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FACILE METHODS FOR PREPARATION OF THIAZOLOPYRIDINE AND TETRAHYDROTHIAZOLOPYRIDINE DERIVATIVES

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Abstract –The improved routes to prepare tetrahydrothiazolo[5,4-*c*]-pyridine-2-carboxylic acid lithium salts (**2** and **3**) were developed. **Route A** is consisted of the improved preparation of thiazolopyridine intermediates, and **Route B** is applicable for a large scale synthesis of tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxylic acid derivatives. The methods we developed may serve as facile means for preparing thiazolopyridine and tetrahydrothiazolopyridine derivatives.

INTRODUCTION

Recently we reported a potent factor Xa (fXa) inhibitor (**1**)**,** which is expected to function as an orally effective anticoagulant having a tetrahydrothiazolo[5,4-*c*]pyridine ring.[1] In the X-Ray crystal analysis of the complex of **1** and des-Gla fXa, we confirmed the existence of an intramolecular S-O close contact in the 2-carbamoylthiazole moiety of **1**.[2] It is known that an intramolecular S-O close contact plays an important role on the mechanism of several biological effects.[3] The intermediates (**2**) and (**3**) of **1** are interesting building blocks, because not only do they have a bifunctional group, an aliphatic amine and a

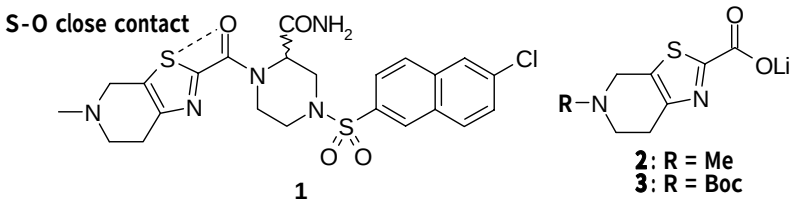
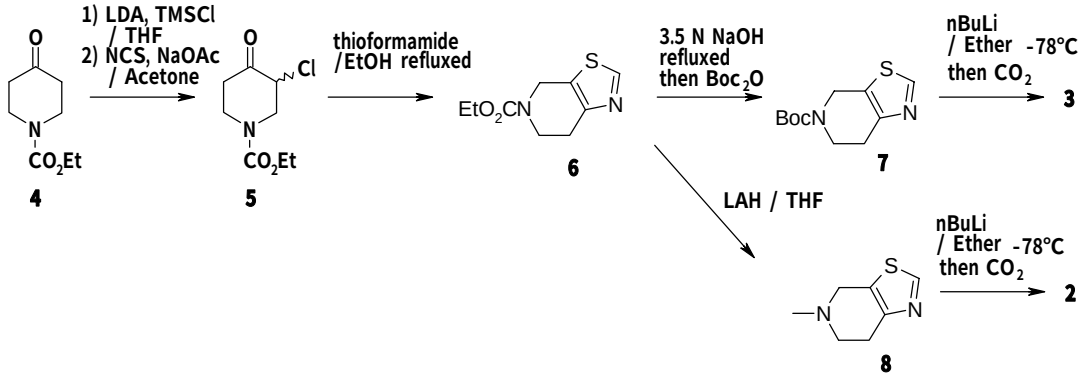


Figure 1: Structures of **1** containing an S-O close contact and key intermediates (**2**) and (**3**).

carboxylic acid, which are applicable for synthesis of various compounds, but they also contain an intramolecular S-O close contact unit, which restricts the conformation of a compound. In this paper, we report the efficient methods for preparing **2** and **3**.

