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A three-step synthesis of 4-(4-iodo-1*H*-pyrazol-1-yl)piperidine, a key intermediate in the synthesis of Crizotinib

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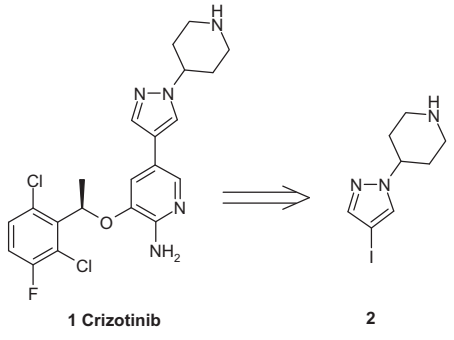
ABSTRACT

4-(4-Iodo-1*H*-pyrazol-1-yl)piperidine is a key intermediate in the synthesis of Crizotinib. We report a robust three-step synthesis that has successfully delivered multi-kilogram quantities of the key intermediate. The process includes nucleophilic aromatic substitution of 4-chloropyridine with pyrazole, followed by hydrogenation of the pyridine moiety and subsequent iodination of the pyrazole which all required optimization to ensure successful scale-up.

Crizotinib (**1**) (XALKORI®) is a potent and selective anaplastic lymphoma kinase (ALK) inhibitor that was approved by the US Food and Drug Administration in August 2011 for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC).[1] As a result of the positive results observed during an early clinical trial, the clinical program was rapidly accelerated which required extensive route evaluation to enable delivery of bulk quantities of the clinical candidate.

4-(4-Iodo-1*H*-pyrazol-1-yl)piperidine (**2**) is a key intermediate in the synthesis of Crizotinib (**1**, Scheme 1). Intermediate **2** was previously sourced as the corresponding *tert*-butyl carbamate **5** during the enabling route to make pre-clinical batches of Crizotinib (**1**).[2] The Boc-protected piperidine **5** has only been reported to be synthesized via the activation of 4-hydroxy-1-Boc-piperidine (**3**) followed by displacement with 4-iodopyrazole (Scheme 2).



Scheme 1. Crizotinib (**1**) and key intermediate 4-(4-iodo-1*H*-pyrazol-1-yl)piperidine (**2**).

This route successfully delivered multi-kilogram amounts of the target substrate, however it was not suitable for further scale-up due to the expensive starting material, lengthy work-up, and significant formation of the elimination by-product **6** during the displacement reaction.

The unprotected substrate **2** was selected for the commercial synthetic route as a result of development of the downstream chemistry. The use of unprotected substrate **2** improved the atom efficiency for the synthesis of Crizotinib (**1**) by eliminating the subsequent deprotection step in the enabling route (substrate **7** to **1**). Herein we describe the development and optimization of the synthetic route, via a completely different approach, to the construction of the pyrazole–piperidine framework (Scheme 2).[3] We initially investigated the shortest route to the target molecule, a two-step synthesis involving nucleophilic substitution of 4-chloropyridine **8** with 4-iodopyrazole followed by selective reduction of the pyridine moiety in **9** to furnish the target molecule **2**. Although the conversion of **8** into **9** proceeded in quantitative yield, all the hydrogenation conditions screened led to dehalogenation of **9**. Therefore, a more stepwise approach was considered whereby a separate halogenation step would be utilized to incorporate the desired iodine fragment and furnishing a three-step route to the key intermediate **2**.

