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Development of a Practical Synthesis of Toll-like Receptor Agonist PF-4171455: 4-Amino-1-benzyl-6-trifluoromethyl-1,3-dihydroimidazo [4,5-*c*] pyridin-2-one

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ABSTRACT: The development and implementation of a scalable process for the manufacture of the Toll-like receptor (TLR7) agonist PF-4171455 (**1**) is described. Initial routes used to synthesise **1** in milligram quantities were unsuitable for large-scale synthesis to provide bulk material. As part of the transfer between Medicinal Chemistry and Research-API, collaboration provided a fit for purpose route for the kilo-scale synthesis of **1**. Key aspects of the synthesis included (i) a safe and practical synthesis of a key nitropyridone intermediate **7** over four steps, (ii) a sequential regioselective chlorination to selectively functionalise **7** and (iii) use of a carbamate as a tethered carbonyl group, allowing an efficient regiospecific synthesis of **1**.

INTRODUCTION

Toll-like receptors (TLRs) are a family of conserved transmembrane receptors which form part of the innate immune system that detects pathogen-associated molecular patterns and helps to mount an immune response to challenges by specific pathogens. Certain TLRs are known to recognise viral nucleic acids, and serve to protect host cells from viral infection. Of these, both TLR7 and TLR8 recognise single-stranded RNA, and have been studied for potential applications in infectious disease and as vaccine adjuvants. As part of a programme to identify small molecule agonists of the TLR7 receptor for antiviral applications, PF-4171455 (**1**)[1] emerged as a potent and selective TLR7 agonist and was advanced through preclinical toxicology studies. In order to support the planned studies, bulk quantities of **1** were required. Herein we describe the development of a robust, scalable route to **1**.

Initial Routes to PF-4171455 (1). The original route towards PF-4171455 (**1**) is shown in Scheme 1. The synthesis commenced with the acylation of ethyl 3-amino-4,4,4-trifluorocrotonate **3** with ethyl malonyl chloride **2** using triethylamine in dichloromethane. The resultant enamide **4** was then cyclised to pyridone ester **5** in high yield by deprotonation with 60% sodium hydride dispersion in tetrahydrofuran. Ester hydrolysis followed by decarboxylation in refluxing concentrated hydrochloric acid furnished pyridone **6** in excellent yield. Nitration of **6** with fuming nitric acid in a mixture of acetic acid and ethyl acetate afforded the nitro compound **7** in reasonable yield which was then selectively chlorinated at the 4-position in neat phenylphosphonic dichloride to give chloropyridone **8**. Displacement of the chloride with benzylamine in tetrahydrofuran afforded aminopyridone **9** which was chlorinated in the 2-position with phenylphosphonic dichloride to provide chloropyridine **10**. Nitro reduction with iron in aqueous acetic acid gave the diaminopyridine **11** which was subsequently cyclised with carbonyl diimidazole in acetonitrile to give deazapurinone **12** in excellent yield. Copper mediated displacement of the chloride with benzylamine[2] and final deprotection of the benzyl fragment with concentrated sulphuric acid[3] afforded PF-4171455, **1**.

In examining the route to consider both safety and practicality, several major concerns were apparent. The acylation to prepare enamide **4** led to a crude mixture of desired enamide and an overacylated byproduct **14**[4] resulting from unwanted *C*-acylation followed by *N*-acylation (Figure 1).

The other major impurity was unreacted trifluorocrotonate due to the overacylation pathway as only 1.2 equivalents of malonyl chloride was used. The enamide **4** was typically purified by a very challenging column chromatography which was impractical on large scale. The use of extremely flammable sodium hydride as the base for the cyclisation would be undesirable. The decarboxylation in hydrochloric acid was high yielding, but mixing was a potential issue on scale as the pyridone ester **5** formed a separate layer above the reaction mixture upon addition. The use of nitric acid in acetic acid and ethyl acetate presented a significant risk due to the potential for formation of acetyl nitrate, solutions of which may decompose violently above 60 °C;[5] hence, alternative reagents for this transformation would be required. The middle part of the sequence, i.e. selective 4-chlorination, benzylamine displacement and 2-chlorination had good yields, and the reagents were deemed appropriate for further scale-up although some enabling work would be required for the workup and isolation of the chlorination steps. The iron reduction, whilst not convenient for very large scale due to challenges with mixing, was deemed appropriate for early bulk campaigns, and the cyclisation was trivial.

The main problem in utilising this route was the copper-mediated benzylamine displacement, which required 4 days to

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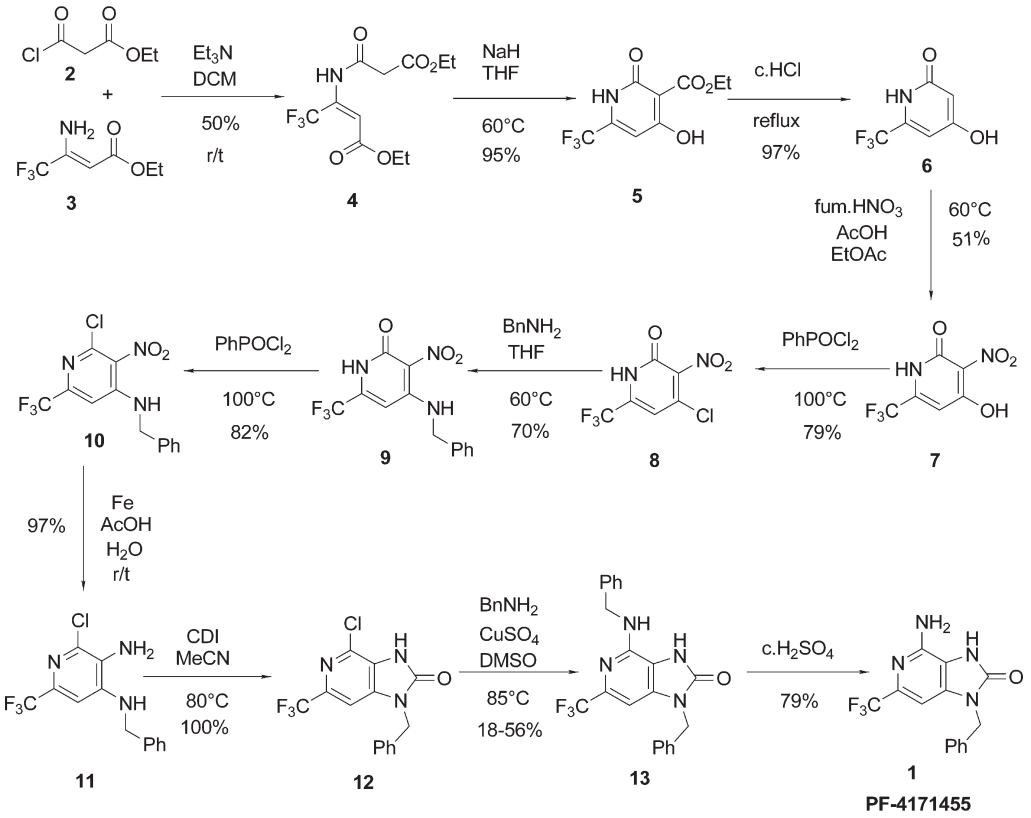
Scheme 1. First-generation route



