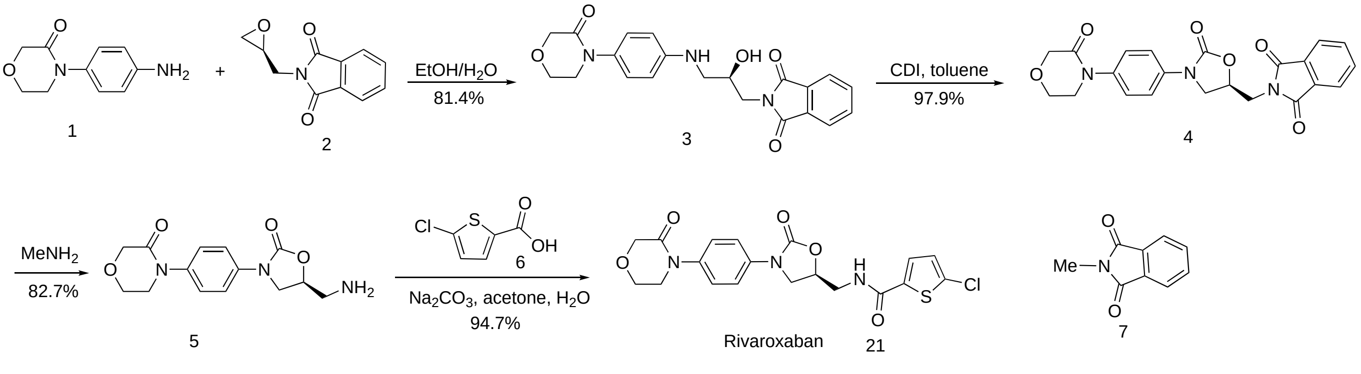

Rivaroxaban 21

Figure 1. Structure of Rivaroxaban

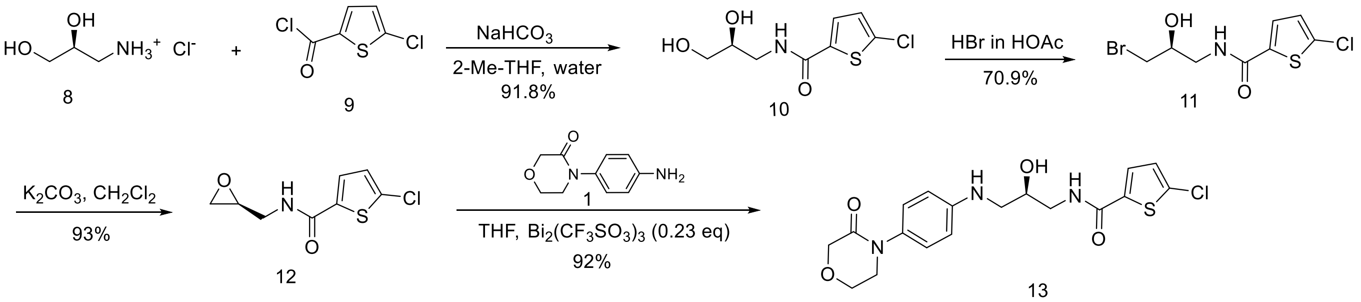
containing cerebral stroke, deep venous thrombosis, angina pectoris, transitory ischemic attack and peripheral arterial occlusive disease.[1,2]

The synthetic research of rivaroxaban has attracted extensive attention, since it was approved in September 2008.[3-9] Among them, the synthetic route disclosed by Bayer AG was the most frequently studied (Scheme 1) in the light of its short reaction steps.[9] However, the by-product *N*-methylphthalimide **7** was generated during the de-protection procedure, which not only increased the waste, but also reduced the atom ecomomy. The approach with the ring-opening of epoxide **12** and (4-aminophenyl)morpholinone **1** was disclosed to prepare amino alcohol compound **13** by Bayer in 2004 (Scheme 2).[10] After the starting material dihydroxyamine **8** was changed to chlorohydroxyamine **15**, the severely corrosive HBr/HOAc solution was eliminated, and the optimized method of epoxide was applied to the synthesis of rivaroxaban (Scheme 3).[11] The use of phthaloyl protection was not required, and the atom economy was improved. However, there are still some problems that are not conducive to industrial production, for example, the release of irritating sulfur dioxide caused by thionyl chloride, the burden of sewage treatment due to the use of *N,N*-dimethylformamide (DMF) in the step of epoxy formation, and the troublesome recovery of imidazole by-product generated from carbonyldiimidazole (CDI) in the last step.