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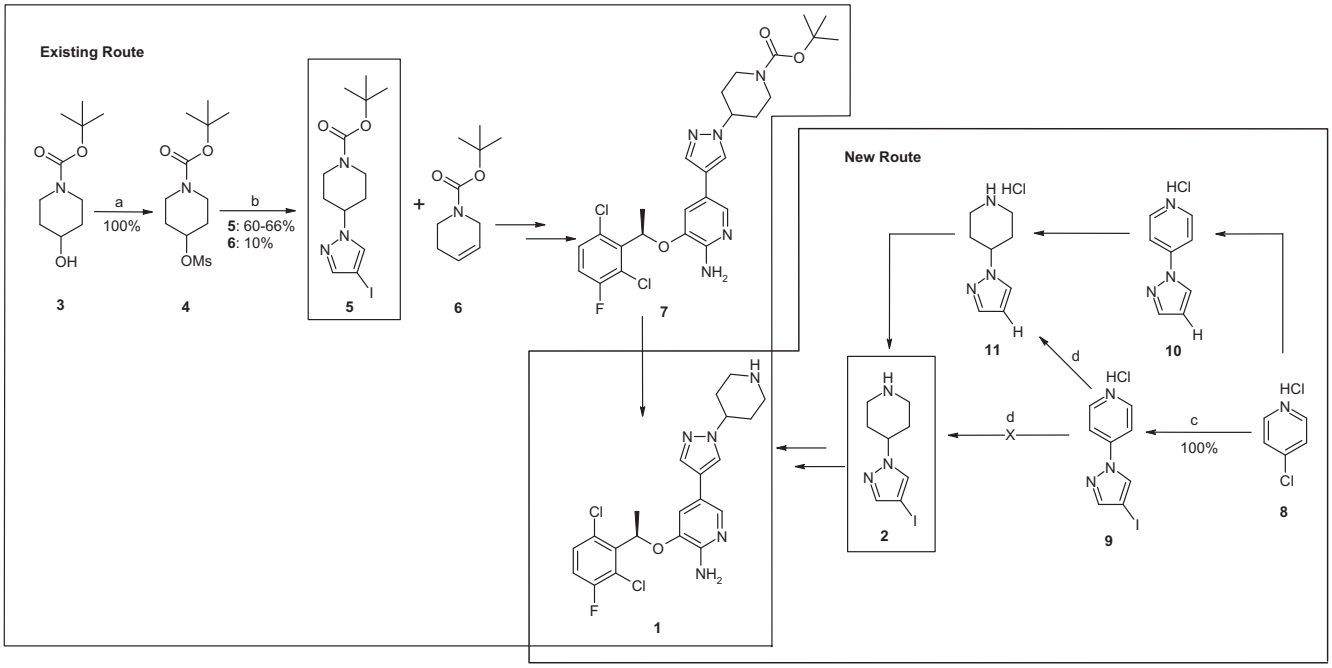


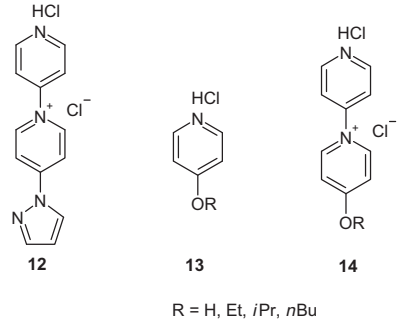
Scheme 2. Reagents and conditions: (a) MsCl (1.4 equiv), Et_3N (1.45 equiv), DMAP (0.1 equiv), *tert*-butyl methyl ether, 0 °C; (b) Method 1: 4-iodopyrazole (0.9 equiv), NaH (1.1 equiv), DMF, 100 °C, 12 h; Method 2: 4-iodopyrazole (0.9 equiv), Cs_2CO_3 (1.1 equiv), NMP, 78–82 °C, 6 h; column from 5% EtOAc in heptanes; (c) 4-iodopyrazole (5.0 equiv), toluene, reflux, 5 h, 60% isolated yield; (d) catalyst: Pd, Pt, PtO_2, Rh, or Ru; solvent: AcOH, EtOH, H_2O, or toluene/2-PrOH; additive: I_2, ZnI_2, or HI/H_2O, 0% of **2**, 100% of **11**.