RESULTS AND DISCUSSION

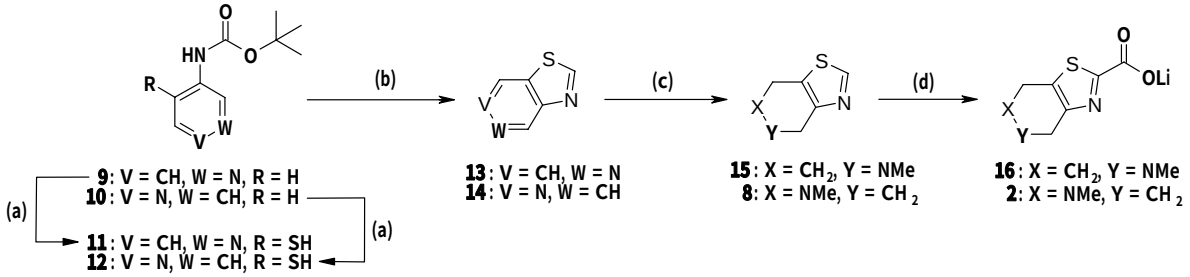
In our early research on fXa inhibitors, we had used a general route illustrated in Scheme 1 to prepare **2** and **3**.[2, 3] This consisted of the cyclization of α-chloro-ketone (**5**)[4] with thioformamide to construct the fused thiazole ring, followed by the exchange of protecting groups and the introduction of a carboxyl group by lithiation and bubbling of CO_2. This route has some drawbacks, however, against its practical use for the large scale production. Firstly, in the purification of α-chloro-ketone (**5**), it is difficult to separate **5** from the starting material (**4**) by either distillation or silica gel column chromatography. Secondly, in the preparation of thioformamide from formamide with either P_2S_5 or Lawsson's reagent, there are respective problems exemplified by the dangerous formation of H_2S or the cost performance for the expensive reagent. Thirdly, a number of steps are required for the exchange of protecting groups. To solve these problems, we explored a new synthetic route for **2** and **3**.



Scheme 1: Previous synthetic route for the preparation of **2** and **3**.

One synthetic route (**Route A**), which involves *N*-methylation and reduction of a quaternary pyridinium salt,[2] is shown in Scheme 2. **Route A** has some advantages for the preparation of both thiazolo[5,4-*c*]pyridine and thiazolo[4,5-*c*]pyridine, in which the protecting group is not needed for an amino moiety of the tetrahydrothiazolopyridine ring. However, the methods reported[5] for the preparation of thiazolo[4,5-*c*]pyridine (**13**) and thiazolo[5,4-*c*]pyridine (**14**) have some problems, the requirements of a number of steps and low yields in cyclizations to obtain thiazolopyridines, especially in the [5,4-*c*] type (9-25%). To prepare these thiazolopyridines more conveniently, we selected 3- or 4-*tert*-butoxycarbonylaminopyridine (**9** or **10)** as the starting material because the aminopyridines that are protected by appropriate acyl groups are easily prepared[6] and used for introduction of a functional group

at the adjoining position with lithiation and electrophilic substitution[7]. Reaction of Boc-protected aminopyridines (**9**) and (**10**), *via* their lithiated pyridines, with S_8 as an electrophile reagent and afforded mercapto compounds (**11**) and (**12**). The mercapto compounds (**11**) and (**12**) were respectively cyclized to **13** and **14** in HCO_2H with moderate yields (45-72%). *N*-Methylation and reduction of the resultant quaternary pyridinium salt, followed by introduction of the carboxy group gave the desired 5-methyltetrahydropyridine-2-carboxylic acid lithium salts (**2**) and (**16**) respectively. Each total yield of **16** or **2** from **9** or **10** to was 19% or 14 %.

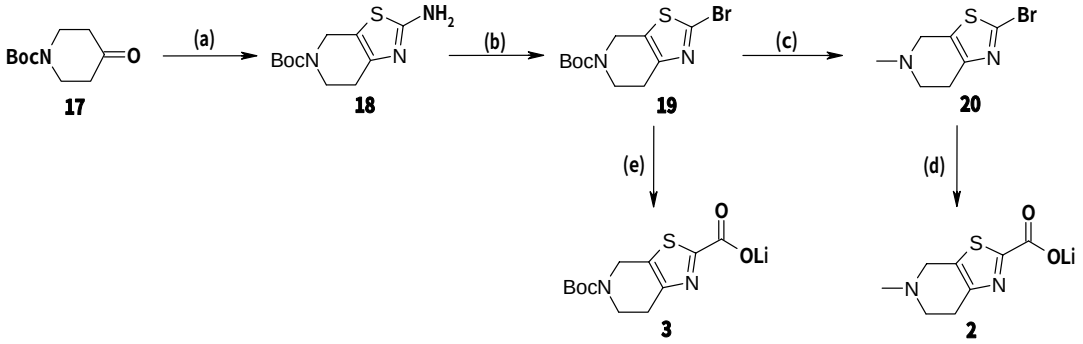


Scheme 2: Improved route for the preparations of tetrahydrothiazolopyridine-2-carboxylic acids (**Route A**).
Reagents and Conditions: (a) *n*-BuLi, S_8 / THF, -78 ~ 0 °C, 34 - 46%; (b) HCO_2H, refluxed, 45 - 72%; (c) i) MeI / DMF, 80 °C, ii) $NaBH_4$ / H_2O, 2 steps 70 - 78%; (d) *n*-BuLi, CO_2 / THF, -78 ~ 0 °C, quant.