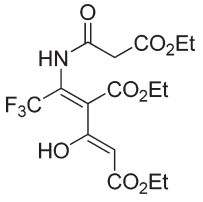


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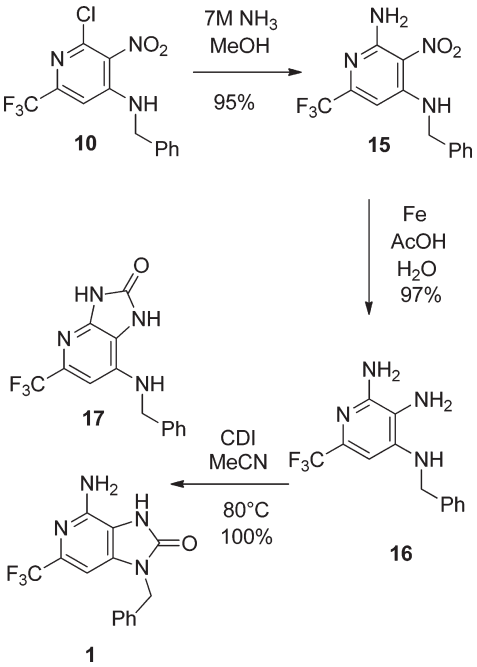
Figure 1. *C*-acylated impurity.

reach completion. This used stoichiometric amounts of copper sulphate, thus making it unattractive from a "green" perspective, and having large amounts of metal species in the penultimate step could require additional processing to control copper levels in the API. However, most importantly the reaction was extremely capricious in yield, and as the scale increased to tens of grams, the yield sharply dropped to provide extremely low amounts of product.

Due to the very low solubility of PF-4171455 **1** in organic solvents, the final step would be problematic on scale as the initial procedure involved neutralisation of the sulfuric acid and then extraction of the product with large amounts of ethyl acetate. Additionally, if purification was required after initial isolation, the low solubility could significantly reduce the options available.

The poor reactivity of the chlorodeazapurinone **12** represented a major challenge, and the most obvious solution to address the problem was to perform the displacement before the nitro reduction. An alternative synthesis was performed as shown in Scheme 2.

Scheme 2. Second-generation route



Advanced intermediate chloropyridine **10** was reacted with 7 M ammonia in methanol, affording the displaced product **15** in high yield. Iron reduction provided the triaminopyridine **16** in excellent yield. Carbonyl diimidazole in acetonitrile was then

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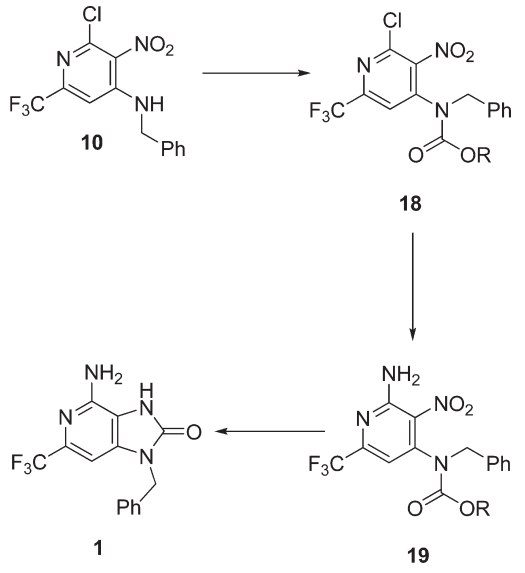
Scheme 3. New proposed route



used to effect cyclisation to PF-4171455 **1** but unfortunately a mixture of regioisomers PF-4171455 **1** and **17** was obtained, which could only be separated by a very difficult chromatography. Additionally, the reaction profile showed a number of unidentified byproducts which may have been formed through partial decomposition of the electron-rich pyridine **16**.

Neither of these two approaches was ideal, each posing different challenges. If the nitro group was reduced early in the sequence, the reactivity in the chloro displacement was markedly reduced as demonstrated in Scheme 1. Conversely, if both chlorine substituents were displaced before nitro reduction, significant regioselectivity issues for the cyclisation were observed as demonstrated in Scheme 2.

One approach considered was to install a suitably protected amino group at the 2-position such as dibenzyl or diallylamine, which would be unable to participate in the cyclisation. However, this seemed a very inelegant strategy as the deprotection would have added one step, and isolation of pure material could be an issue due to poor solubility of PF-4171455 **1**.

A more attractive approach was capping the 4-benzylamino substituent **10** with a carbamate group. It was anticipated that the carbamate functionality would reduce the electron density on the pyridine ring, promoting the chloro displacement and stabilising the diaminopyridyl product of the subsequent reduction. Most importantly it was anticipated that upon reduction of the nitro group in aminopyridine **19**, cyclisation of the newly formed amino group onto the tethered carbamate in situ would provide the deazapurinone PF-4171455 **1** in a regioselective fashion as shown in Scheme 3.[6] This was the strategy adopted to produce material for exploratory toxicology studies prior to candidate nomination, targeting initial deliveries of 50 g.

Route Development and Early Optimisation. The initial part of the approach involved developing a scalable route toward nitropyridine intermediate **10** to provide material for the new end-game. A key objective was to remove the need for column chromatography in the formation of enamide **4** (Scheme 4). It was considered that triethylamine could deprotonate the malonyl chloride, thereby generating a ketene as a more reactive intermediate which could lead to increased levels of *C*-acylation. Hence, triethylamine was replaced with pyridine which is commonly applied as base and catalyst for acylation reactions. A smaller exotherm was noted when using pyridine,[7] and the reaction profile was improved in favor of desired product, but both unreacted enamine **3** and the over acylated product **14** were still formed. It was decided to take the crude mixture[8] into the cyclisation in the hope that the bulk could be purified at the solid pyridone **5**.

It was reasoned that sodium hydride was wholly unnecessary as the choice of base, and instead the much safer potassium *tert*-butoxide was employed.[9] Gratifyingly, treatment of crude enamide **4** with potassium *tert*-butoxide in tetrahydrofuran gave the cyclised product **5** with complete consumption of **4** by LC−MS. It was observed that having taken on the crude material, the reaction medium became increasingly thick and difficult to stir which had not been observed when using clean enamide **4**. Change of solvent from tetrahydrofuran to ethanol kept the reaction sufficiently mobile, and upon concentration, the product could be isolated cleanly by dissolving in water and then acidifying to approximately pH 3 with citric acid. Filtration of the resulting precipitate provided pyridone ester **5** in 63% yield over two steps.

