An efficient synthesis of baricitinib

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A highly efficient method for the synthesis of baricitinib was developed. The starting material *tert*-butyl 3-oxoazetidine-1-carboxylate was converted to intermediate 2-(1-(ethylsulfonyl)azetidin-3-ylidene)acetonitrile *via* the Horner–Emmons reaction, deprotection of the *N*-Boc-group and a final sulfonamidation reaction. Then the nucleophilic addition reaction was carried out smoothly to afford the borate intermediate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene under reflux. Finally, the desired compound baricitinib was obtained by the Suzuki coupling reaction of 4-chloro-7-*H*-pyrrolo[2,3-*d*]pyrimidine with the above borate intermediate. All compounds were characterised by IR, MS, ^{1}H NMR and ^{13}C NMR. The overall yield in this synthetic route was as high as 49%. Moreover, this procedure is straightforward to carry out, has low cost and is suitable for industrial production.

Keywords: baricitinib, Janus kinase, synthesis, Suzuki cross-coupling

The Janus kinase (JAK) is a family of four tyrosine receptor kinases that play a pivotal role in cytokine receptor signalling pathways *via* their interaction with signal transducers and activators of transcription proteins.[1–6] The four JAK family members are Janus kinase 1 (JAK1), Janus kinase 2 (JAK2), Janus kinase 3 (JAK3) and tyrosine kinase (TYK2), whose lengths range from 120 to 140 kDa. It has been shown that JAK2 activation may be critical for tumour growth and progression, indicating its selection as a therapeutic target. Moreover, since JAK3 is required for immune cell development, targeting JAK3 could be a useful strategy for generating a novel class of immunosuppressant drugs. JAK1 and TYK2 have been implicated in disease and immune suppression.

Over the past decade there have been extensive efforts to identify and design novel small-molecule JAK inhibitors with varied profiles of subtype selectivity to address unmet medical needs (Fig. 1).[7] Ruxolitinib is a Janus kinase inhibitor with selectivity for subtypes JAK1 and JAK2. It was approved by the U.S. Food and Drug Administration (FDA) for the treatment of intermediate or high-risk myelofibrosis in November 2011. Selective inhibitors of JAK are viewed as having considerable potential as disease-modifying anti-inflammatory drugs for the treatment of rheumatoid arthritis. Tofacitinib, which was the first oral non-biological disease-modifying antirheumatic drug, was approved for the management of rheumatoid arthritis (RA) at the end of 2012.[8] Baricitinib and filgotinib are being evaluated in phase III and phase II clinical trials respectively for the treatment of rheumatoid arthritis. Baricitinib (also known as LY3009104 or INCB028050) is a novel and potent small molecule inhibitor of the Janus kinase family of enzymes with selectivity for JAK1 and JAK2. In *in vitro* studies baricitinib inhibited JAK1 and JAK2 in the low nanomolar range, while it demonstrated low inhibitory activity for JAK3 and moderate activity for TYK2.[9–13] The data from two phase III studies showed that baricitinib can achieve impressive responses in RA patients who have not responded well to established therapies. Therefore, improvement in the preparation of baricitinib is of practical significance.

Results and discussion

As shown in Scheme 1, Rodgers *et al*. have reported the first synthetic route to baricitinib.[14] *tert*-Butyl 3-oxoazetidine-1-carboxylate (**1**) was employed as the starting material. This was transformed to compound **2** by a Horner–Emmons reaction, followed by deprotection of the *N*-Boc group in acidic conditions. The intermediate **4** was obtained by the sulfonamidation reaction of compound **3** with ethanesulfonyl chloride. The other part of baricitinib was acquired by utilising 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**5**) as the starting material. Compound **5** reacted with [2-(chloromethoxy)ethyl] trimethylsilane (SEM-Cl) to afford the intermediate **6**, which was converted by reaction with **7** *via* the intermediate **8** to 4-(1*H*-pyrazol-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-*d*]pyrimidine (**9**) *via* a Suzuki coupling reaction and a hydrolysis reaction. After the nucleophilic addition reaction and deprotection of the SEM group, baricitinib was obtained