On the other hand, we conceived of another alternative strategy for the synthesis of **2** and **3**. Because **Route A** involves a few problems, such as the inadequacy for the Boc derivative (**3**) and the use of HCO_2H, which has a stimulative smell, as the solvent. Alternative improved synthesis (**Route B**) of **2** and **3** is outlined in Scheme 3. Kozikowski's method[8] has been applied to the conversions of **17** to**19**. The enamine formation of **17** followed by the reaction with elemental sulfur and subsequent addition of cyanamide constructed the tetrahydrothiazolo[5,4-*c*]pyridine ring to give **18**, which was easily purified by crystallization to obtain the solid in 63% yield. A substitutive deamination reaction[9] with *t*-BuONO and $CuBr_2$ afforded the 2-bromoderivatives (**19**) in 49% yield, when DMF was employed as the solvent because of the insolubility of **18** against some solvents such as MeCN and THF. Reductive amination after deprotection of the Boc group of **19** gave compound (**20**) in 90% yield. The desired compounds (**2**) and (**3**) were obtained by the halogen-metal exchange reaction and the introduction of carboxylate. In the large scale synthesis of **2**, purification on a silica gel column needed only two steps, deamination and reductive amination, and the total yield was 28%.

In conclusion, we have established improved routes to prepare lithium tetrahydrothiazolo[5,4-*c*]-pyridine-2-carboxylates (**2**) and (**3**) by developing **Route A**, which consisted of the preparation of thiazolopyridine intermediates, and **Route B**, which is applicable for a large scale synthesis of

tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxylic acid derivatives. The methods we developed may serve as the facile means for preparing thiazolopyridine and tetrahydrothiazolopyridine derivatives.



Scheme 3: Improved route for the preparations of tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxylic acids (**Route B**).
Reagents and Conditions: (a) i) pyrrolidine, $TsOH \cdot H_2O$ / cyclohexane refluxed, ii) S_8, cyanamide / MeOH, 63%; (b) *t*-BuONO, $CuBr_2$ / DMF, 50 °C, 49%; (c) i) TFA / CH_2Cl_2, ii) $NaBH(OAc)_3$, Et_3N, AcOH, 36% aq. HCHO / CH_2Cl_2, 2 steps 90%; (d) *n*-BuLi, CO_2 / ether, -78 ~ 0 °C, 99%, (e) *n*-BuLi, CO_2 / ether, -78 °C, 66%, .

EXPERIMENTAL

General. All solvents and reagents were used as acquired from commercial sources without purification. Melting points were determined on a Yanagimoto apparatus and are uncorrected. Column chromatography was performed on Merck silica gel 60 (0.063-0.200 mm). Thin layer chromatography (TLC) was performed on Merck TLC plates pre-coated with silicagel 60 F_{254}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM-EX400 spectrometer, and chemical shifts are given in ppm (δ) from tetramethylsilane, which was used as the internal standard. Mass spectra were performed using a JEOL JMS-AX505W (EI) or a JEOL JMS-HX110 (FD, FAB) spectrometer.

3-(*tert*-Butoxycarbonyl)amino-4-mercaptopyridine (11)

To a stirred solution of **9** (2.00 g, 10.3 mmol) in dry THF (200 mL) was added *n*-BuLi (1.54 M in hexanes; 16.7 mL, 25.8 mmol) at -78 °C under an argon atmosphere. The reaction temperature was warmed up to 0 °C, stirred for 2 h and recooled to -78 °C. To the mixture was added S_8 (400 mg, 1.57 mmol) in one portion. After the reaction temperature was increased to rt, the reaction mixture was stirred for 1 h. To the mixture was added H_2O (100 mL) and the organic layer was discarded. To the aqueous layer was added 3 N HCl until the aqueous solution was pH 3 ~ 4. This solution was extracted with CH_2Cl_2 and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane/AcOEt, 2/1) and crystallization from AcOEt- hexane gave **11** (783 mg, 34%) as a colorless solid: mp 176-178 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.48 (9H, s), 7.41

(1H, d, *J* = 6.3 Hz), 7.57 (1H, d, *J* = 6.3 Hz), 8.46 (1H, s), 8.93 (1H, s), 12.85 (1H, br s). MS (FAB) *m/z* 227 $(M + H)^+$. Anal. Calcd for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24; N, 12.38; S, 14.17. Found: C, 53.14; H, 6.02; N, 12.15; S, 13.88.