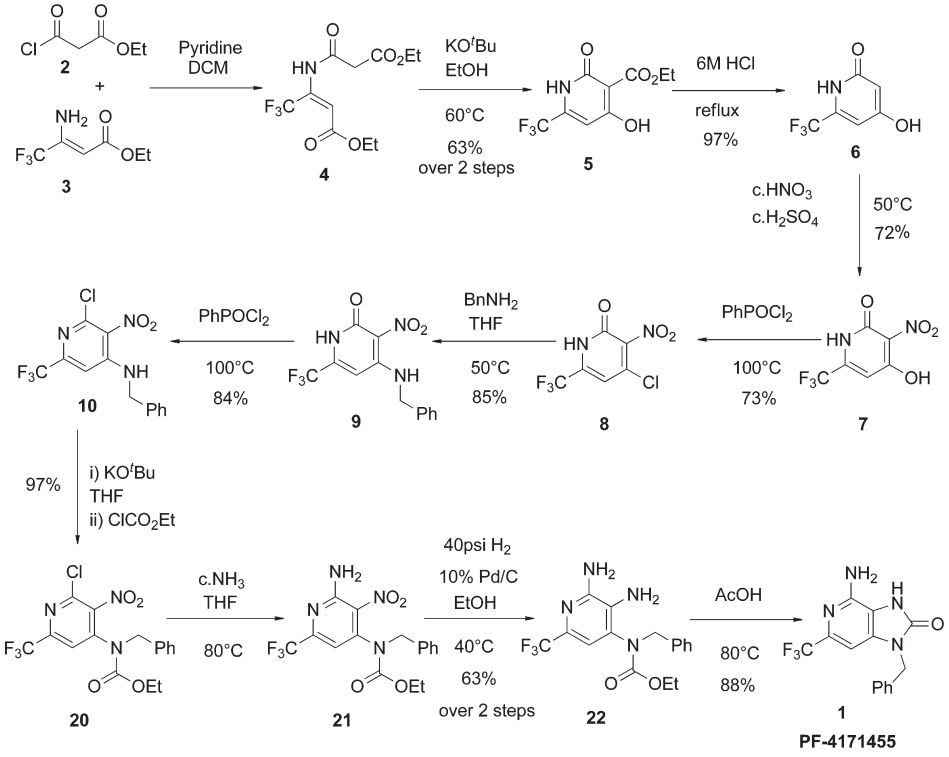
In the decarboxylation, the acid strength was reduced by half. Slurrying the pyridone **5** in 6 M hydrochloric acid and then heating with overhead stirring to effect dissolution provided the pyridone **6** in 94% yield.

For the nitration, alternative conditions were required to avoid the possibility of forming acetyl nitrate. It was anticipated that the classical mixture of nitric acid and sulphuric acid would be suitable for this transformation. Pyridone **6** was dissolved in concentrated sulphuric acid and the exotherm observed upon addition allowed to dissipate. One equivalent of concentrated nitric acid was then added dropwise, with the reaction monitored carefully by quenching of small samples and analysis by LC−MS to ensure nitration was progressing, to avoid a build-up of nitrating agent and the potential for associated thermal hazards. Upon completion of addition, the reaction was carefully quenched into an ice and water mixture and isolated by extraction with ethyl acetate to provide nitropyridone **7** in good yield.

For the chlorination of the 4-hydroxyl function of **7** the number of equivalents of phenylphosphonic dichloride was markedly reduced from 80 to just 5. Although chloropyridone **8** was isolated in high yield, the workup was slightly laborious. After quenching into water followed by treatment with sodium hydrogen carbonate, the pyridine **8** was extracted into ethyl acetate as the sodium salt. Upon concentration it was dissolved in fresh water and then precipitated by the addition of hydrochloric acid. For the amine displacement at least 3 equivalents of benzylamine was necessary: the first to deprotonate the pyridone, the second to react, and the third to sequester the HCl produced. Hence, reaction of chloropyridone with 3.5 equivalents of benzylamine in tetrahydrofuran gave complete conversion to the desired product. Evaporating the reaction mixture to dryness and then quenching with aqueous hydrochloric acid precipitated the benzylaminopyridone **9** which could be isolated cleanly by filtration in good yield.

The second chlorination took minimal optimisation to scale, again just requiring a reduction in the number of equivalents of phenylphosphonic dichloride from 55 to 6.5. The workup for this second chlorination proved far more straightforward than the first and chloropyridine **10** was isolated in high yield. Treatment of chloropyridine **10** with potassium *tert*-butoxide at 0 °C in

Scheme 4. Final route to PF-4171455 1



tetrahydrofuran afforded the anion as a bright purple solution. This was then quenched with ethyl chloroformate to provide the ethyl carbamate **20** in excellent yield. Displacement of the chloride of ethyl carbamate **20** with concentrated ammonia in a sealed vessel at 80 °C gave aminopyridine **21** in good yield with no reaction observed at the carbamate. The crude product was then hydrogenated under 40 psi hydrogen, catalysed by 10% palladium on charcoal to give the diaminopyridine **22** which was recrystallised from *tert*-butylmethyl ether to provide clean material for the final step. Fortunately, the diaminopyridine **22** did not automatically cyclise to the deazapurinone upon reduction as the low solubility of PF-4171455 **1** would have led to great difficulty in removing the catalyst. Cyclisation to the deazapurinone target PF-4171455 **1** was easily achieved by dissolving diaminopyridine **22** in acetic acid and warming to 80 °C whereby the final material precipitated from solution and was isolated by simple filtration with excellent purity and an overall yield of 12% over 11 linear steps to provide PF-4171455 **1** on 50-g scale.

The route was selected for delivery of material to support candidate nomination and early toxicology and clinical studies. Close collaboration between Worldwide Medicinal Chemistry and the Research-API group directed the chemistry being performed oneither side of the formal point of transfer. For further scale-up, the nitropyridone **7** was selected as the in-house starting material and successfully sourced for use in batches to support preclinical safety studies and early clinical supply.

Development for Kilo Lab and Pilot Plant. Enabling of the chemistry for the early campaigns was directed at rapidly delivering processes for the developed route that could be run on kilo-lab and pilot-plant scale to support the early program demands. In the first of the in-house steps, the conversion of nitropyridone **7** to chloropyridone **8**, screening was performed with alternative, more atom-efficient, chlorinating agents, but none gave improvement over the currently used phenylphosphonic dichloride.[10] In development of this step, an early challenge encountered was the reaction stalling upon scale-up into 1-L-scale glassware. A number of hypotheses were tested including mode and rate of agitation, but it was discovered that nitrogen flow across the reaction was the key factor. At high nitrogen flow rates, the reaction would stall, whereas at lower nitrogen flow rates the reaction would proceed to completion. This was attributed to the need for a critical concentration of hydrogen chloride to remain in the reaction mixture. At the reaction temperature of 95 °C, hydrogen chloride is in equilibrium between the reaction mixture and the head space, and high nitrogen flow rates reduced the concentration of hydrogen chloride in the headspace, thus reducing the concentration in the reaction mixture.