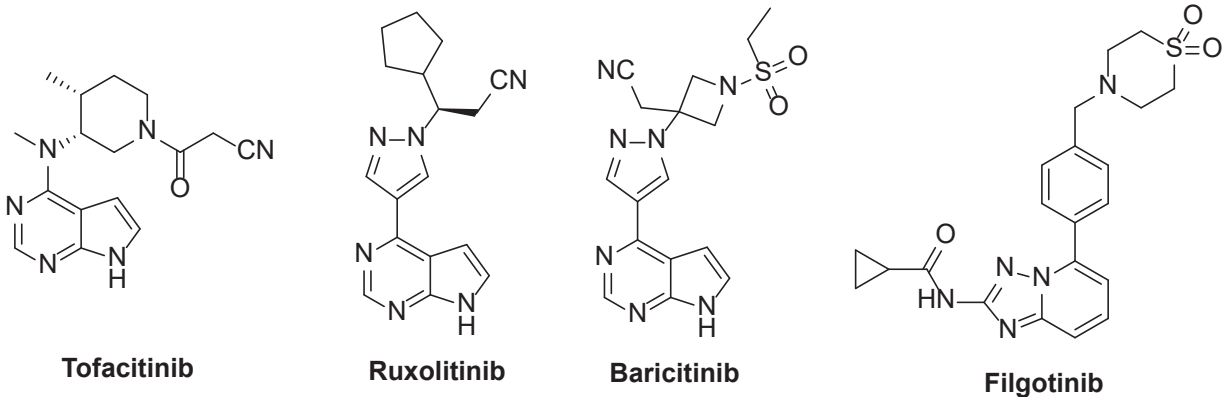

Fig. 1 Structures of some selective inhibitors of JAK.

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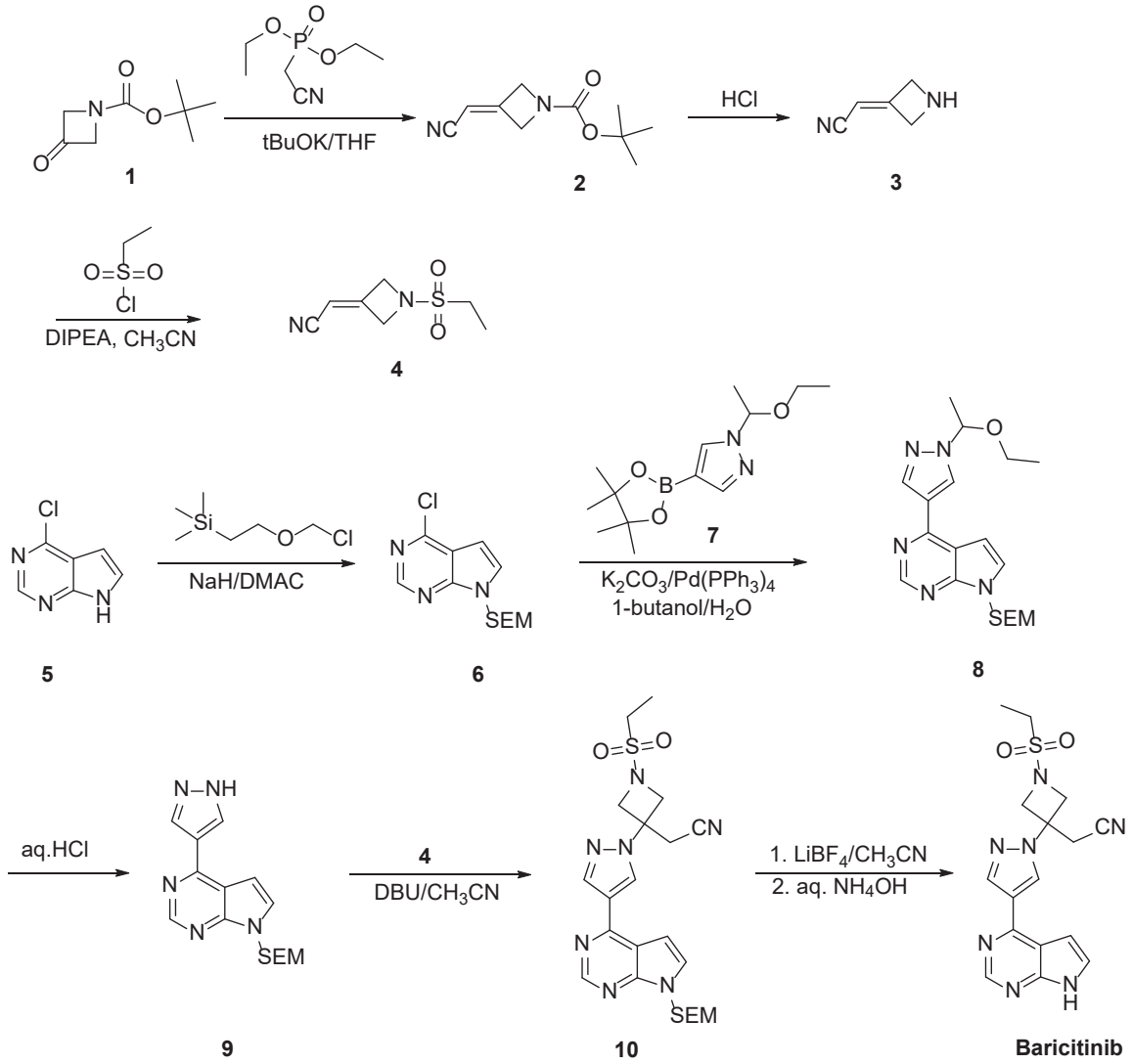


