Synthesis of *Tert*-butyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

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Abstract.*Tert*-butyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (**1**) is an important intermediate in many biologically active compounds such as crizotinib. In this work, compound (**1**) was synthesized through three steps, using *tert*-butyl-4-hydroxypiperdine-1-carboxylate as starting material. And the structures of *tert*-butyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxy late was confirmed by MS and ^{1}HNMR spectrum. The total yield of the three steps was 49.9%.

Introduction

Crizotinib (PF-02341066) is a potent and selective Mesenchymal epithelial transition factor/Anaplastic lymphoma kinase (c-Met/ALK) inhibitor that is currently in phase III clinical trials. As a result of the positive results observed during initial phase I studies in patients with ALK-positive nonsmall-cell lung cancer (NSCLC), the clinical program was rapidly accelerated resulting in a significant increase in API demand [1, 6]. As more and more people have been plagued by lymphoma, developing lymphoma inhibitors is one of the research hotspots for the treatment of lymphoma. de Koning P D [7] et al reported a synthetic route of crizotinib. It was synthesized through eight steps. Taking 1-(2,6-dichloro-3-fluorophenyl)ethan-1-ol as starting material, crizotinib was prepared by reduction, bromination, substitution[8, 9]. In other reports such as Steven J. Fussell [10] et al established a synthetic route of crizotinib using 4-(4-iodo-2*H*-imidazol-2-yl) pyridine as raw material, through substitution, hydride reduction and condensation to give the title compound.

Most of the synthetic methods of *tert* –butyl – 4 - (4 - (4 , 4 , 5 , 5 – tetramethy l – 1 , 3, 2 – dioxaborolan – 2 –y l) – 1 *H* -pyrazol-1-yl) piperidine-1-carboxylate which reported in the literature have the drawbacks such as long synthetic route, lower yield and harmful to environment. However *tert*-butyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl) piperidine-1-carboxylate is a key intermediate for synthesizing crizotinib. Therefore, the optimization of the synthetic route and methods of *tert* - b uty l- 4 - (4- (4 ,4 ,5 ,5- tetramethy l-1,3,2 -dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate is necessary.

In this study, we designed and optimized the synthetic methods for *tert*-butyl-4-(4-(4,4,5,5-tetramethy l - 1 , 3 , 2- dioxaborolan-2-y l) -1*H*-pyrazol -1-yl) piperidine-1-carboxylate (**1**) and make it more suitable for industrial production. The structures of crizotinib and *tert* – buty l- 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl) piperidine-1-carboxylate(**1**) were shown in Fig. 1.

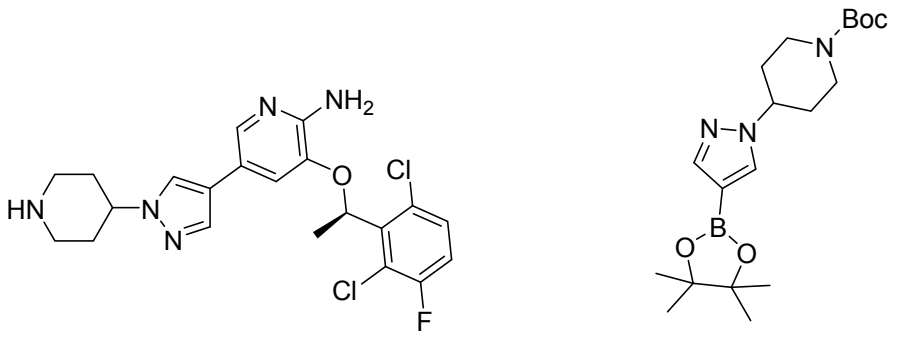


Fig. 1 Structures of crizotinib and compound 1

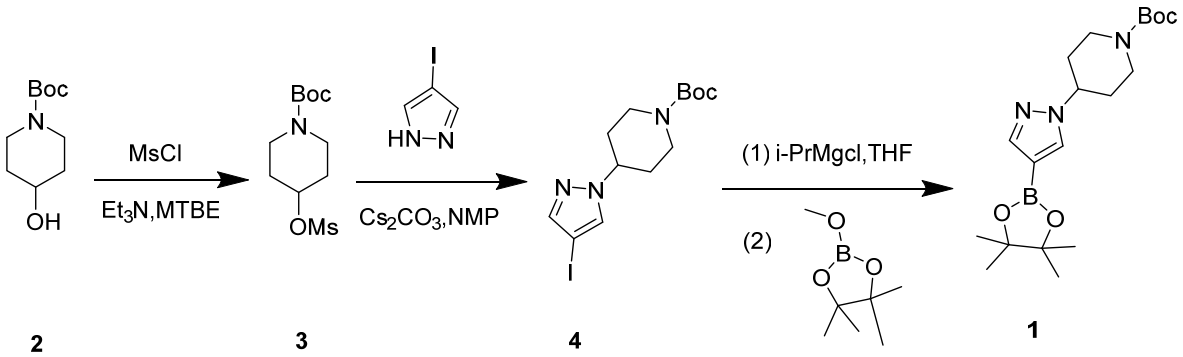
Materials and methods

All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik,

Flawil, Switzerland) and were uncorrected. The IR spectra were recorded by means of the KBr pellet technique on a Bruker FTS 135 spectrometer. NMR spectra were performed using Bruker 400 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy). All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified. Yields were not optimized. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical,China).