Table 1
Conditions for the nucleophilic substitution to give 4-(1*H*-pyrazol-1-yl)pyridine HCl (**10**)

Entry	Amount of 1*H*-pyrazole (equiv)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	1.0	Toluene	90	16	52[b]
2	2.0	Toluene	90	16	86
3	3.0	Toluene	90	16	100
4[c]	1.2	EtOAc	Reflux	24	40[d]
5	3.0	EtOAc	Reflux	24	65[b]
6	3.0	MeCN	Reflux	24	100
7	3.0	2-PrOH	Reflux	6	97.5[e]
8	3.0	H_2O	80	6	81[f]

[a] Reactions were monitored by ^1H NMR spectroscopy of crude samples.
[b] Both the starting material, 4-chloropyridine HCl **8** and intermediate 4-pyrazol-[1,4′]bipyridinyl-1-ylium chloride HCl **12** were present in the reaction mixture.
[c] The reaction used 4-chloropyridine (**8**) as the free base.
[d] Only the intermediate 4-pyrazol-[1,4′]bipyridinyl-1-ylium chloride **12** was present in the reaction mixture.
[e] Contains 2.5% of **13**, R = *i*Pr.
[f] Contains 5% of **13** and 7% of **14**, R = H.

Nucleophilic aromatic substitution of 4-chloropyridine hydrochloride (**8**) with 1*H*-pyrazole was initially performed in toluene (Table 1, entries 1–3). It was clearly shown that the number of equivalents of 1*H*-pyrazole utilized in the reaction directly impacted on the extent of conversion and ultimately the yield obtained. By increasing the amount of 1*H*-pyrazole to 3.0 equiv (entry 3), intermediate **12** (Fig. 1) is effectively converted into two equivalents of the desired product **10** through the reaction of 1*H*-pyrazole at the 4-position of the Northern pyridine fragment. The reaction mixture in toluene was an oily slurry, which posed potential scale-up issues, therefore a range of further solvents was subsequently investigated. Reaction in alcoholic solvents and water resulted in impurities **13** and **14** (Table 1, entries 7 and 8) ranging from 3% to 50%. In-depth kinetic studies showed that the formation of such impurities was difficult to control and an alternative solution was desirable.



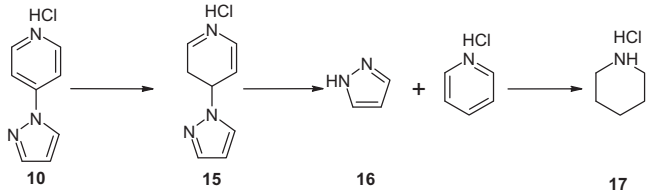
12 **13** **14**

Figure 1. Nucleophilic substitution intermediate **12** and impurities **13** and **14.**

The nucleophilic substitution in acetonitrile with 3 equiv of 1*H*-pyrazole (Table 1, entry 6) gave the best results in terms of conversion, physical properties of the reaction mixture, and simplicity of isolation. Upon successful completion of the reaction, the mixture was quenched with 1.0 equiv of Hünig's base to scavenge the HCl by-product and the pyridine salt **10** was subsequently isolated by filtration. Due to solubility differences, this left all of the excess reagents and by-products in the mother liquors and hence purged them from the product **10**.

With **10** in hand, the next step involved hydrogenation of the pyridine moiety. A number of catalysts and solvents were highlighted after initial screening to furnish successfully piperidine **11**. Side products formed during the hydrogenation were identified as 1*H*-pyrazole (**16**) and piperidine hydrochloride (**17**); these are postulated to arise from the elimination and rearomatization of the partially reduced substrate **15** during the course of the hydrogenation (Scheme 3).