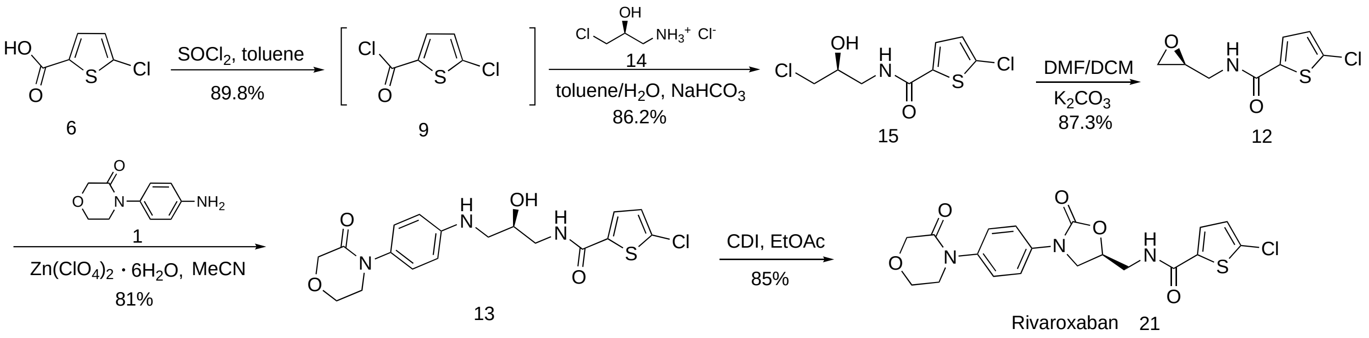
Given the importance and growing demands for drug substance of rivaroxaban, and reported shortcomings in previous synthetic technologies, there is still a need to optimize the process with less by-product, reduced



Scheme 1. The Synthetic Route Disclosed by Bayer AG[9]



Scheme 2. The Epoxy Ring-Opening Disclosed by Bayer AG[10]



Scheme 3. The Modified Epoxy Ring-Opening Approach[11]

cost and higher quality. Herein we report the development of an improved and practical synthesis for rivaroxaban, including the optimization of reaction conditions, the study of epoxy ring-opening mechanism, and the control of process related impurities.

Initially, the synthetic investigation followed the pathway shown in Scheme 3, which included condensation of the thiophene-2-carboxylic acid **6** with the amine hydrochloride **14** via the active acyl chloride **9**, formation of the epoxy intermediate **12**, followed by ring-opening to give intermediate **13** and the final cyclization to afford rivaroxaban.

The thiophene acid **6** could be conveniently converted into the acyl chloride **9** by thionyl chloride, oxalyl chloride or bis(trichloromethyl) carbonate. Since thionyl chloride releases irritating sulfur dioxide and oxalyl chloride has a low boiling point of (62-65 °C), the relatively greener and more stable bis(trichloromethyl) carbonate was selected for further process parameter optimization. Three solvents, dichloromethane (DCM), tetrahydrofuran (THF) and toluene were screened for this acyl chloride conversion (entries 1-3 in Table 1), out of which toluene gave a complete conversion and clean reaction. Then the equivalent of bis(trichloromethyl) carbonate was investigated (entries 4-7 in Table 1) by considering the theoretical equivalent. It was found that with the minimum level of 0.35 equiv. of bis(trichloromethyl) carbonate afforded incomplete conversation (entry 4 in Table 1), while improving the equivalent to 0.4, the yield of **6** was improved to 95% with complete transformation. Finally, the temperature investigation demonstrated that 50 ± 5 °C gave the best results in terms of conversion rate and impurity issues (entries 5, 8 and 9 in Table 1).

The formation of amide **15** with the acyl chloride **9** and the hydrochloride **14** was carried out using common conditions, of which the reaction proceeded by the addition of triethylamine (TEA, 2.5 equiv.) and 4-dimethylaminopyridine (DMAP, 0.05 equiv.) in toluene gave 91% yield in two steps.

Formation of the epoxy intermediate **12** was explored by considering different bases and solvents. Investigations into the effects of solvents proved that acetone gave the highest yield, whereas acetonitrile, ethanol and toluene gave worse results. (entries 1-4 in Table 2). Based on the screening results of several

Table 1. Optimization of Conversion of Acid **6** to Acyl Chloride **9**

Entry	Solvent	Bis(trichloromethyl) carbonate Equiv.	Temp. (°C)	Conversion of acid 6 (by TLC)
1	dichloromethane	0.50	50 ± 5	≥95%, a lot of small unknown impurities
2	tetrahydrofuran	0.50	50 ± 5	60-70%, brown solution
3	toluene	0.50	50 ± 5	≥95%, and clean reaction
4	toluene	0.35	50 ± 5	80-90%
5	toluene	0.40	50 ± 5	≥95%, and clean reaction
6	toluene	0.50	50 ± 5	≥95%
7	toluene	0.60	50 ± 5	≥95%
8	toluene	0.40	35 ± 5	70-80%
9	toluene	0.40	65 ± 5	black reaction mixture

General procedure: Compound **6** (1.0 g, 6 mmol) was added into the solvent (10 mL), followed by the addition of bis(trichloromethyl) carbonate (0.35-0.60 equiv.) and DMF (0.1 equiv.). The mixture was heated at 35-65 °C for 12-16 h. Then reaction mixture (0.5 mL) was quenched into the cold methylamine solution in ethanol with shaking for 5 min, and monitored by TLC to check the conversion and impurity.