Once understood, this factor could be easily controlled. The reaction was monitored closely over the 19 h reaction time to ensure the correct balance of desired product to dichloro impurity. The workup was simplified by precipitating the crude product from the reaction mixture by addition of water. The first isolated material contained varying quantities of phenylphosphonic acid that was readily removed by reslurrying in water. On pilot-plant scale, this process was run, starting with 24.9 kg of nitropyridone **7** to provide 20.2 kg of chloropyridone **8** containing 14.7% dichloro impurity.

In the formation of the benzylaminopyridone **9**, the 3.5 equivalents of benzylamine employed previously gave excellent levels of conversion, with less than 3% starting remaining. The workup was further simplified by reducing the reaction volume (to ~3 mL/g) and adding aqueous hydrochloric acid, which dissolved the benzylamine hydrochloride byproduct and

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precipitated the product. The initially isolated product contained a significant amount of the bis-benzyl impurity (12.4% on pilot-plant scale); this was effectively reduced (to 0.62% on pilot-plant scale) by adding *tert*-butylmethyl ether and reducing the volume by distillation to approximately 50%. This process was run on 20.0 kg of chloropyridine **8** to give 22.1 kg of benzylaminopyridone **9** in a yield of 64% across the first two steps.

Phenylphosphonic dichloride was retained as the reagent in the second chlorination to give chloropyridine **10**. In development of this step, information learned from the first step-around controlling the nitrogen flow rate and the workup was applied. However, two water reslurries were required for this step to remove the residual phenylphosphonic acid, possibly as a result of the higher loading of phenylphosphonic dichloride employed. Although the reaction and the processing on scale took longer than those for the preparation of the chloropyridone **8**, after workup, good-quality chloropyridine **10** was obtained. In the largest campaign, 20 kg of benzylaminopyridone **9** was converted to 15.7 kg of chloropyridine **10** in 77% yield.

For the conversion of chloropyridine **10** to ethyl carbamate **20**, screening demonstrated that a strong base was required and a low temperature was critical for high levels of conversion. A number of bases were screened at 20 °C, but none performed as well as the previously used potassium *tert*-butoxide at low temperature (0 °C and below). With potassium *tert*-butoxide at −10 °C, greater than 98% conversion was achieved, whereas at 0 °C conversion was typically 90%. Even slight deviations above this temperature during a reaction gave a marked reduction in conversion and an increased level of byproduct. For example, one reaction in which the temperature rose to 4 °C after addition gave 17% starting material remaining.

Although nitro groups frequently impart crystallinity to compounds, the ethyl carbamate **20** was not readily isolated as a solid. For the workup, the reaction was quenched with water, washed with aqueous sodium chloride and reduced in volume to give a tetrahydrofuran solution that was used in the next step.

The initial conditions for conversion of the ethyl carbamate **20** to aminopyridine **21** relied on the use of concentrated ammonia and tetrahydrofuran heated to 80 °C in a sealed vessel; the reaction generated ~80 psi of pressure and was not amenable to scale-up into available kilo-lab or pilot-plant facilities. Examination of the concentrated ammonia and tetrahydrofuran conditions at 50 °C in a standard vessel gave excellent conversion (<2% ethyl carbamate **20** remaining after 18 h). As with the previous step, the product aminopyridine **21** was not readily isolated as a solid. For the workup of this step, the reaction was washed with aqueous sodium chloride and distilled and replaced with ethanol, to give an ethanol solution that was used in the hydrogenation.

In the reduction of the aminopyridine **21** to the diaminopyridine **22**, examination of the HPLC analysis from initial hydrogenation reactions showed four key impurities, the triamine **23**, the des-carbamate **24**, the *N*-hydroxy cyclised **25**[11] and the nitroso **26**[12] (see Figure 2).

In addition to these four impurities a small amount of the API, PF-4171455 **1**, was also formed. Initial catalyst screening showed that 10% and 20% Pd−C from Degussa (E101) gave the best results in terms of conversion and minimising impurities. The 10% Pd−C from Degussa (E101) was further screened at a range of loadings (between 2% and 15%). There was very good linear (first-order) correlation between the catalyst loading and the rate of reaction, as judged by hydrogen uptake, and the higher

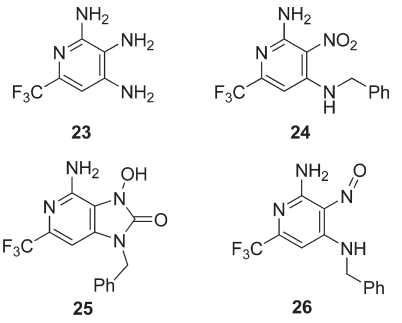

Figure 2. Impurities from the nitro reduction of aminopyridine **21**.

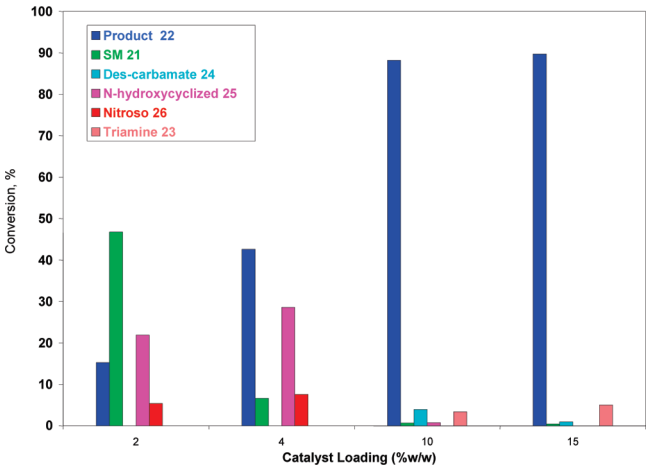

Figure 3. Ratio of product to impurities in the reduction of aminopyridine **21** with varying levels of 10% Pd−C from Degussa (E101).

loadings also gave much better ratios of product to impurities (Figure 3).

Further experiments were performed using the 10% Pd−C and varying both the pressure and temperature (see results in Table 1). One of the key aims from this series of experiments was to minimise the amount of the nitroso compound **26** observed in the reaction profile, eliminating the need to specifically control this impurity in the workup. Under a number of conditions, none of the nitroso compound was detected, and of these 100 psi and 20 °C gave the highest level of conversion and lowest overall level of impurities. Through the development of this step, it was observed that the other impurities could be controlled through the crystallisation and isolation.