4-(*tert*-Butoxycarbonyl)amino-3-mercaptopyridine (12)

Starting with **10** and following the procedure for the preparation of **11** gave **12** (46%) as a pale yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.52 (9H, s), 7.89 (1H, d, *J* = 6.4 Hz), 7.99 (1H, d, *J* = 6.4 Hz), 8.20 (1H, s), 9.91 (1H, br s), 13.68 (1H, br s). MS (FAB) *m/z* 227 $(M + H)^+$. Anal. Calcd for $C_{10}H_{14}N_2O_2S \cdot 0.5H_2O$: C, 51.04; H, 6.43; N, 11.91; S, 13.63. Found: C, 51.32; H, 6.35; N, 11.76; S, 13.69.

Thiazolo[4,5-*c*]pyridine (13)

A solution of **11** (9.20 g, 40.7 mmol) in HCO_2H (60 mL) was refluxed for 4 h. The reaction mixture was concentrated. To the residue was added 5 N KOH (50 mL). The mixture was extracted with Et_2O and the organic layer was dried over $MgSO_4$. Evaporation of the solvent and crystallization from Et_2O gave **13** (3.97g, 72%) as a colorless solid: mp 103-105 °C (lit.,[5a] mp 105-106 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 5.4 Hz), 8.60 (1H, d, *J* = 5.4 Hz), 9.07 (1H, s), 9.46 (1H, s). MS (FAB) *m/z* 137 $(M + H)^+$. Anal. Calcd for $C_6H_4N_2S$: C, 52.92; H, 2.96; N, 20.57; S, 23.55. Found: C, 52.98; H, 2.96; N, 20.65; S, 23.33.

Thiazolo[5,4-*c*]pyridine (14)

A solution of **12** (33.2 g, 147 mmol) in HCO_2H (250 mL) was refluxed for 2 days. The reaction mixture was concentrated. To the residue was added 5 N KOH (50 mL). The mixture was extracted with Et_2O and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by column chromatography (CH_2Cl_2/MeOH, 50/1) and crystallization from Et_2O gave **14** (9.03 g, 45 %) as a colorless solid: mp 105-108 °C (lit.,[5b] mp 105-106 °C, lit.,.[5c] mp 102-105 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (1H, d, *J* = 5.4 Hz), 8.70 (1H, d, *J* = 5.4 Hz), 9.23 (1H, s), 9.34 (1H, s). MS (FAB) *m/z* 137 $(M + H)^+$. Anal. Calcd for $C_6H_4N_2S$: C, 52.92; H, 2.96; N, 20.57; S, 23.55. Found: C, 52.80; H, 2.98; N, 20.40; S, 23.57.

2-Amino-5-*tert*-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (18)

To a solution of 1-*tert*-butoxycarbonyl-4-piperidone (150 g, 752 mmol) in cyclohexane (500 mL) were added pyrrolidine (66.0 mL, 790 mmol) and $TsOH \cdot H_2O$ (716 mg, 3.76 mmol). The reaction mixture was refluxed for 2 h with Dean-Stark trap. After cooling, the mixture was filtered and the filtrate was evaporated. To the solution of the residue in dry MeOH (200 mL) was added S_8 (24.1 g, 94.1 mmol) in one portion. To the stirred mixture was added dropwise the solution of cyanamide (31.7 g, 753 mmol) in dry MeOH (25 mL) at 0 °C. The reaction mixture was stirred for 5 h and the solid was separated out. Filteration and collection in the mixture gave **18** (122 g, 63%) as a pale yellow solid: mp 91-94 °C. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 1.41 (9H, s), 2.40-2.46 (2H, m), 3.57 (2H, t, J = 5.6 Hz), 4.29 (2H, s), 6.79 (2H, s). MS (EI) *m/z* 255 (M^+). Anal. Calcd for $C_{11}H_{17}N_3O_2S \cdot 0.1H_2O$: C, 51.38; H, 6.74; N, 16.34; S, 12.47. Found: C, 51.73; H, 6.96; N, 16.44; S, 12.14.