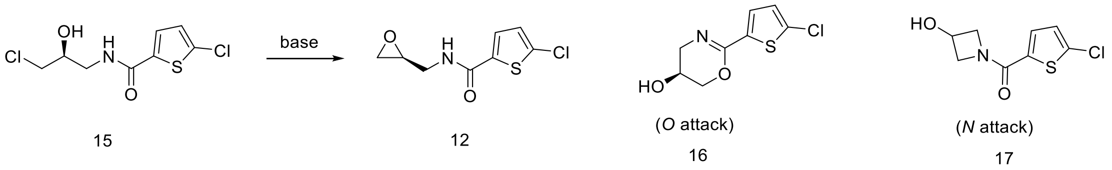
Table 2. Optimization of Formation of Epoxy **12**

Entry	Solvent	Base	Equiv.	Tempt. (°C)	Conversion (by TLC)	Yield
1	acetone	K_2CO_3	1.5	35 ± 5	≥95%	85.5%
2	toluene	K_2CO_3	1.5	35 ± 5	≥95%	65.7%
3	acetonitrile	K_2CO_3	1.5	35 ± 5	≥95%	80.5%
4	ethanol	K_2CO_3	1.5	35 ± 5	≥95%	61.5%
5	acetone	NaOH	1.5	35 ± 5	≥95%, a lot of small unkown impurities	/
6	acetone	$NaHCO_3$	1.5	35 ± 5	≤10%	/
7	acetone	$KHCO_3$	1.5	35 ± 5	≥95%, a lot of small unkown impurities	/
8	acetone	NEt_3	1.5	35 ± 5	≤10%	/
9	acetone	K_2CO_3	1.85	35 ± 5	≥95%	92.5%
10	acetone	K_2CO_3	1.10	35 ± 5	40-50%	/
11	acetone	K_2CO_3	2.00	35 ± 5	≥95%	89.5%
12	acetone	K_2CO_3	1.85	25 ± 5	70-80%	/
13	acetone	K_2CO_3	1.85	55 ± 5	≥95%	72.5%

General procedure: Compound **15** (5.0 g, 0.02 mol) was added into the solvent (50 ml), followed by the addition of base. Then the mixture was stirred at room temperature or under heating for 12-15 h. The reaction mixture was monitored by TLC to check the conversion and impurity. The yield was calculated by the isolation of product with silica gel column purification. "/": The epoxy **12** was not isolated, no yield data.

common bases, such as K_2CO_3, NaOH, $NaHCO_3$, $KHCO_3$ and TEA, K_2CO_3 was selected for this transformation (entries 1, 5-8 in Table 2). Further studies on the amount of base and the reaction temperature indicated that (entries 1, 9-13 in Table 2), the complete conversion and highest yield were observed with 1.85 equiv. base at 35 ± 5 °C (entry 9 in Table 2).

It is worth mentioning that, an obvious impurity was produced in a level of 10-15% at 50-60 °C. The mass spectrum and ^{1}H-NMR analysis of this separated impurity showed the same molecular weight as the epoxy **12**, so its structure was speculated to be oxazinol **16** or amide **17** (Scheme 4). In order to identify the accurate structure, the impurity marker of amide **17** was prepared with azetidinol and acyl chloride **9**. The ^{1}H-NMR spectrum of amide **17** confirmed that it was inconsistent with the separated impurity. Therefore, this major impurity was identified to be oxazinol **16**. It is intriguing to note that, the temperature was critical for the control of this impurity **16**. When the reaction was run at lower than 40 °C, the generated impurities **16** and **17** were less than 1.0% and 0.2% respectively in the reaction mixture, then after the work-up and separation procedures, both of them were reduced to be less than 0.10%. Then, using the optimized process conditions, the reaction was carried out on a 20-gram scale in 88% yield by crystallization.



Scheme 4. The Impurity Formation in Epoxy Step

The ring-opening of epoxides with various amines have been thoroughly studied for many years,[12-14] but this reaction did not always proceed smoothly or even failed in the cases of substrates with weak reactivity and huge steric hindrance. Charging excess amount of amine or epoxy, or elevating temperature were frequently employed to promote the transformation, however, these measures are not economic or resulted in undesired side reactions. Considering the weak reactivity of the aniline **1**, the reaction would probably not go well if common conditions were applied. Indeed, most of the starting material remained when *t*-BuONa, K_2CO_3 or triethylamine were used (entries 1-4 in Table 3).

Many studies have confirmed that the ring opening of epoxy could be satisfactorily promoted by various lithium or magnesium reagent, such as LiOH, LiBr, $LiClO_4$, $MgCl_2$ and $Mg(t\text{-}BuO)_2$. Therefore, several lithium and magnesium salts or bases were tried. Based on the result of entry 6 in Table 3, the complete conversion was only achieved in the presence of magnesium trifluoromethanesulfonate and magnesium perchlorate, which was consistent with the results in the patent. The magnesium trifluoromethanesulfonate was preferred considering the much better stability than magnesium perchlorate.