With diaminopyridine **22** being the first isolated solid over three steps, crystallisation was critical to ensure high-quality PF-4171455 **1**. Additionally, during the workup there was a requirement to minimise the temperature to prevent thermal conversion of diaminopyridine **22** to PF-4171455 **1**. Early development of the workup showed that crystallisation from a nonpolar solvent (e.g., *tert*-butylmethyl ether) afforded good recovery, but no reduction in the level of the triamine **23**. Further development showed that reducing the ethanol volume and adding an anti-solvent (e.g., toluene, heptane or *tert*-butylmethyl ether) gave good quality material, crucially maintaining ~1% ethanol was key to minimising the amount of triamine **23** in the isolated product. The final workup procedure involved concentrating the ethanol solution after filtration to 2 mL/g under vacuum below 50 °C, addition of *tert*-butylmethyl ether (20 mL/g) and concentrating

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Table 1. Ratio of product to impurities in the reduction of aminopyridine 21 with varying temperature and pressure

pressure (PSI)	temp (°C)	% product **22**	% SM **21**	% triamine **23**	% des-carbamate **24**	% *N*-hydroxy cyclised **25**	% nitroso **26**	% PF-4171455 **1**
50	20	88.2	0.7	3.4	4.0	0.8	ND	1.0
50	40	92	0.49	5.2	1.1	ND	ND	1.2
100	20	92.9	0.1	3.5	1.7	0.9	ND	1.0

to 10 mL/g at atmospheric pressure. The distill and replace process was repeated twice and after cooling to 0 °C the product was isolated by filtration.

In an initial non-GMP campaign, complete removal of ethanol during the workup gave product containing 3.5% of the triamine **23** and 6.6% of PF-4171455 **1**, with 85.8% of the diaminopyridine **22**, in a yield of 51% from chloropyridine **10**. Learnings highlighted above were incorporated for the subsequent GMP campaign in which 15.7 kg of chloropyridine **10** was converted to 11.3 kg of high quality diaminopyridine **22** in a yield of 67% over the three steps.

The final step in the preparation of PF-4171455 **1** was thermal cyclisation in acetic acid. The key challenge with this step was to balance complete consumption of the starting material with overreaction to an acylated byproduct, which although readily purged, did result in a reduction in yield. The optimum temperature was found to be 100 °C for 9 h. For a final step, the processing was very straightforward, with the product precipitating on cooling at approximately 50 °C and after cooling to 20 °C, the product was filtered and washed with acetic acid and ethanol to give 8.8 kg of PF-4171455 **1** of appropriate quality in 89% yield on pilot=plant scale.

Collaboration between Worldwide Medicinal Chemistry and Research-API during the early investment in synthetic route identification was vital in ensuring the overall program could progress in a rapid manner. The initial route to PF-4171455 used in Worldwide Medicinal Chemistry consisted of 11 steps and gave an overall yield of less than 1%. This route was found not to be amenable to scale-up on the basis of a number of factors. Prior to compound nomination, the key API delivery was a 50 g lot for exploratory toxicology studies using a new route with the same number of steps but with a 10.5% overall yield. The collaboration ensured that the route identified at this stage was suitable for multikilogram scale and allowed for very smooth knowledge transfer between both partners. The familiarity with the chemistry allowed an 8.8 kg GMP batch of PF-4171455 **1** to be completed in similar overall yield (11%) within six months of compound nomination.

EXPERIMENTAL SECTION

3-(2-Ethoxycarbonyl-acetylamino)-4,4,4-trifluoro-but-2-enoic Acid Ethyl Ester (4). To a solution of ethyl 3-amino-4,4,4-trifluorocrotonate **2** (300 g, 1.638 mol) in pyridine (160 mL, 1.97 mol, 1.2 equiv) and DCM (1.5 L) in a water bath at ambient temperature was added neat ethyl malonyl chloride **3** (252 mL, 1.97 mol, 1.2 equiv) dropwise over approximately 50 min, maintaining the temperature below 30 °C. The resulting brown solution was stirred in the water bath for 2 h (to a temperature of 22 °C) and then removed from the water bath. The resulting dark-green solution was stirred at ambient temperature for 66 h. The resulting solution was washed with 1 M HCl (aq) (600 mL), and sat. aq $NaHCO_3$ (800 mL). Each aqueous phase was sequentially re-extracted with further DCM (800 and 600 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated to a dark green oil (538.7 g) which was judged to contain ~60% enamide **4** by 1H NMR. The crude enamide **4** was used directly in next step.

4-Hydroxy-2-oxo-6-trifluoromethyl-2-dihydropyridine-3-carboxylic Ethyl Ester (5). To a magnetically stirred solution of crude enamide **4** (150 g, 60% by weight, 0.3 mol) in EtOH (600 mL) in a water bath at ambient temperature was added potassium *tert*-butoxide (62.3 g, 0.555 mol) in a portionwise fashion over 25 min such that the temperature did not exceed 40 °C. Upon completion of addition, the reaction mixture was heated at 70 °C for 2 h and then allowed to cool to room temperature and stirred overnight. At this stage, the reaction was a deep-red suspension. The solvent was then removed in vacuo to give a solid. A saturated solution of citric acid (400 mL) was added to the solid and the resulting suspension stirred for 30 min. The suspension was then filtered to give a pale-pink solid which was washed with several portions of citric acid solution. The filter cake was triturated with pentane, filtered and dried in vacuo at 40 °C for 18 h to give pyridone ester **5** as a pale-pink solid (72 g, 95% yield, equivalent to 63% over the two steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22 (t, J = 7 Hz, 3H), 4.21 (q, J = 7 Hz, 2H), 6.76 (s, 1H), 11.95 (br s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 14.06, 61.03, 102.32, 105.99, 121.03 (q, J = 274 Hz), 144.25 (q, J = 34 Hz), 162.51, 165.00, 165.36. Anal. Calcd for $C_9H_8F_3NO_4$: C, 43.04; H, 3.21; N, 5.58. Found: C, 42.66; H, 3.20; N, 5.36. HRMS m/z Found 252.0480 $[M + H]^+$ $C_9H_8F_3NO_4$ requires 252.0478. Mp 176−177 °C. IR (KBr) 3110, 2996, 2910, 2830, 1659, 1505, 1437, 1378, 1271, 1197, 1156, 1093, 1012, 864, 677 cm^{-1}.

4-Hydroxy-6-trifluoromethyl-1*H*-pyridin-2-one (6). To a mechanically stirred 6 M HCl (aq) (1 L) at ambient temperature was added pyridone ester **5** (165 g, 0.657 mol) in a portionwise manner and the resulting suspension heated at reflux overnight. After several hours at reflux a pale yellow solution had formed followed by the formation of a pale-yellow suspension. The reaction mixture was cooled with an ice bath to 0 °C and neutralised via the dropwise addition of 0.88 ammonia solution (~500 mL). At pH 7 a thick white suspension had formed. The suspension was filtered, the filter cake washed with cold water and dried in vacuo at 50 °C over P_2O_5 for 66 h to give pyridone **6** as a white solid (110.6 g, 94%). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 6.12 (s, 1H), 6.66 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 98.01, 103.05, 121.58 (q, J = 273 Hz), 144.47 (q, J = 33 Hz), 165.90, 168.57. Anal. Calcd for $C_6H_4F_3NO_2$: C, 40.24; H, 2.25; N, 7.82. Found: C, 40.33; H, 2.34; N, 7.56. HRMS m/z Found 202.0088 $[M + Na]^+$ $C_6H_4F_3NO_2$ requires 202.009183. Mp 250−251 °C. IR (KBr) 3124, 3050, 2931, 1679, 1619, 1460, 1357, 1300, 1206, 1019, 987, 854, 724 cm^{-1}.