Synthesis of compounds

The structures and the synthetic route were shown in Scheme 1.



Scheme 1. The synthetic route of compound 1

Reagents and conditions: (a) Et_3N, MTBE, MsCl, 20℃, 1h; (b) Cs_2CO_3, NMP , 4-iodo-1*H*-pyrazole, 80℃, 20h; (c) THF, i-PrMgCl, 20℃-30℃, 14h.

Synthesis of *tert*-butyl-4-((methylsulfonyl)oxy)piperidine-1-carboxylate (3)

Methanesulfonyl chloride (85.4g, 0.746mol) was slowly added to a mixture of *tert*-butyl-*4*-hydroxypiperidine-1-carboxylate (100g, 0.498mol), tiethylamine (55.3g, 0.545mol) and *tert*-butyl methyl ether (800mL) at -10℃. The reaction was stirred for 1h at 20℃. After completion of reaction as indicated by TLC, the solution was poured into ice-water (300mL) with strong stirring at 40℃. The organic layer was washed twice with *tert*-butyl methyl ether, combined the organic layer. Heptane (200mL) was added to the organic layer with stirring 1h, filtered, the filtrate was distilled to afford bright white powder (**3**) (133.4g, 96%). Mp 97-99℃, ESI-MS m/z: $[M+H]^+$302.

Synthesis of *tert*-butyl-4-(4-iodo-1*H*-pyrazol-1-yl)piperidine-1-carboxylate(4)

A solution of 4-iodo-1*H*-pyrazole (70.0g, 0.361mol), cesium carbonate (152.7g, 0.496mol) and 1-methyl-2-pyrrolidinone (350mL) was stirred at 80℃, then the solution of *tert*-butyl-4-((methy lsulfony l)oxy)piperidine-1-carboxylate (130.9g, 0.496mol) and 1-methyl-2-pyrrolidinone (350mL) was slowly added at 80℃, stirred for 20h and monitored by TLC. The mixture was cooled and poured into *tert*-butyl methyl ether (700mL) with strong stirring, white solid was precipitated, filtered off and dried to obtain the title compound (**4**) (88.5g, 65%). Mp 95-97℃, ESI-MS m/z: $[M+Na]^+$400.

Synthesis of *tert*-butyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate(1)

Tert-butyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carb oxylate(**4**) (88g, 0.233mol) was dissolved in THF (350mL) at -10℃, then i-PrMgCl (175mL, 0.35mol) was slowly added to the solution keeping the temperature at 0℃, then stirred at 20℃ for 2h, this solution was used in the next stage. 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (36.9g, 0.256mol) was dissolved in THF (350mL), then the spare solution was added, stirred for 12h. After the reaction was finished, the solution of NH_4Cl (87g, 1.63mol), H_2O (300mL) and ethyl acetate (400mL) was added to the reaction solution, stirred for 30min, then evaporated the organic layer to obtain oil, absolute ethyl alcohol (200mL) was added to dissolve the oil at 60℃, then hot water (700mL) was added, stirred for 3h for 60℃. The reaction solution was cooled to room temperature, stirred for 6h. The precipitated solid was filtered and dried to get the production (**1**) (70.2g, 80%). Mp 94-95℃, ESI-MS m/z: $[M+Na]^+$400. ^{1}H-NMR (300MHz, DMSO) δ: 7.98 (s,1H), 7.60 (s,1H), 4.37 (s,1H), 4.02 (m,2H), 2.88 (s,2H), 1.97 (m,2H), 1.78 (m,2H), 1.41 (s,9H), 1.25 (s,12H).

Conclusions

In conclusion, one novel *tert* – buty l-4-(4 -(4, 4, 5,5-tetramethy l-1, 3,2 – dioxaboro l an -2-yl)-1 *H*-pyrazo l- 1 -y l) piperidine – 1 –carboxy late was synthesized from *tert* –buty l- 4-hydroxypiperidine-1-carboxylate through three steps. The synthetic route of (**1**) can be used to synthesize *ter t* –buty l-4- (4-(4, 4,5,5- tetramethyl- 1,3, 2-dioxaborolan- 2-y l)- 1 *H*-pyrazo l-1-y l) piperidine-1-carboxylate. And the structure of *tert* – buty l-4 -(4 -(4,4 , 5,5 –tetramethy l- 1, 3,2 –dioxaborolan -2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate was confirmed by MS and ^{1}HNMR spectrum.

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