Table 3. Screening Result of Additives in Ring-opening Reaction

Entry	Base or salt	Conversion	Entry	Base or salt	Conversion (by TLC)
1	*t*-BuONa	≤30%	7	$Mg(ClO_4)_2$	≥95%
2	K_2CO_3	≤10%	8	$MgCl_2$	≤30%
3	NEt_3	≤30%	9	$MgSO_4$	≤10%
4	LiCl	≤30%	10	$MgCO_3$	≤10%
5	$LiClO_4$	≤50%	11	Mg(*t*-BuO)$_2$	≤30%
6	$Mg(OSO_2CF_3)_2$	≥95%	12	$Mg(OH)_2$	≤10%

General procedure: Compound **12** (1.0 g, 4.6 mmol) and compound (**1**) (0.88 g, 4.6 mmol, 1.0 equiv.) were added into MeCN (20 mL), followed by the addition of salt or base (1.0 equiv.). The mixture was heated at 30 ± 5 °C for 8-10 h. Then reaction mixture was monitored by TLC to check the conversion and impurity.

The plausible ring-opening pathway of epoxide **12** was proposed by referring to the reported explanations of similar epoxy aminolysis catalyzed by metal salts,[15,16] and a combination of the experimental results mentioned above. The catalytic mechanism could be explained that the coordination of the oxirane oxygen atom with the magnesium cation induced the polarization of the oxirane C−C bond, increased the electrophilicity of adjacent carbon atoms, and thereby greatly facilitated the attack by aniline substrate (Figure 2).

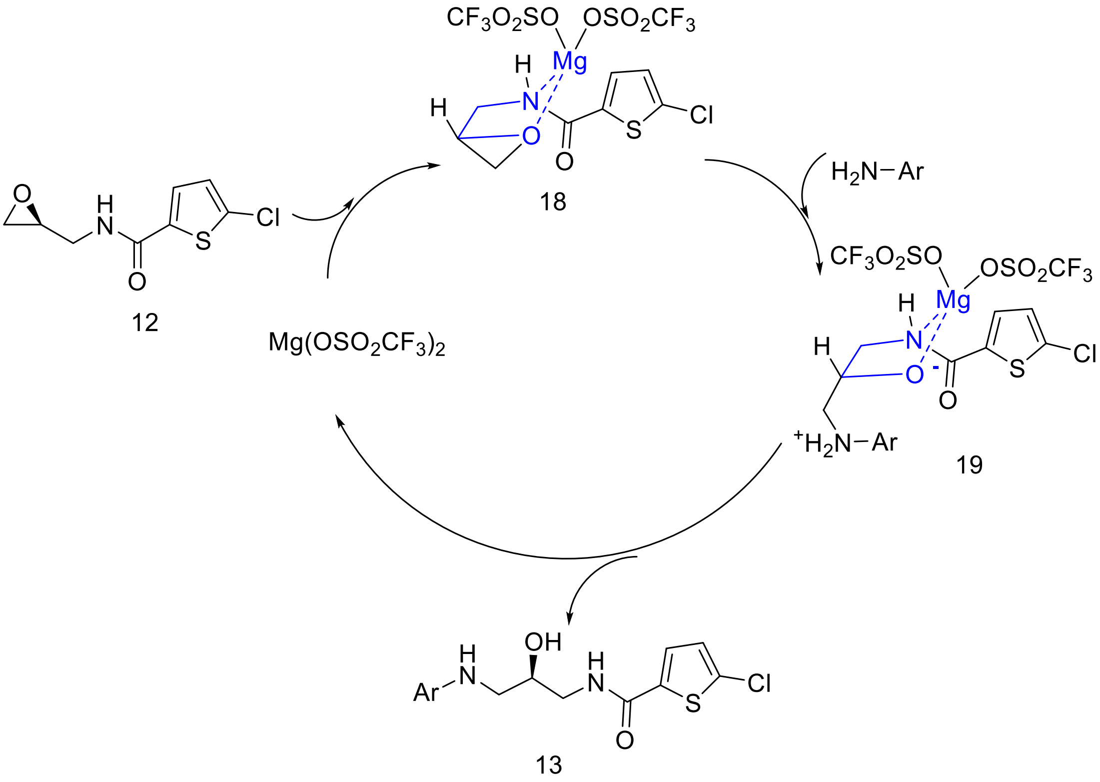


Figure 2. Proposed Mechanism of the Epoxide 12 Aminolysis

After selecting the magnesium trifluoromethanesulfonate as the catalyst of epoxy aminolysis reaction, other factors, such the solvents, equivalent and temperature were further optimized. The screening results of solvents demonstrated that acetonitrile still was the best choice (entries 1-4 in Table 4). While the equivalent of magnesium trifluoromethanesulfonate was decreased to 0.35 equiv. from original 1.0 equiv., a complete conversion was still achieved. A further decrease to 0.2 equiv. led to incomplete conversion. Therefore, 0.35 equiv. was decided to be the optimal level (entries 5-8 in Table 4). The temperature investigation confirmed that a range of 30 ± 5 °C gave the complete conversion and clean reaction (entries 9-11 in Table 4). Finally, one 260-gram scale experiment was successfully completed by employing the optimized process parameters with a yield of around 90% after crystallization.