4-Hydroxy-3-nitro-6-trifluoromethyl-1*H*-pyridin-2-one (7). Pyridone **6** (53 g, 0.3 mol) was added portionwise to concentrated sulphuric acid (130 mL) in 1−2 g portions, with stirring after each addition until all solids had dissolved. During the addition, the temperature increased to 50 °C. When all the

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pyridone **6** had been added, the solution was a pale-brown colour, and the temperature was 43 °C. Concentrated nitric acid (~70%, 20 mL, 0.31 mol, 1.05 equiv) was added three drops at a time, over a period of approximately 1.5 h. The addition was exothermic, but the rate of addition maintained the temperature between 40 and 50 °C without external heating or cooling. When all of the concentrated nitric acid had been added, the solution was a bright-orange colour. Once all the nitric acid had been added, the reaction mixture was stirred, achieving ambient temperature over 1.5 h, and stirred at this temperature for a further 2.5 h. The reaction mixture was then poured slowly onto an efficiently stirred mixture of ice (800 g) and water (500 g). The resulting fluffy white solid was filtered, dissolved in EtOAc (200 mL) and poured into a separating funnel to remove approximately 10 mL of water present. The organic phase was collected, dried over Na_2SO_4, filtered and concentrated to give an off-white solid (32.6 g). The main aqueous filtrate (approx 1.4 L) was then extracted with EtOAc (3 × 500 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated to give an off-white solid (23.7 g). Both solid batches were dissolved in warm EtOAc (200 mL), and heptane (200 mL) was added to effect precipitation. This was filtered to give a white solid that was washed with heptane (200 mL). The solid was dried in vacuo at 40 °C for 18 h to give nitropyridone **7** (37.5 g). Further precipitate had emerged in the filtrate (now 600 mL) and was filtered and dried in vacuo at 40 °C for 18 h to give additional nitropyridone **7** (9.0 g). The combined yield of nitropyridone **7** was 46.5 g (70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.80 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 102.30, 120.26 (q, J = 275 Hz), 126.66, 142.90 (m), 157.00, 159.22. Anal. Calcd for $C_6H_3F_3N_2O_4$: C, 32.16; H, 1.35; N, 12.50. Found: C, 31.93; H, 1.39; N, 12.29. HRMS m/z Found 225.0121 $[M + H]^+$ $C_6H_3F_3N_2O_4$ requires 225.0118. Mp 164−165 °C. IR (KBr) 3073, 2978, 2906, 2810, 1672, 1532, 1487, 1454, 1374, 1270, 1211, 1156, 1080, 947, 841, 793 cm^{-1}.

4-Chloro-3-nitro-6-trifluoromethyl-1*H*-pyridin-2-one (8). To a mixture of phenylphosphonic dichloride (103.0 kg, 529 mol, 4.7 equiv) and DCM (10.0 kg, added as a line wash) was added nitropyridone **7** (24.90 kg, 111 mol) and the mixture heated to 95 °C and stirred at that temperature for 15 h. The mixture was cooled to 20 °C and an IPC taken that confirmed that the reaction had gone to completion (pass criteria <5% SM, result of SM none detected). The reaction mixture was added to water at 20 °C (374 L) maintaining the temperature in the range 20−28 °C. The resulting mixture was stirred at 20 °C for 1 h to confirm that a suspension had formed and the suspension granulated at 20 °C for 5 h 30 min. The resulting suspension was filtered and the filter cake washed with water (2 × 25 L). Water (250 L) was added to the agitated filter dryer and the mixture heated to 57 °C. A solution was observed during this operation, and after cooling to 20 °C, 50 L of filtrate was removed and the remaining mixture stirred at 57 °C for 5 h 30 min, then cooled to 20 °C over 6 h. The mixture was filtered and the filter cake washed with water (2 × 25 L). The resulting solid was dried in vacuo at 50 − 55 °C for 44 h to give pyridone **8** (20.23 kg, 75% based on 100% potency, water content <1%, dichloro impurity 15% by area normalisation). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 113.23, 119.98 (q, J = 275 Hz), 136.28, 137.45, 144.60 (q, J = 36 Hz), 156.55. Anal. Calcd for $C_6H_2F_3ClN_2O_3$: C, 29.71; H, 0.83; N, 11.55. Found: C, 30.10; H, 0.88; N, 11.13. HRMS m/z Found 242.9782 $[M + H]^+$ $C_6H_2F_3ClN_2O_3$ requires 242.9779. Mp 169−170 °C. IR (KBr) 3174, 3123, 2921, 2810, 2435, 1679, 1545, 1484, 1385, 1271, 1216, 1151, 999, 872, 849, 818, 711 cm^{-1}.

4-Benzylamino-3-nitro-6-trifluoromethyl-1*H*-pyridin-2-one (9). Chloropyridone **8** (20.0 kg, 83 mol) was charged to THF (66.8 kg) at 20 °C followed by addition of a solution of benzylamine (30.0 kg, 280 mol, 3.4 equiv) in THF (22.3 kg). The lines were washed with THF (14.6 kg) and the mixture heated to reflux and stirred at this temperature for 22 h. The mixture was cooled to 20 °C and an IPC taken that confirmed the reaction had gone to completion (pass criteria SM <3%, result of SM 2.6%). The mixture was heated and distilled at atmospheric pressure until the volume was approximately 60 L and then cooled to 20 °C. Water (268 L) and 2 M HCl (aq) (83 L of water and 20.6 L of conc. HCl) and water (33 L) were sequentially added, and the mixture was granulated at 20 °C for 24 h. The mixture was filtered and washed with water (2 × 40 L) and dried in vacuo at 50 °C for 4 days to give water-wet benzylaminopyridone **9** (35.48 kg).

The water wet material isolated above was charged to *t*-BME (367.0 kg) and mixture heated to reflux and distilled until the volume was approximately 248 L. The mixture was cooled to 20 °C, granulated at that temperature for 2 h, filtered and washed with *t*-BME (18.4 kg × 2) dried at 45 °C in vacuo for 25 h to give benzylaminopyridone **9** (22.1 kg, 64% over the two transformations from nitropyridone **7**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.69 (d, J = 6 Hz, 1H), 6.54 (s, 1H), 7.25−7.38 (m, 5H), 9.10 (br s, 1H), 12.63 (br s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 45.97, 95.03, 119.75 (q, J = 275 Hz), 120.88, 127.00, 127.40, 128.73, 137.77, 139.40 (m, J = 32 Hz), 151.25, 157.17. Anal. Calcd for $C_{13}H_{10}F_3N_3O_3$: C, 49.85; H, 3.22; N, 13.41. Found: C, 50.00; H, 3.23; N, 13.19. HRMS m/z Found 314.0759 $[M + H]^+$ $C_{13}H_{10}F_3N_3O_3$ requires 314.0747. Mp 206−207 °C. IR (KBr) 3329, 3066, 2863, 1663, 1578, 1531, 1450, 1375, 1345, 1266, 1211, 1133, 885, 811, 735, 699 cm^{-1}.