Scheme 1 The reported synthetic route to baricitinib.

through eight steps. This synthetic route had drawbacks of high cost, low overall yield and the requirement of strict operating conditions.

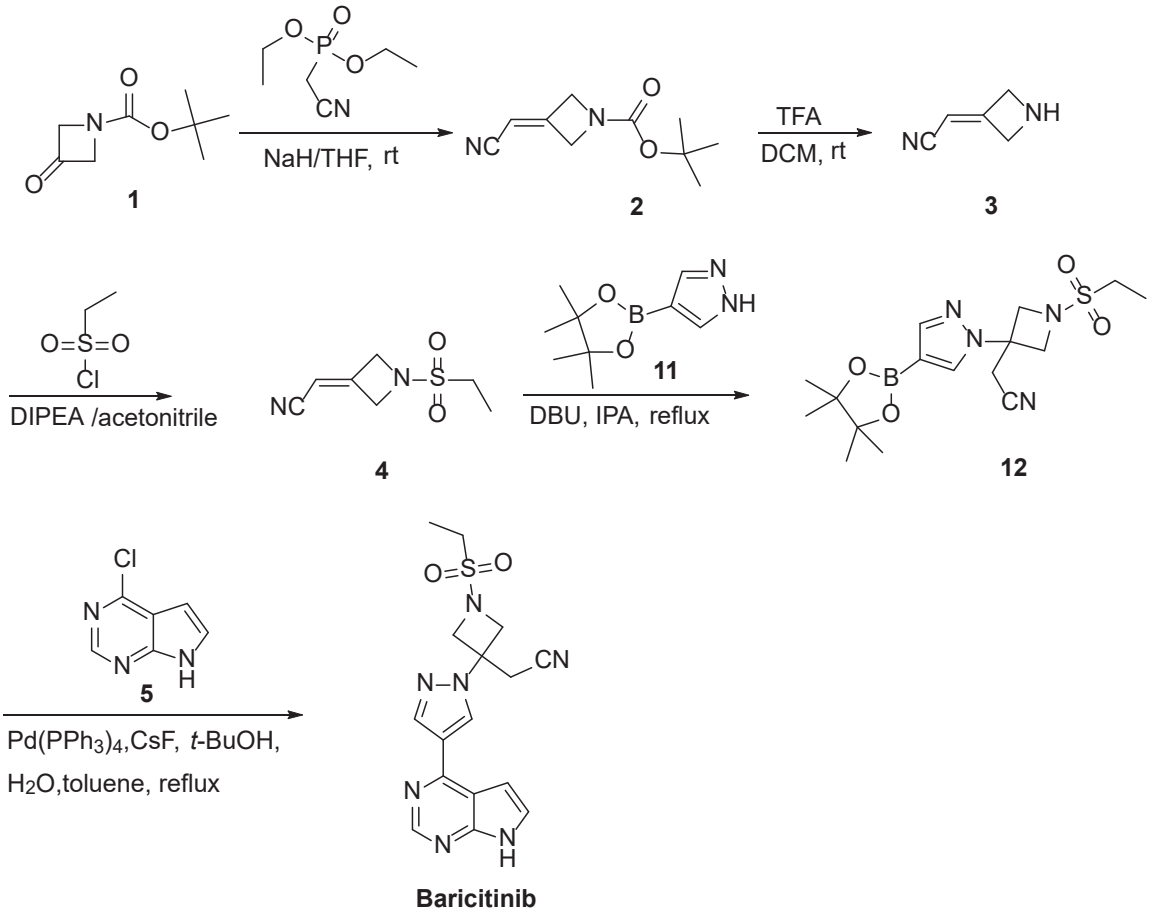
In order to improve the procedure, we designed a novel synthetic route for the synthesis of baricitinib (Scheme 2). Similarly, we also applied *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) as the starting material. First, we optimised the preparation of compound **4**. In the Horner–Emmons reaction, NaH was used as the base instead of *t*-BuOK, which led to a yield as high as 84%. Then the deprotection of the *N*-Boc group was carried out smoothly under trifluoroacetic acid (TFA) cleavage conditions to afford compound **3**, which was reacted with ethanesulfonyl chloride without further purification. Next, the nucleophilic addition reaction between compound **4** and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-l*H*-pyrazole (**11**) proceeded successfully in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). With the intermediate compound **12** in hand, we optimised the conditions of the Suzuki coupling reaction with compound **5**. Several coupling systems were evaluated, such as $Pd(PPh_3)_4$–K_2CO_3–*t*-butanol/H_2O, $Pd(PPh_3)_4$–Na_2CO_3–*t*-butanol/H_2O and $Pd(OAc)_2$–K_2CO_3–dioxane/H_2O. The $Pd(PPh_3)_4$–CsF–*t*-butanol/toluene/H_2O system afforded the most satisfactory yield. Finally, baricitinib was obtained efficiently and the overall yield was as high as 49% based on *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**).