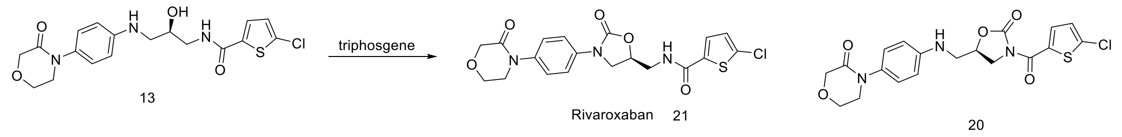
Table 4. Process Parameter Optimization of Ring-Opening

Entry	Solvent	Equiv. of $Mg(OTf)_2$	Tempt. (°C)	Conversion (by TLC)
1	MeCN	1.0	30 ± 5	≥95%
2	toluene	1.0	30 ± 5	≤30%
3	acetone	1.0	30 ± 5	80-90%
4	THF	1.0	30 ± 5	50-60%
5	MeCN	0.20	30 ± 5	80-90%
6	MeCN	0.35	30 ± 5	≥95%
7	MeCN	0.50	30 ± 5	≥95%
8	MeCN	1.0	30 ± 5	≥95%
9	MeCN	0.35	5 ± 5	50-60%
10	MeCN	0.35	30 ± 5	≥95%
11	MeCN	0.35	55 ± 5	≥95%; Not clean

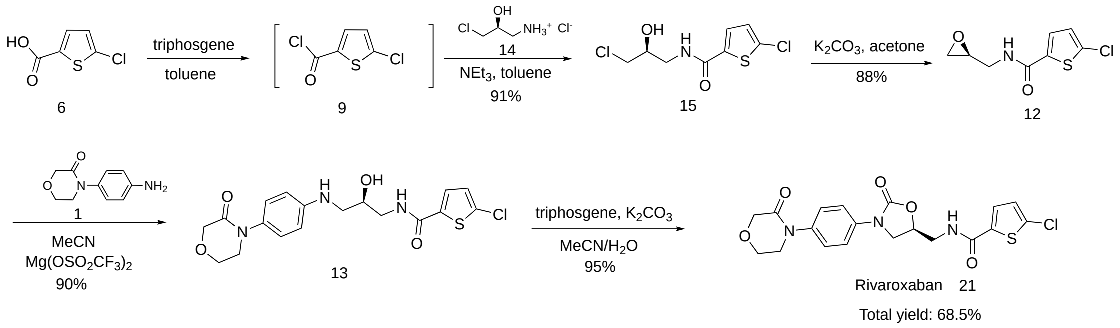
Compound **12** (1.0 g, 4.6 mmol) and compound (1) (0.88 g, 4.6 mmol, 1.0 equiv.) were added into solvent (20 mL), followed by the addition of magnesium trifluoromethanesulfonate. The mixture was stirred under heating for 8-10 h. Then reaction mixture was monitored by TLC to check the conversion and impurity.

For the final cyclization step of making rivaroxaban, the results of our preliminary experiments with N,N'-carbonyldiimidazole (CDI) demonstrated that one major regioisomer **20** was formed in a level of 5-10% (Scheme 5), and the alcohol **13** could not be consumed completely. In addition, it was troublesome to recover imidazole, by-product of CDI, due to its great polarity and high solubility in water. Therefore, bis(trichloromethyl) carbonate was preferred and attempted as an alternative reagent. The initial trials confirmed this cyclization proceeded smoothly with a yield of 85%, and the regioisomer was nearly not observed. Through the further screening of process parameters, a mixture of MeCN and H_2O (2/1, w/w) was found to be the optimal solvent system, and charging of 0.5 equiv. bis(trichloromethyl) carbonate and

1.8 equiv. K_2CO_3 afforded rivaroxaban in 95% yield with a high purity of 99.7% by HPLC (a/a, any single impurity < 0.10%).



Scheme 5. The Cyclization Impurity Structure



Scheme 6. The Final Synthetic Scheme of Rivaroxaban

The synthesis of rivaroxaban was accomplished by five chemical reactions with a total yield of 68.5% (Scheme 6). The reaction conditions of ring-opening of epoxy **12** were thoroughly studied, and the promotion mechanism by magnesium salt was also discussed. Bis(trichloromethyl) carbonate was used twice in this synthesis to prepare acyl chloride and to form oxazolinone respectively. This synthesis development is also in compliance with our strategy of “control from the root design” in organic process research and development: design and control from the very beginning, the R&D stage, of a project with the principles of Green & Sustainable Chemistry for industrial application.

