Organic Process Research & Development

Article

pubs.acs.org/OPRD

A Novel Scalable Process to the GSK3β Inhibitor AZD8926 Based on a Heterocyclic Ziegler Coupling

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ABSTRACT: Development of a new, safe, and scalable route to the GSK3β inhibitor, AZD8926, is presented. In brief, the process constitutes of (i) a synthesis of 1-(pyran-4-yl)-2-trifluoromethyl-imidazole, **14**; (ii) a Ziegler-type coupling of lithiated **14** with commercially available 2-chloro-5-fluoropyrimidine via 1,2-addition over the 3,4-C−N bond; (iii) a copper-catalyzed dehydrogenative aromatization using oxygen as the stoichiometric oxidant; and (iv) an aromatic C−N bond formation using either a Buchwald−Hartwig coupling or an acid-catalyzed amination. This process circumvents the main issue in the early-phase route, in which serious process safety constraints were associated with the hazardous properties of the structure, formation, and reduction of 5-methyl-4-nitroisoxazole, **2** (4200 J/g). The new process has been demonstrated on a multigram, 2-L scale. The overall yield was improved from 4 to 14%, and the number of steps decreased from 12 to 10.

INTRODUCTION

AZD8926 (**9**) is a potent glycogen synthase kinase-3β (GSK3β) inhibitor which has potential for treating several CNS disorders, such as Alzheimer's disease (AD), schizophrenia, and chronic as well as acute neurodegenerative diseases.[1] When **9** entered into clinical development phase, a closer evaluation of process safety and scale-up efficiency factors was performed. Initial scale-up work for clinical material utilized the original medicinal chemistry route[2] (Scheme 1), and 7.9 kg of the active pharmaceutical ingredient (API) was produced in approximately 4−6% overall yield after optimization. Several issues were identified as impediments to long-term use of this route:

- Problems with the high energy of substances **2** (4200 J/g) and **3** (1500 J/g) as well as problems with desired reactions, including low onset temperatures and accumulation issues.
- Low yield in the synthesis of the enaminone **5** (30−36%).
- The fluorination of the enaminone **5** generated an unstable intermediate, and before the reaction was complete it was necessary to proceed with guanidine cyclization to **6**.
- The Selectfluor reagent is expensive, and despite extensive optimization, the isolated yield after fluorination and cyclization to the pyrimidine **6** was only 50−55%.
- The use of palladium (Pd) catalysis in the final step required rework to reduce residual levels of Pd in the API.

These factors made the route unsuitable for further scale-up and long-term supply of API. A large literature survey was made, and our retrosynthetic analysis of **9** was directed towards earlier introduction of cross-coupling chemistry and construction of the imidazole moiety in a different way to avoid intermediates with high energy content. Furthermore 5-fluoro-substituted pyrimidines, commercially available in multikilogram quantities, were investigated as potential starting materials to avoid expensive fluorination reagents. In the search for suitable coupling partners, the 2-CF_3-imidazole **14** (Scheme 2) was identified, but up to this point compound **14** was unknown in the literature. Herein we report the development of a scalable route to the key intermediate **14** and thereafter the development of a new scalable process to AZD8926 (**9**).