Benzyl-(2-chloro-3-nitro-6-trifluoromethylpyridin-4-yl)amine (10). Benzylaminopyridine **9** (20.0 kg, 64 mol) was charged to a mixture of phenylphosphonic dichloride (82.4 kg, 423 mol, 6.75 equiv) and DCM (10.0 kg line wash) at 20 °C and heated to 95 °C and stirred at that temperature for 22 h. The mixture was cooled to 20 °C and an IPC taken that confirmed the reaction had gone to completion (pass criteria <5% SM, result of SM < 1%). The reaction mixture was added to water (at 20 °C) (300 L) maintaining the temperature in the range 20−35 °C. The resulting mixture was stirred at 20 °C for 1 h to confirm that a suspension had formed and the suspension granulated at 20 °C for 16 h. The resulting suspension was filtered using an agitated filter dryer and the filter cake washed with water (2 × 25 L). Water (200 L) was added to the agitated filter dryer and the mixture heated to 57 °C over 6 h and stirred at this temperature for 3 h then cooled to 20 °C over 5 h 30 min. The mixture was stirred at this temperature for 1 h and then filtered, and the filter cake was washed with water (2 × 20 L). Water (200 L) was added to the agitated filter dryer, and the mixture was heated to 57 °C over 6 h and stirred at this temperature for 3 h and cooled to 20 °C over 4 h. The mixture was stirred at this temperature for 1 h 30 min and then filtered, and the filter cake was washed with water (2 × 20 L). The resulting solid was dried in vacuo at 55−65 °C for 3 days to give chloropyridine **10** (15.7 kg, 77%, water content <0.5%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.63 (d, J = 6 Hz, 2H), 7.24−7.38 (m, 5H), 8.63 (t, J = 6 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 45.55, 106.07, 120.25 (q, J = 275 Hz), 126.97, 127.38, 128.64, 132.66, 136.96, 142.54, 146.00 (q, J = 34 Hz),

148.33. Anal. Calcd for $C_{13}H_9F_3ClN_3O_2$: C, 47.08; H, 2.74; N, 12.67. Found: C, 47.12; H, 2.70; N, 12.64. HRMS *m/z* Found 332.0424 $[M + H]^+$ $C_{13}H_9F_3ClN_3O_2$ requires 332.0408. Mp 110−111 °C. IR (KBr) 3342, 1612, 1541, 1459, 1357, 1286, 1192, 1150, 1056, 970, 867, 756, 701 cm^{-1}.

Benzyl-(2-chloro-3-nitro-6-trifluoromethylpyridin-4-yl) carbamic Acid Ethyl Ester (20). A solution of potassium *tert*-butoxide (5.84 kg, 52.0 mol) in THF (46.8 kg) at −10 °C was added to a solution of chloropyridine **10** (15.7 kg, 47.3 mol) in THF (257.2 kg) at −10 °C over 30 min maintaining the temperature below −8 °C. The vessel containing the potassium *tert*-butoxide solution and the transfer lines were washed through with THF (27.9 kg), and the resulting mixture was stirred at −10 °C for 1 h before a solution of ethyl chloroformate (5.90 kg, 54.4 mol) in THF (29.3 kg) at −10 °C was added over 30 min, maintaining the temperature below −7 °C. The vessel containing the neat ethyl chloroformate, the ethyl chloroformate solution and the transfer lines were washed through with THF (14.0 kg) (cooled to −10 °C in the ethyl chloroformate solution vessel), and the resulting mixture was stirred at −10 °C for 1 h. The reaction was quenched by the addition of water (63 L) over 12 min, maintaining the content temperature less than 25 °C, followed by the addition of a solution of sodium chloride (22.1 kg) in water (63 L). The resulting mixture was stirred for 15 min and allowed to separate over 30 min. After a pH check on the lower layer (acceptable range 5−9, result = 7.8), the lower layer was separated and an IPC taken prior to distillation.[13] The mixture was distilled at atmospheric pressure until ∼94 L remained, and this solution was used in the next step. Data from a purified sample: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (t, J = 7 Hz, 3H), 4.11 (q, J = 7 Hz, 2H), 5.04 (s, 2H), 7.25−7.34 (m, 5H), 8.22 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 13.75, 52.86, 63.27, 119.65 (q, J = 275 Hz), 120.43, 127.82, 128.11, 128.44, 135.64, 143.07, 143.17, 146.13, 147.46 (q, J = 37 Hz), 152.84. Anal. Calcd for $C_{16}H_{13}F_3ClN_3O_4$: C, 47.60; H, 3.25; N, 10.41. Found: C, 48.09; H, 3.34; N, 10.33. HRMS *m/z* Found 404.0635 $[M + H]^+$ $C_{16}H_{13}F_3ClN_3O_4$ requires 404.0619. IR (neat) 3087, 2986, 1730, 1553, 1425, 1310, 1253, 1154, 1011, 949, 880, 759, 702 cm^{-1}.

(2-Amino-3-nitro-6-trifluoromethylpyridin-4-yl)-benzyl-carbamic Acid Ethyl Ester (21). An 0.880 M ammonia solution (31.9 kg) was added to a solution of ethyl carbamate **20** (assumed 18.1 kg, 44.9 mol) in THF (∼94 L) from the previous step at 50 °C over 40 min maintaining the temperature in the range 45−50 °C. The lines were washed with water (15 L) and the resulting mixture stirred at 50 °C for 24 h. The mixture was cooled to 20 °C and an IPC taken (pass criteria <5% SM, result of 15%). The mixture was heated to 50 °C, and 0.880 M ammonia solution (4.0 kg) was added, maintaining the temperature in the range 45−50 °C. The lines were washed with water (5 L), and the resulting mixture was stirred at 50 °C for 17 h and cooled to 20 °C; a sample was taken for IPC (pass criteria <5% SM, result of SM = 3%). A solution of sodium chloride (25.3 kg) in water (72.4 L) was added, the mixture was stirred for 1 h 15 min and then allowed to separate for 5 h 30 min. The aqueous layer was removed and the organic layer distilled to a volume of ∼54 L. Absolute EtOH (287 kg) was added and the resulting mixture distilled to a volume of ∼54 L. Absolute EtOH (209 kg) was added and the resulting mixture distilled to a volume of ∼163 L to give a solution of aminopyridine **21** in EtOH (110 kg) that was used in the next step. Data from a purified sample: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, J = 7 Hz, 3H), 4.04 (q, J = 7 Hz, 2H), 4.93 (s, 2H), 6.90 (s, 1H), 7.22 −7.34 (m, 5H), 7.57 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 13.83, 52.47, 62.68, 106.30, 120.30 (q, J = 276 Hz), 127.63, 128.04, 128.43, 136.38, 145.93, 148.17 (q, J = 35 Hz), 153.29, 153.43.[14] Anal. Calcd for $C_{16}H_{15}F_3N_4O_4$: C, 50.01; H, 3.93; N, 14.58. Found: C, 50.02; H, 3.87; N, 14.55. HRMS *m/z* Found 385.1136 $[M + H]^+$ $C_{16}H_{15}F_3N_4O_4$ requires 385.1118. IR (neat) 3492, 3334, 3195, 2986, 1722, 1612, 1525, 1422, 1338, 1257, 1153, 1021, 944, 887, 839, 739, 704 cm^{-1}.