EXPERIMENTAL

All commercially available materials and solvents were used directly without further purification. 4-(4-Aminophenyl)morpholin-3-one was ordered from Zhejiang Regen Chemical Co., Ltd. (*S*)-1-Amino-3-chloropropan-2-ol was provided by Topharman Shandong Co., Ltd. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker 400 MHz or 100 MHz) instrument with TMS as internal standard. Mass spectra (ESI-HRMS) was measured on a Waters Xevo G2-XS QTOF equipment. HPLC purity was detected on ThermoFisher U3000 system or equivalent. IR spectroscopy was recorded by Thermo Nicolet iS5 (KBr pellet).

3-Chloro-2-hydroxyamide (15). 5-Chlorothiophene-2-carboxylic acid **6** (225 g, 1.38 mol, 1.0 eq.) and DMF (10.2 g, 0.14 mol) were added into toluene (1.1 L), followed by the addition of bis(trichloromethyl) carbonate (163.2 g, 0.55 mol) in one portion at 20 °C. Then the heating was started and the mixture was stirred at 50 ± 5 ^oC for 12-16 h, and then the reaction was monitored by TLC (the reaction solution was quenched into the cold $MeNH_2$ solution in EtOH with shaking for 5 min). After the reaction was completed, the reaction solution was concentrated at 45 ± 5 ^oC under reduced pressure to afford acyl chloride **9** as yellow oil, which was used in the next step.

The hydrochloride **14** (201.5 g, 1.38 mol, 1.0 eq.) and DMAP (8.4 g, 0.07 mol, 0.05 eq.) were added into toluene (985 mL), followed by the addition of NEt_3 (349.1 g, 3.45 mol, 2.5 eq.) with stirring in period of 1 h at 15-20 °C. After the mixture was cooled to 5 ± 5 °C, the acyl chloride **9** (dissolved in 225 mL of toluene) was added in a period of 1 h. The resulting mixture was then stirred at 5 ± 5 °C for 2 h, and then slowly warmed to 15-20 °C, and the stirring was continued until the reaction was completed (around 10 h). The desired amide **15** and triethylamine hydrochloride were both precipitated. Then H_2O (500 mL) was added and the resulted mixture was stirred for 2 h to dissolve the triethylamine hydrochloride. The suspension was collected by suction, drying in hot air oven at 55 ± 5 °C to afford the compound of amide **15** as an off-white solid (320.2 g) in 91% yield. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.65 (t, J = 5.7 Hz, 1H), 7.68 (d, J = 4.0 Hz, 1H), 7.18 (d, J = 4.0 Hz, 1H), 5.43 (d, J = 5.3 Hz, 1H), 3.90–3.80 (m, 1H), 3.64 (dd, J = 11.2, 4.4 Hz, 1H), 3.54 (dd, J = 11.2, 5.8 Hz, 1H), 3.43–3.34 (m, 1H), 3.28–3.18 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160.90, 139.52, 133.38, 128.58, 128.47, 69.53, 48.34, 43.48. ESI-HRMS *m/z*: $[M + H]^+$, calcd for $C_8H_8Cl_2NO_2S$ 253.9804; found 253.9813. IR: 3365.57, 1622.27, 1426.71, 1105.73, 805.34.

Epoxy compound 12

The amide **15** (285.8 g, 1.12 mol, 1.0 eq.) was added to acetone (2.87 L) with stirring at 20-30 °C to give a clear solution. Then potassium carbonate (286.9 g, 2.08 mol, 1.85 eq.) was added into the solution in one portion, then the mixture was stirred at 35 ± 5 °C for 12-15 h until the reaction was completed. Then the reaction mixture was cooled to 15-25 °C, and stirred for 2 h. The solid in mixture was filtered (inorganic salts), and the filtrate was concentrated under vacuum at 30-40 °C to around 300-350 mL. After cooled to 15-25 °C, H_2O (1.43 L) was added into the residual by additional funnel in a period of 2 h at 15-25 °C. The resulting mixture was stirred at 20 ± 5 °C for 4 h. The precipitated solid was filtered, and dried at 55-60 °C for 16 h to give 214.8 g of epoxy **12** an off-white solid in 88% yield. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 7.68 (d, J = 4.1 Hz, 1H), 7.19 (d, J = 4.0 Hz, 1H), 3.52 (dt, J = 14.6, 4.3 Hz, 1H), 3.27 (dt, J = 14.3, 5.4 Hz, 1H), 3.14–3.02 (m, 1H), 2.82–2.68 (m, 1H), 2.56 (dd, J = 5.0, 2.6 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160.85, 139.26, 133.53, 128.64, 128.56, 50.54, 45.30, 41.55. ESI-HRMS *m/z*: $[M + H]^+$, calcd for $C_8H_9ClNO_2S^+$ 218.0043; found 218.0040. IR: 3298.11, 1617.81, 1557.09, 1427.53, 1330.88, 746.23.