RESULTS AND DISCUSSION

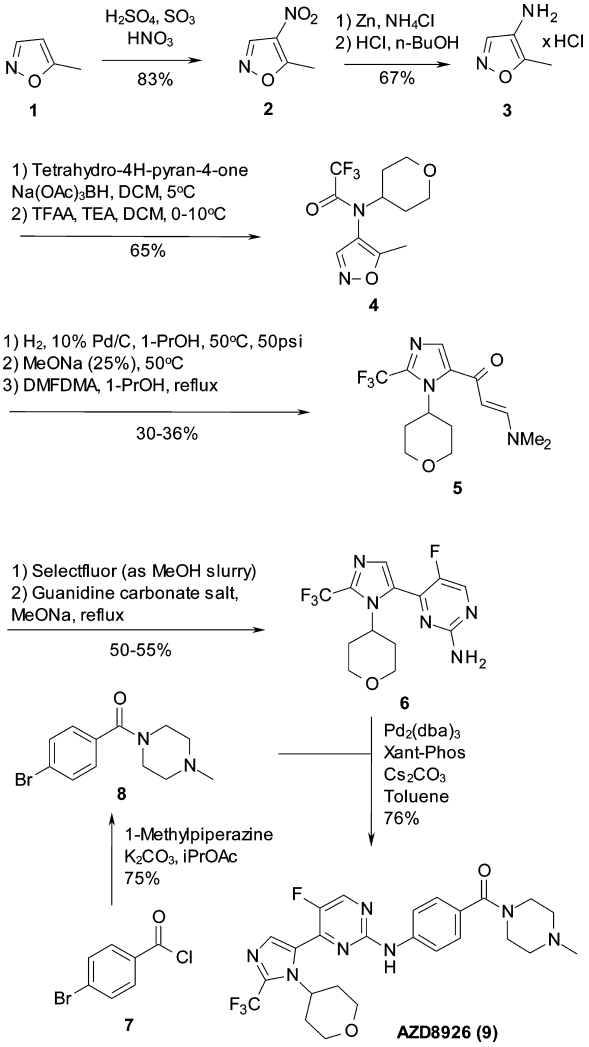
Coupling Partner, 1-(Pyran-4-yl)-2-trifluoromethyl-imidazole, 14. In order to utilize the proposed new route using 2-CF_3-imidazole, **14**, as a building block (Scheme 2), a new methodology for the preparation of such compounds had to be developed because the existing methods were not applicable to large-scale synthesis due to the use of either photochemical or expensive methods or environmentally unfriendly reagents.[3] In the first step of the synthesis ethyl trifluoroacetate and the amine **10** using triethylamine (TEA) and toluene as solvent gave amide **11**. The first approach to prepare the chloroimine **12** adopted carbon tetrachloride (CCl_4) and THF as a solvent combination together with triphenylphosphine (TPP) and the amide **11**.[4] Both TPP and CCl_4 are undesirable and not a long-term solution. Several classical methods to form the chloroimine **12** from the amide **11** were then tested; however, often complex mixtures were obtained, or no reaction occurred. The best result was achieved using triphosgene and TEA. An undesired byproduct, ethyl carbamoyl chloride, was detected which is a known possible side reaction when using TEA with triphosgene.[5]

The byproduct formation was reduced when a solution of triphosgene was charged over several hours at 50 °C to a mixture of the amide **11** and TEA in a nonpolar solvent. Toluene was the most nonpolar solvent used due to the solubility profile of the amide **11**. A variety of bases other than TEA were tested, such as Hünigs base, carbonates, and pyridine, without good results. The chloroimine **12** was treated

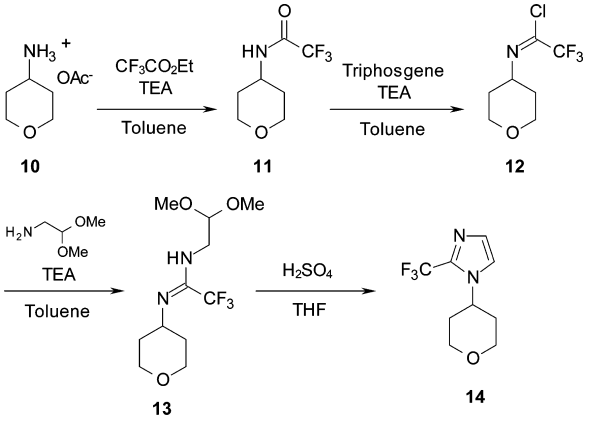
Received: December 20, 2012

   dx.doi.org/10.1021/op300365e | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

Scheme 1. Optimized medicinal chemistry route to AZD8926 (9)



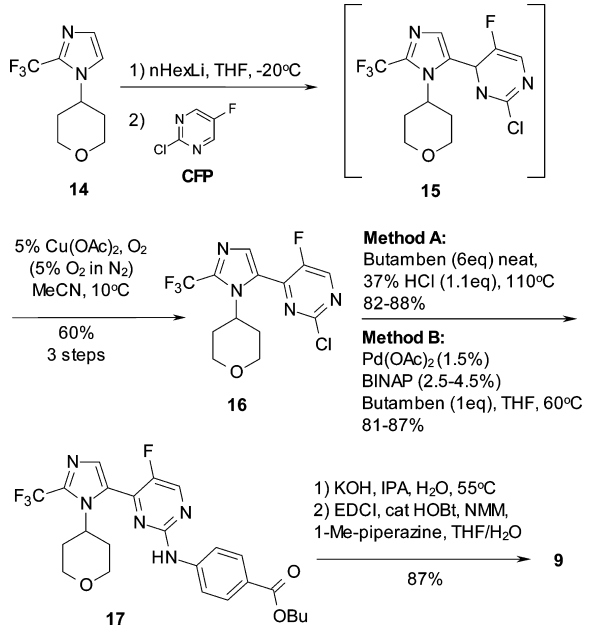
Scheme 2. Preparation of imidazole 14 from tetrahydropyran 10



with aminoacetaldehyde dimethyl acetal in toluene at room temperature to form compound **13**, and upon treatment with sulfuric acid (H_2SO_4) in THF at room temperature the imidazole **14** was synthesized. Use of aminoacetals and different acids to form imidazoles from chloroimines is known in the literature.[6] The imidazole **14** (Scheme 2) was isolated after four telescoped synthetic steps as a sugar-like solid in an overall yield of 34% from compound **10**. The method was rapidly scaled to approximately 500 g in a 5-L reactor, and no more optimization was performed.