The initial screening experiments highlighted two potentially useful catalysts, 5% Rh/C 20A and 5% Pd/C 87L and these were used in subsequent kinetic studies and further development work. Several factors were investigated simultaneously and are listed in Table 2: catalyst, solvent, catalyst loading, pressure, and reaction



Scheme 3. Proposed reaction pathway for the formation of 1*H*-pyrazole (**16**) and piperidine hydrochloride (**17**).

time. Conducting the reaction in water, methanol, and ethanol showed no significant differences in the reaction rate and product distribution (entries 1, 4 and 5), whereas reaction in 2-propanol resulted in a significantly slower reaction rate and increased the production of the piperidine impurity **17** (entry 6). The rate of hydrogenation increased with the catalyst loading as seen by comparing entries 1 and 9, however the selectivity was not improved. Increasing the pressure offered little improvement on the reaction rate and selectivity (entries 1 and 8). Increasing the temperature failed to increase the rate of reaction but did again result in a significant increase in the production of impurity **17** (entries 1 and 7). An iterative approach allowed us to find optimum conditions for the formation of piperidine **11** whereby a high catalyst loading, low temperature, and high pressure in either water or methanol resulted in excellent levels of conversion into the desired product with product distributions of 20:1 and 33:1 (entries 10 and 11). While conducting these two reactions, multiple samples were taken over the course of the reaction and subsequent analysis showed that the formation of both impurities **16** and **17** could not be avoided as they were generated continuously during the reaction.

Over the course of our investigation into the hydrogenation of pyridine **10**, we noted that the pH of the reaction mixture had a significant impact on the reaction rate whereby the hydrogenation started with a pH of 3 and increased to 6 over the course of the transformation. It was also noted that above pH 6, the rate of the reaction decreased significantly and a remedial charge of HCl or acetic acid was necessary to ensure completion of the hydrogenation stage. It was also found that intermediate **12** had a detrimental effect on the reaction conversion. In fact, the presence of only 2% of **12** was enough to stall the hydrogenation reaction completely and therefore its levels in **10** needed careful control.

The final step in the sequence involved iodination of piperidine **11** to furnish the target key intermediate **2**. This transformation was initially investigated using isolated 4-(1*H*-pyrazol-1-yl)piperidine **11** di-hydrochloride salt.[4] Table 3 indicates that *N*-iodosuccinimide (entry 1) gave high conversion into the desired product in a short reaction time of 30 min. Alternative reagents (entries 2 and 3) also provided high conversions but with an increase in the number of impurities produced in the reaction.[5] When using the mono-hydrochloride salt **11** telescoped from the earlier steps, additional acid was required to prevent the pH from becoming too high and causing the reaction to stall (entries 4 and 5). In addition to the originally used *N*-iodosuccinimide, alternative iodination conditions showed promise with excellent conversions and reaction profiles (entries 6 and 7).

During iodination, 1*H*-pyrazole (**16**) produced during the hydrogenation reaction was converted into 4-iodopyrazole (**18**)

Table 2
Conditions for the hydrogenation of 4-pyrazol-1-yl-piperidine HCl **11**

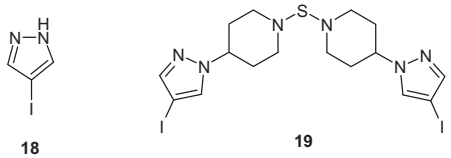
Entry	Solvent[a]	Catalyst	Loading[a] (%)	Temp (°C)	Pressure (psi)	Time (h)	Conversion into **11**[b] (%)	Ratio of **11**:**17**[b]
1	H_2O	5% Rh/C 20A	10	50	150	16	100	10:1
2	H_2O	5% Pd/C 87L	10	50	150	40	94	14:1
3	H_2O	5% Pd/C 87L	5	50	150	24	26	N/A
4	MeOH	5% Rh/C 20A	10	50	150	12	100	10:1
5	EtOH	5% Rh/C 20A	10	50	150	16	100	10:1
6	2-PrOH	5% Rh/C 20A	10	50	150	16	58	7:1
7	H_2O	5% Rh/C 20A	10	80	200	16	100	3.6:1
8	H_2O	5% Rh/C 20A	10	50	250	12	100	17:1
9	H_2O	5% Rh/C 20A	20	50	150	6	100	11:1
10	H_2O	5% Rh/C 20A	20	30	250	16	100	20:1
11	MeOH	5% Rh/C 20A	20	30	250	16	100	33:1

[a] Hydrogenation was performed in 10 mL/g solvent with respect to 4-(1*H*-pyrazol-1-yl)pyridine hydrochloride (**10**).
[b] Reaction conversion and selectivity were estimated by ^{1}H NMR spectroscopy.