Amino alcohol 13

4-(4-Aminophenyl)morpholinone **1** (260 g, 1.35 mol, 1.0 eq.) and epoxy **12** (324.3 g, 1.49 mol, 1.1 eq.) were added into MeCN (2.6 L) with stirring at 20-30 °C. Then magnesium trifluoromethanesulfonate

(152.3 g, 0.47 mol, 0.35 eq.) was added in one portion, and the resulted mixture was stirred for 10 h at 30 ± 5 °C. The reaction mixture was concentrated under vacuum to a small volume (around 1 L) at 30 ± 5 °C, and then H_2O (1.82 L) was added into the mixture in an additional funnel in a period of 2 h at 10-20 °C. The resulting mixture was stirred at 5 ± 5 °C for another 3 h. The precipitated solid was filtered, and then transferred into a solvent mixture of MeCN and H_2O (1:5, v/v, 3.12 L). After stirring at 60 ± 5 °C for 2 h, the mixture was cooled to 0-10 °C and stirred for 2 h. The precipitated solid was filtered, and dried at 55-65 °C for 16 h to give 499.1 g of amino alcohol **13** as an off-white solid in 90% yield. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.61 (s, 1H), 7.68 (t, J = 5.7 Hz, 1H), 7.68 (d, J = 4.1 Hz, 1H), 7.18 (d, J = 4.0 Hz, 1H), 7.02 (d, J = 8.7 Hz, 1H), 6.59 (d, J = 8.8 Hz, 1H), 5.64 (t, J = 5.9 Hz, 1H), 5.08 (d, J = 5.1 Hz, 1H), 4.13 (s, 1H), 4.00–3.89 (m, 2H), 3.87–3.74 (m, 1H), 3.66–3.56 (m, 2H), 3.41–3.33 (m, 1H), 3.30–3.19 (m, 1H), 3.11 (dt, J = 11.7, 5.9 Hz, 1H), 3.03–2.92 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 165.76, 160.37, 147.44, 139.23, 132.73, 130.28, 128.00, 127.94, 126.47, 111.93, 67.81, 67.75, 63.56, 49.61, 47.40, 43.87. ESI-HRMS m/z: $[M + H]^+$, calcd for $C_{18}H_{21}ClN_3O_4S^+$ 410.0941; found 410.0948. IR: 3365.81, 1634.02, 1518.55, 1427.21, 1123.89, 808.04, 549.51.

Rivaroxaban

Potassium carbonate (133.3 g, 0.964 mol, 1.8 eq.) was charged into H_2O (550 mL) and MeCN (1.39 L) with stirring until all the solid was completely dissolved. Then amino alcohol **13** (220 g, 0.537 mol, 1 eq.) was added in one portion with stirring. After the mixture was cooled to 5 ± 5 °C, bis(trichloromethyl) carbonate (79.6 g, 0.268 mol, 0.5 eq.) was charged in five portions during 1 h at 5 ± 5 °C. Then the internal temperature was warmed 35 ± 5 °C in 2 h, and the mixture stirred for another 6-8 h until the reaction was complete. The reaction mixture was cooled to 10 ± 5 °C and stirred for another 6 h, the precipitated solid was filtered, and then transferred into a solvent mixture of H_2O (500 mL) and MeCN (633 mL). The resulting suspension was slurried at 50 ± 5 °C for 3 h. After the mixture was cooled to 5 ± 5 °C, and stirred for 4 h, the solid was filtered, and dried at 55-65 °C for 16 h to give rivaroxaban (222.3 g) as a white solid in 95% yield. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.98 (t, J = 5.8 Hz, 1H), 7.69 (d, J = 4.1 Hz, 1H), 7.56 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 9.0 Hz, 2H), 7.19 (d, J = 4.0 Hz, 2H), 4.84 (dq, J = 11.2, 5.6 Hz, 2H), 4.25–4.13 (m, 3H), 4.02–3.93 (m, 2H), 3.85 (dd, J = 9.1, 6.1 Hz, 2H), 3.74–3.66 (m, 2H), 3.61 (t, J = 5.6 Hz, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 166.44, 161.28, 154.58, 138.94, 137.54, 136.97, 133.74, 128.92, 128.65, 126.43, 118.81, 71.81, 68.21, 63.95, 49.49, 47.91, 42.70. ESI-HRMS m/z: $[M + H]^+$, calcd for $C_{19}H_{19}ClN_3O_5S^+$ 436.0743; found 436.0742. IR: 3354.74, 1737.15, 1668.29, 1517.43, 1428.40, 991.57.