Cross-Coupling Investigations. With the key intermediate **14** in hand, a number of cross-coupling methods were considered, involving either the 5*H*-imidazole using C−H activation conditions[7] or a 5-metal-imidazole as an intermediate applying Suzuki or Negishi conditions.[8] One of the synthetic strategies was to use 2,4-dichloro-5-fluoropyrimidine (**DCFP**) as starting material, which is commercially available in multikilogram quantities. A screen of catalysts for the C−H activation coupling between compound **14** and **DCFP** were conducted in a few solvents (DMF, toluene, and 2-propanol) and with a variety of bases (Cs_2CO_3, KOAc, t-BuONa, and *N*,*N*-dicyclohexylmethylamine). All the work was performed in a glovebox, but the desired compound **16** (Scheme 3) was

Scheme 3. New route to AZD8926 (9) from imidazole 14



never detected. The Negishi coupling was investigated in a series of experiments using THF as solvent. A large variety of catalysts were tested, and with one exception the reactions gave poor or moderate conversion to the desired compound **16**. The only interesting result, with a conversion of 69%, was achieved when the lithiated compound **14** was first reacted with I_2 and the formed 5-iodo-imidazole was treated with Rieke-zinc[9] to form imidazol-5-yl zinc iodide and thereafter coupled with **DCFP** using $Pd(dba)_2$ as the catalyst.

Fortunately, Bursavich and co-workers reported[10a] a convenient synthesis to diverse 2-amino-4-heteroarylpyrimidines via a 2-chloropyrimidine intermediate, and our second synthetic strategy generated compound **16** via this Ziegler-type reaction.[10] Nucleophilic attack of *in situ* lithiated **14** on commercially available 2-chloro-5-fluoropyrimidine (**CFP**) afforded compound **16**, in reasonable yield, after subsequent oxidative workup (Scheme 3). It was decided to focus our efforts on the Ziegler reaction as a possible strategy for multikilogram production.

Lithiation and Addition. In order to achieve a process fitted for a wider range of plants, it was desired to avoid the

dx.doi.org/10.1021/op300365e | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

need for cryogenic equipment during the lithiation of **14**. This could be achieved with a good temperature range between −20 to −5 °C which gave a stable conversion of >95%. Only THF and 2-methyl-tetrahydrofuran (2-MeTHF) were investigated as solvents. The use of 2-MeTHF gave a homogeneous solution during lithiation compared to THF which gave a slurry; however, regarding byproduct **18** formation,[11] THF gave a more selective addition of 5-Li-imidazole to **CFP** to form the intermediate **15**. Due to the inhomogeneous reaction when using THF it was noted that the in-process control (IPC) by LC−MS varied if care was not taken during sampling of the reaction mixture. This approach to obtain a representative sample was considered unrobust for the pilot plant. Therefore an in-line mid-IR method was developed to follow the course of the lithiation reaction by measuring the disappearance of **14**. Hexyl lithium was chosen as lithiating agent for safety and economical reasons in the pilot plant, but *n*-butyl lithium gave very similar results. A slight excess of the hexyl lithium (1.05−1.1 equiv) was added, followed by a controlled addition of **CFP** (1.05−1.1 equiv) dissolved in THF. The reaction temperature was maintained below −15 °C during the addition to obtain a high conversion. The reaction was very fast, and the conversion was complete within 15 min, but a prolonged reaction time did not lead to an increased level of byproduct **18**.[11]