Conclusion

In summary, we have developed a straightforward and improved approach for the synthesis of baricitinib. This novel synthetic route employed *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**5**) as the starting materials to afford baricitinib *via* the Horner–Emmons reaction, deprotection of the *N*-Boc group, a sulfonamidation reaction, a nucleophilic addition reaction and then a Suzuki coupling reaction. The overall yield of this procedure was as high as 49%. Moreover, this procedure has simple operating requirements and low costs and is suitable for industrial production.

Experimental

All the reagents were obtained from commercial sources and used without further purification. Melting points were determined on a RY-1 hot stage microscope and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DPX-300/500 MHz instrument in DMSO-d_6 or $CDCl_3$. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS as an internal standard. Mass spectra (MS) were obtained on an Agilent 1100 LC/MS spectrometer. IR spectra were obtained on a PerkinElmer 1600 series FTIR spectrometer. Elemental analyses were performed using an Arial Font Vario EL analyser. All reactions were monitored by TLC on silica gel GF-254 glass plates.



Scheme 2 The novel synthetic route to baricitinib.

Synthesis of tert-*butyl 3-(cyanomethylene)azetidine-1-carboxylate* (**2**)

A suspension of NaH (260 mg, 11 mmol) in 25 mL of THF was cooled in a 100 mL flask in an ice bath. A solution of diethyl cyanomethylphosphonate (1.1 mL, 6.72 mmol, 1.15 equiv.) in THF (20 mL) was added dropwise. The reaction was warmed to room temperature for 1 h then cooled back to 0 °C for 1 h to give a milky yellow solution. Then a solution of *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) (1.0 g, 5.84 mmol) in THF (10 mL) was added drop-wise over 1 h. The resulting reaction mixture was stirred overnight, then quenched with water and concentrated to remove THF. The resulting aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine and dried with $MgSO_4$. The filtrate was concentrated down to a yellow oil which was purified by silica chromatography using a gradient of 20–30% EtOAc/hexanes to afford compound **2**: Yield 939 mg (84%); m.p. 75–77 °C; IR (KBr): 2987, 2222, 1684, 1406, 1162 cm^{-1}. Anal. calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42; found: C, 61.95; H, 7.46; N, 14.38%. MS (m/z): 217 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 9H), 4.62 (t, *J* = 1.9 Hz, 2H), 4.70 (t, *J* = 3.2 Hz, 2H), 5.38 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.9, 39.5, 79.4, 92.8, 115.2, 155.6, 158.4.