2-Bromo-5-*tert*-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (19)

To a stirred suspension of $CuBr_2$ (181 g, 0.808 mol) in dry DMF (500 mL) was added *tert*-butyl nitrite (104 g, 1.01 mol). To the stirred mixture at 50 °C was added **18** (172 g, 0.674 mol) in portions. The reaction mixture was stirred at 50-60 °C for 2 h and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane/AcOEt, 5/1) and crystallization from Et_2O gave **19** (105 g, 49%) as a colorless solid: mp 42-44 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (9H, s), 2.85 (2H, br s), 3.72 (2H, t, J = 5.6 Hz), 4.56 (2H, br s). MS (FAB) *m/z* 319 [$(M + H)^+$, Br^{79}], 321 [$(M + H)^+$, Br^{81}]. Anal. Calcd for $C_{11}H_{15}N_2BrS$: C, 41.39; H, 4.74; N, 8.78; Br, 25.03; S, 10.05. Found: C, 41.33; H, 4.68; N, 8.77; Br, 25.21; S, 10.15.

2-Bromo-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (20)

To a stirred solution of **19** (74.7 g, 234 mmol) in CH_2Cl_2 (160 mL) was added trifluoroacetic acid (500 g) at 0 °C in an ice bath. The mixture was stirred at rt for 10 min and concentrated *in vacuo*. To the residue was added Et_2O (300 mL) to obtain a colorless solid. To the suspension of this solid in CH_2Cl_2 (150 mL) was added Et_3N (63.7 mL, 460 mmol). To the stirred mixture at rt were added AcOH (39.4 mL, 689 mmol), 36 % aq. HCHO (39.4 mL), and sodium triacetoxyborohydride (80.3 g, 367 mmol). The mixture was stirred for 1 h at rt under an argon atmosphere and poured into 1N NaOH (750 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography (CH_2Cl_2/MeOH, 100/1) gave **20** (49.0 g, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (3H, s), 2.79 (2H, t, J = 5.8 Hz), 2.88-2.93 (2H, m), 3.58 (2H, s). ^{13}C NMR (400 MHz, $CDCl_3$) δ 26.7, 45.0, 52.0, 52.2, 130.1, 133.3, 149.1. MS (EI) *m/z* 232 (M^+, Br^{79}), 234 (M^+, Br^{81}). HR-MS (EI; M^+, Br^{81}) Calcd for $C_7H_9N_2BrS$ 233.9649, Found 233.9652.

Lithium 5-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxylate (2)

To a stirred solution of **20** (48.9 g, 210 mmol) in dry Et_2O (500 mL) was added *n*-BuLi (1.53 M in hexanes; 137 ml, 210 mmol) at -78 °C under an argon atmosphere. The reaction mixture was warmed up to 0 °C, stirred for 20 min, and recooled to -78 °C. After the bubbling of CO_2 gas for 5 min, the reaction was warmed up to rt and concentrated *in vacuo*. Collection of the residue and washing with hexane gave **2** (48.9 g, 99%) as a pale brown amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (3H, s), 2.64-2.77 (4H, m), 3.54 (2H, s). MS (FAB) *m/z* 199 $(M + H)^+$. Anal. Calcd for $C_8H_9N_2O_2LiS \cdot 1.6H_2O$: C, 41.24; H, 5.28; N, 12.02. Found: C, 41.44; H, 4.89; N, 11.72.

Lithium 5-*tert*-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxylate (3)

To a stirred solution of **19** (1.28 g, 4.00 mmol) in dry Et_2O (150 ml) was added *n*-BuLi (1.50 M in hexanes; 2.67 mL, 4.00 mmol) at -78 °C under an argon atmosphere. The reaction mixture was stirred for 20 min at -78 °C. After the bubbling of CO_2 gas for 5 min, the reaction was warmed up to rt and concentrated *in vacuo*. Collection of the residue and washing with AcOEt gave **3** (762 mg, 66%) as a pale yellow amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42 (9H, s), 2.71 (2H, br s), 3.60-3.66 (2H, m), 4.55 (2H, s). MS (FD) *m/z* 285 $(M + H)^+$. Anal. Calcd for $C_{12}H_{15}N_2O_4LiS \cdot 0.8H_2O$: C, 47.31; H, 5.49; N, 9.19. Found: C, 47.31; H, 5.18; N, 8.88.

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