Benzyl-(2,3-diamino-6-trifluoromethylpyridin-4-yl)carbamic Acid Ethyl Ester (22). Palladium hydroxide on carbon catalyst (10%, water wet, 0.89 kg) was added to a solution of aminopyridine **21** (assumed 7.8 kg, 20.3 mol) in EtOH from the previous step (55 kg) and EtOH (24 kg), followed by a water line wash (2 L). The mixture was hydrogenated at 20 °C and 7.9 barg (bar gauge) for 3 h, and a sample was taken for IPC (pass criteria <5% SM, <2% nitroso intermediate, >80% product, results of SM = 1.3%, nitroso intermediate = 0.87% and product = 98%). The catalyst was removed by recirculation over a Gauthier filter. The filtrate was collected and the Gauthier filter washed by recirculation with EtOH (50 kg) and combined with the original filtrate.

The above process was repeated at the same scale (with IPC results of SM = 1.2%, nitroso intermediate = 0.85% and product = 98%), and the EtOH filtrates from both streams were combined using additional EtOH (totalling 25 kg) as line washes.

The mixture from the combined streams was distilled at reduced pressure (temperature maintained below 50 °C) until a volume of approximately 36 L remained. *t*-BME (261 kg) was added and the mixture distilled until a volume of approximately 180 L remained. *t*-BME (132 kg) was added and the mixture distilled until a volume of approximately 180 L remained. *t*-BME (130 kg) was added and the mixture distilled until a volume of approximately 180 L remained. *t*-BME (130 kg) was added and the mixture cooled to 0 °C at a rate of 1 °C/min, and the mixture granulated at 0 °C for 1 h. The mixture was then filtered and washed twice with *t*-BME (39 kg and 37 kg). The resulting solid was dried at 55 − 65 °C for 16 h (result *t*-BME = 0.15%, EtOH = none detected) to give diaminopyridine (11.3 kg, 31.9 mol, 67% over the three transformations from chloropyridine **10**).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12 (m, 3H), 4.09 (m, 2H), 4.25 (m, 1H), 5.03 (m, 1H), 5.43 (br s, 1H), 6.16 (br s, 1H), 6.33 (s, 1H), 7.22−7.31 (m, 5H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 14.47, 50.73, 61.30, 110.87, 122.39 (q, J = 272 Hz), 127.29, 128.05, 128.25, 129.54, 129.95 (q, J = 33 Hz), 137.66, 149.85, 154.78.[14] Anal. Calcd for $C_{16}H_{17}F_3N_4O_2$: C, 54.24; H, 4.84; N, 15.81. Found: C, 53.32; H, 4.71; N, 15.45. HRMS *m/z* Found 355.1372 $[M + H]^+$ $C_{16}H_{17}F_3N_4O_2$ requires 355.1376. IR (KBr) 3486, 3439, 3383, 3311, 3215, 2928, 1687, 1607, 1493, 1436, 1337, 1278, 1142, 1010, 964, 871, 767, 699, 663 cm^{-1}.

4-Amino-1-benzyl-6-trifluoromethyl-1,3-dihydroimidazo [4,5-*c*]pyridin-2-one (1). A suspension of diaminopyridine **22** (11.3 kg, 31.9 mol) in glacial AcOH (108 kg) was heated to 100 °C and maintained at that temperature before being cooled to 20 °C at a rate of 2 °C/min. A sample was taken for IPC (pass criteria SM < 1%, result of SM = 0.41%). The mixture was filtered and washed with glacial AcOH (24.4 kg) and absolute EtOH (18.0 kg). The resulting solid was dried at 55−65 °C for 29 h to give API PF-4171455 **1** (8.8 kg, 28.5 mol, 89%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.02 (s, 2H), 6.22 (s, 2H), 7.00 (s, 1H), 7.21−7.32 (m, 5H), 10.77 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 43.69, 93.62, 111.24, 122.10 (q, J = 274 Hz), 127.26, 127.54, 128.66, 135.34, 136.76, 137.47 (q, J = 33 Hz), 143.76, 153.55. Anal. Calcd for

$C_{14}H_{11}F_3N_4O$: C, 54.55; H, 3.60; N, 18.17. Found: C, 54.48; H, 3.61; N, 17.97. HRMS *m/z* Found 309.0953 $[M + H]^+$ $C_{14}H_{11}F_3N_4O$ requires 309.0958. Mp 350 °C. IR (KBr) 3413, 3183, 2856, 1706, 1659, 1616, 1463, 1405, 1276, 1230, 1188, 1101, 926, 812, 699, 664 cm^{-1}.

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(8) Characterisation of a purified sample **4**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17−1.21 (m, 6H), 3.46 (s, 2H), 4.07−4.13 (q, 4H), 6.37 (s, 1H), 10.26 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 14.52, 43.23, 61.17, 61.35, 116.38, 121.20 (q, *J* = 275 Hz), 131.28 (q, *J* = 34 Hz), 163.85, 164.90, 167.37. HRMS *m/z* Found 298.0884 $[M + H]^+$ $C_{11}H_{14}F_3NO_5$ requires 298.0897.

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(11) High yields of aromatic hydroxylamine can be obtained by hydrogenation over platinum in lower alcohols containing 1−2% dimethylsulfoxide: (a) Rylander, P. *Aldrichimica Acta* **1979**, *12*, 53. Palladium catalysis has been used with hydrazine or phosphinic acid as the reductant:(b) Rondestvedt, C. S., Jr.; Johnson, T. A. *Synthesis* **1977**, 850. (c) Entwistle, I. D.; Gilkerson, T.; Johnstone, R. A. W.; Telford, R. P. *Tetrahedron* **1978**, *34*, 213.

(12) When nitro compounds are treated with most reducing agents, either nitroso compounds are not formed, or they react further under the reaction conditions and cannot be isolated: March, J. *Advanced Organic Chemistry* 4th ed.; Wiley: New York, 1992; p1217.

(13) An IPC was taken to ensure a low level of the starting material chloropyridine **10** prior to starting the distillation at atmospheric pressure to act as a control for potential thermal hazards. If the level of chloropyridine **10** was greater than 5%, then a thermal stability test was required before starting the distillation. The result for the process described was 1.9% chloropyridine **10**.

(14) The ^{13}C NMR spectra for **21** and **22** list 13 peaks, yet there are 14 nonequivalent carbons in each of these two molecules. It is likely the missing signal overlaps with one of the other signals.

NOTE ADDED AFTER ASAP PUBLICATION

This article was published on the Web on May 25, 2011. Two authors were added. The corrected version was reposted on June 10, 2011.