Table 3
Conditions for the iodination of 4-(1*H*-pyrazol-1-yl)piperidine HCl (**11**) at 20 °C

Entry	Iodination reagent	Amount of reagent (equiv)	Additives	Amount of additive (equiv)	Solvent	Time (h)	Conversion[a] %	Total impurities[a] %
1[b]	*N*-Iodosuccinimide	1.0	None	—	H_2O	0.5	100	None
2[b]	Tetrabutylammonium triiodide	1.0	None	—	AcOH	16	100	30
3[b]	Benzyltrimethyl ammonium dichloroiodide	1.0	None	—	AcOH	16	100	30
4[c]	*N*-Iodosuccinimide	1.0	None	—	H_2O, EtOH, CH_2Cl_2	16	32–64	1–4
5[c]	*N*-Iodosuccinimide	1.0	Conc. HCl	1.0	H_2O	0.5	100	None
6[c]	Iodine/30% hydrogen peroxide	0.6/1.0	AcOH	5.0	H_2O	45–60	100	None
7[c]	Sodium iodide/potassium iodate	0.68/0.34	Conc. HCl	2.0	H_2O	16	100	None

[a] The reaction conversion and amount of unknown impurities were determined by GC analysis. Sample preparation included a quench with 2 M NaOH and extraction with CH_2Cl_2.
[b] Iodination was performed with substrate **11** di-hydrochloride salt.
[c] Iodination was performed with non-isolated substrate **11** hydrochloride aqueous solution from hydrogenation.



18 19

Figure 2. 4-Iodopyrazole (**18**) and thiodiamine **19** impurities.

(Fig. 2) at a rate similar to that of the desired substrate **11**. Both by-products, 4-iodopyrazole (**18**) and piperidine **17** have solubilities very different to that of the desired product **2**, and consequently, they were removed during the isolation of **2** by crystallization in ethyl acetate.

Once the iodination reaction was complete, the mixture was initially quenched with sodium thiosulfate followed by pH adjustment to pH 12. The desired product **2** was extracted with THF followed by solvent replacement into ethyl acetate to enable crystallization, and isolated by filtration. An overall 73% isolated yield was obtained over the two steps, whereby hydrogenation had an in situ 90% conversion and iodination had quantitative conversion and an 81% isolated yield.

Interestingly, when the iodination mixture was quenched with sodium thiosulfate, thiodiamine impurity **19**[6] (Fig. 2) was found in the isolated product at levels up to 10%. This thiodiamine **19** was later found to be generated when the pH was $\geqslant 8$ in the presence of sodium thiosulfate, and could be converted into the desired product **2** by exposure to aqueous HCl at 20 °C for 2 h.[7] In order to avoid the formation of **19**, sodium sulfite was subsequently used to quench the iodination reaction mixture.

In conclusion, we have developed a new three-step synthetic route to 4-(4-iodo-1*H*-pyrazol-1-yl)piperidine (**2**), a key intermediate in the synthesis of Crizotinib (**1**). It has a number of distinct advantages over the enabling route including completely eliminating the formation of unwanted by-product **6**. The route has proved to be easily scalable, robust, and well streamlined. This three-step synthesis has since successfully been scaled-up on a multi-kilogram scale and has delivered >180 kg of **2** in high purity.

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Supplementary data

Supplementary data (experimental procedures and spectral data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.044.

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