Regioisomer of rivaroxaban 20

The amino alcohol **13** (5 g, 12.2 mmol, 1 eq.), DMAP (0.15 g, 1.2 mmol, 0.1 eq.) and CDI (2.37 g, 14.6 mmol, 1.2 eq.) were added into DMF (50 mL). After the mixture was stirred at 90-100 °C for 4 h, it was concentrated at 70-80 °C under reduced pressure to remove most of the DMF. Toluene (50 mL) and H_2O

(50 mL) were added, and the precipitated solid was filtered to afford the crude product. The pure isomer **20** (2.0 g) was obtained by silica gel column purification (CH_2Cl_2 / MeOH = 200:1, v/v) in 37.7% yield. ^{1}H-NMR (400 MHz, DMSO-*d*$_6$): *δ* 7.76 (d, *J* = 4.2 Hz, 1H), 7.24 (d, *J* = 4.2 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.09 (t, *J* = 6.3 Hz, 1H), 4.86 (dd, *J* = 6.9, 5.3 Hz, 1H), 4.24–4.08 (m, 3H), 3.96–3.90 (m, 2H), 3.90–3.79 (m, 1H), 3.66–3.56 (m, 2H), 3.57–3.39 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-*d*$_6$): *δ* 165.77, 160.30, 152.46, 146.98, 136.30, 135.37, 133.60, 130.78, 127.68, 126.52, 112.05, 73.32, 67.75, 63.56, 49.57, 46.64, 45.28. ESI-HRMS *m/z*: $[M + H]^+$, calcd for $C_{19}H_{19}ClN_3O_5S^+$ 436.0743; found 436.0741. IR: 3424.27, 3318.90, 1768.15, 1655.50, 1526.39, 1420.46, 1323.61, 1192.23, 824.18.

Oxazinol 16

Sodium hydroxide (1.2 g, 30 mmol, 1.5 eq.) was added into MeOH (25 mL) and H_2O (25 mL), then the amide **15** (5.0 g, 20 mmol, 1.0 eq.) was charged to give a clear solution. After the reaction mixture was stirred at 35-45 °C stirred for 6-7 h, the starting material was consumed completely. Then the mixture was concentrated at 35-45 °C under vacuum to give a yellow oil. CH_2Cl_2 (50 mL) was added and the resulting solution was washed with H_2O (25 mL). The separated organic layer was concentrated under vacuum, and then the residual was purified by silica gel column purification (PE: EtOAc = 10:1, v/v) to afford oxazinol **16** (3.0 g) as an off-white solid in 70.1% yield. ^{1}H-NMR (400 MHz, DMSO-*d*$_6$): *δ* 7.40 (d, *J* = 4.0 Hz, 1H), 7.19 (d, *J* = 4.0 Hz, 1 H), 5.02 (t, *J* = 5.6 Hz, 1 H), 4.79–4.68 (m, 1 H), 3.92 (dd, *J* = 14.8, 9.9 Hz, 1H), 3.68 (dd, *J* = 14.8, 7.5 Hz, 1H), 3.60 (ddd, *J* = 12.1, 5.4, 3.7 Hz, 1H), 3.48 (dt, *J* = 12.1, 5.3 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-*d*$_6$): *δ* 157.88, 132.73, 130.26, 129.68, 128.43, 81.51, 62.65, 56.32. ESI-HRMS *m/z*: $[M + H]^+$, calcd for $C_8H_9ClNO_2S^+$ 218.0043; found 218.0045. IR: 3261.28, 1644.59, 1438.87, 1048.22, 827.41.

Azetidinol amide 17

5-Chlorothiophene-2-carboxylic acid **6** (2.5 g, 15.4 mmol, 1.0 eq.), DMF (50 mg, 0.68 mmol, 0.04 eq.), and bis(trichloromethyl) carbonate (1.75 g, 5.9 mmol, 0.38 eq.) were charged into toluene (28.6 mL). The mixture was stirred at 50-60 °C for 4 h to give a clear solution. The reaction mixture was concentrated under vacuum to give a yellow oil. Then toluene (28.6 mL) was charged to get a clear solution of acyl chloride **9**. Azetidin-3-ol hydrochloride (1.73 g, 16 mmol, 1.05 eq.) and $NaHCO_3$ (2.8 g, 33 mmol, 2.2 eq.) were added into H_2O (25 mL) and toluene (28.6 mL). After the mixture was stirred for 30 min at 0-10 °C, the above solution of acyl chloride in toluene was added dropwise over a period of 1 h at 0-10 °C. Then mixture was stirred for 2 h at 0-10 °C. The stirring was stopped, and after standing for 10 min, the organic layer was separated. The toluene was removed by concentration in vacuum to give a yellow oil. The oil was then purified by silica gel column (PE: EtOAc = 10:1, v/v) to afford azetidinol amide **17** (2.2 g) as an off-white solid in 65.7% yield.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): *δ* 7.35 (d, *J* = 4.1 Hz, 1H), 7.19 (d, *J* = 4.1 Hz, 1H), 5.83 (t, *J* = 6.4 Hz, 1H), 4.63 (s, 1H), 4.59–4.49 (m, 1H), 4.21 (d, *J* = 26.4 Hz, 2H), 3.78 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-

d_6): δ 160.98, 137.32, 133.75, 130.43, 128.71, 62.70, 61.19, 59.38. ESI-HRMS *m/z*: $[M + H]^+$, calcd for $C_8H_9ClNO_2S^+$ 218.0043; found 218.0046. IR: 3315.46, 1584.14, 1481.21, 1111.31, 725.64.

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