Synthesis of 2-[1-(ethylsulfonyl)azetidin-3-ylidene]acetonitrile (**4**)

Trifluoroacetic acid (2 mL) was added to a solution of *tert*-butyl 3-(cyanomethylene)azetidine-1-carboxylate (**2**) (250 mg, 1.29 mmol) in dichloromethane (20 mL). The solution was stirred at room temperature for 5 h. Then the reaction mixture was concentrated under reduced pressure to dryness. The residue, which contains the crude desired deprotection product **3**, was then suspended in acetonitrile (20 mL) and cooled to 0 °C. *N*,*N*-Diisopropylethylamine (DIPEA) (1.12 mL, 6.44 mmol, 5 equiv.) was then slowly added while keeping the internal temperature below 5 °C. Then ethanesulfonyl chloride ($EtSO_2Cl$) (0.184 mL, 1.94 mmol, 1.5 equiv.) was added over 1 h while keeping the internal temperature below 5 °C. The resulting reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The concentrated residue was then diluted with dichloromethane and was washed with aqueous sodium chloride solution. The aqueous phase was back-extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and the residue was purified using a silica gel column to afford compound **4**: Yield 192 mg (81%); off-white solid; m.p. 58–60 °C; IR: 3294, 3066, 2978, 2222, 1702, 1321, 1142 cm^{-1}. Anal. calcd for $C_7H_{10}N_2O_2S$: C, 45.15; H, 5.41; N, 15.04; found: C, 45.32; H, 5.35; N, 15.21%. MS (m/z): 209 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (m, *J* = 6.7 Hz, 3H), 3.04 (m, *J* = 7.4 Hz, 2H), 4.69 (t, *J* = 2.5 Hz, 2H), 4.77 (t, *J* = 2.8 Hz, 2H), 5.43 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 7.2, 42.6, 58.5, 58.9, 93.9, 114.9, 156.2, 168.6.

*Synthesis of 2-{1-(ethylsulfonyl)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile* (**12**)

A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (**11**) (156 mg, 0.80 mmol, 1.01 equiv.), compound **4** (149 mg, 0.80 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.061 mL, 0.408 mmol) in acetonitrile (20 mL) was heated at 60 °C for 4 h. After cooling, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with methanol in dichloromethane (0–60%) to afford the desired compound **12**: Yield 255 mg (84%); m.p. 120–122 °C; IR: 3280, 2978, 1639, 1554, 1369 cm^{-1}. Anal. calcd for $C_{16}H_{25}BN_4O_4S$: C, 50.54; H, 6.63; N, 14.73; found: C, 50.67; H, 6.74; N, 14.62%. MS (m/z): 403 $[M + Na]^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.22 (t, *J* = 7.3 Hz, 3H), 1.27 (s, 12H), 3.19 (m, *J* = 7.3 Hz, 2H), 3.59 (s, 2H), 4.14 (d, *J* = 9.0 Hz, 2H), 4.44 (d, *J* = 9.0 Hz, 2H), 7.77 (s, 1H), 8.35 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 4.6, 24.9, 39.5, 43.2, 55.5, 58.2, 83.2, 116.6, 135.8, 145.6.

*Synthesis of 2-[3-(4-{7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl]acetonitrile* (baricitinib)

To a flask were added 2-{1-(ethylsulfonyl)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile

(**12**) (870 mg, 2.3 mmol, 1.1 equiv.), 4-chloro-7-*H*-pyrrolo[2,3-*d*] pyrimidine (**5**) (290 mg, 0.19 mmol), caesium fluoride (1120 mg), tetrakis(triphenylphosphine)palladium (240 mg, 0.1 equiv.), *tert*-butanol (10 mL), water (10 mL) and toluene (10 mL) at ambient temperature. The resulting reaction mixture was heated to reflux under nitrogen for 48 h. Then the reaction mixture was cooled to room temperature and filtered through a Celite bed. The Celite bed was washed with ethyl acetate and the aqueous layer was extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure to remove solvents and the crude product was purified by flash chromatography on a silica gel column eluting with methanol in dichloromethane (0–60%) to afford baricitinib: Yield 560 mg (84%); m.p. 193–195 °C; IR: 3203, 3113, 2998, 2847, 2363, 1584, 1328, 1137 cm^{-1}. Anal. calcd for $C_{16}H_{17}N_7O_2S$: C, 51.74; H, 4.61; N, 26.40; found: C, 51.91; H, 4.49; N, 26.57%. MS (m/z): 372 $[M + H]^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.25 (t, J = 7.3 Hz, 3H), 3.23 (m, J = 7.3 Hz, 2H), 3.69 (s, 2H), 4.24 (d, J = 9.0 Hz, 2H), 4.61 (d, J = 9.0 Hz, 2H), 7.08 (s, 1H), 7.62 (s, 1H), 8.47 (s, 1H), 8.71 (s, 1H), 8.92 (s, 1H), 12.12 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 7.4, 24.9, 39.3, 43.4, 58.5, 99.9, 113.0, 116.6, 126.9, 129.5, 139.9, 149.3, 150.9, 152.2.

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