Oxidative Dehydrogenation. The formation of the dihydropyrimidine **15** and the subsequent aromatization to **16** was initially telescoped using benzoquinone as oxidating agent. The reaction worked well on a 10-g scale, but the extractive workup turned out to be very difficult, since both phases were almost black. Also, loss of fluoride was a competing side reaction giving up to 30% of compound **18**.[11] Air-oxidation of **15** in THF was also found to work reasonably well in the laboratory but was at first considered unsuitable to scale up from a process safety perspective. First, quenching the reaction mixture containing compound **15** with acetic acid (HOAc) followed by an extractive workup before the oxidation gave less byproduct **18** (2−4%), and second, a good phase separation was obtained. Alternative oxidating agents (NMO, H_2O_2, cumene peroxide, and *tert*-butylperoxide) were investigated with varied results. Yamamoto and co-workers have reported a mild, practical procedure for oxidative dehydrogenation with a catalytic amount of a Cu salt, K_2CO_3, and *tert*-butylhydroperoxide.[12] Therefore, H_2O_2 in combination with $Cu(OAc)_2$ as catalyst was investigated, and promising results were obtained. Furthermore, the dehydrogenation of **15** required addition of TEA to proceed at a reasonable rate. However, the reaction was not robust, and decomposition of H_2O_2 by the catalyst was observed. It was decided to proceed with the work using air-oxidation, with $Cu(OAc)_2$ as the catalyst, but in another solvent other than THF due to the intrinsic risk of peroxide formation. The reaction worked best in acetonitrile (CH_3CN), giving 93−97% conversion of **15** to **16** and 60% isolated yield over three complex steps starting from **14**. The following procedure was developed. The reaction mixture of **3-Li-15** was quenched with HOAc in ethylacetate (EtOAc) at −10 to 10 °C, and then water was added. After phase separation and solvent swap to CH_3CN, $Cu(OAc)_2$ (0.05 equiv) and TEA (1 equiv) were added. The solution was cooled to 10 °C, giving a slurry. A mixture of 5% O_2 and 95% N_2, which unlike air was acceptable in our pilot plant from a process safety perspective, was bubbled through the slurry which gradually turned into a solution. After 24 h (92% conversion) the solution was concentrated under reduced pressure. To remove copper from the product, a solution of 5% NH_3 (aq) was added (effective removal down to <50 ppm, without ammonia >2500 ppm). The mixture was cooled to 0 °C, precipitating **16** with an HPLC purity of 99% on a 120-g scale.

Palladium-Catalyzed Amination. To avoid the potential problems with using palladium in the final step and risking contamination of the API, one of the alternatives was to perform a Pd-catalyzed coupling of **16** with a *p*-aminobenzoic ester and thereafter transform the ester to an amide as the final step. For solubility reasons, 4-aminobutyl- and ethyl-benzoate were chosen for the screening experiments. THF was used as solvent for the reactions. Various combinations of ligands, Pd-sources, and bases were investigated. Out of the four 2-(dialkyl)phosphinobiphenyl ligands tested, SPhos in combination with $Pd(OAc)_2$ and K_2CO_3 gave 100% conversion of **16** to **17** within 3 h. The same conversion was achieved using (*R*)-BINAP, but the reaction was considerably slower, gave somewhat lower yield, and required a reaction time ≥7 h. Replacing (*R*)-BINAP with (±)-BINAP prolonged the reaction time considerably, as a consequence of the lower solubility of the racemate. Also the carbene ligand Neolyst CX32 gave high conversion to **17** (98%). For cost reasons (*R*)-BINAP was the preferred ligand. Concerning the Pd-sources investigated, $Pd(OAc)_2$ gave a better selectivity than $Pd(dba)_2$ when used together with SPhos. In a reaction with $Pd(dba)_2$, **17** reacted further with a second molecule of **16** to give 11% of a tertiary amine as a byproduct. Of the bases tested, both *t*-BuOK and *t*-AmONa gave 2- and 5-alkoxy derivatives of **16** as byproducts in various amounts (4−45%). Regarding the base, fortunately K_2CO_3 worked better than Cs_2CO_3. Compound **17** was obtained in 81−87% yield and 99−100% HPLC purity by reacting **16** and 4-amino butyl benzoate (1.03 equiv) in THF at 60 °C under inert atmosphere, using (*R* or ±)-BINAP (0.03 equiv) and $Pd(OAc)_2$ (0.015 equiv) as catalyst and K_2CO_3 (1.4 equiv) as base. The workup consisted of cooling to 30 °C, addition of HOAc (1.4 equiv) in EtOAc and water, phase separation, aqueous wash, solvent swap to ethanol (EtOH), and crystallization. The coupling product **17** was isolated in 81% yield and 99% HPLC purity on a 110-g scale. Analysis of the product for Pd-content showed <10 ppm.

Acid-Mediated Amination. In parallel to palladium-catalyzed amination, an alternative acid-mediated procedure was investigated to avoid the use of a palladium catalyst. A few examples of acid-mediated coupling between 2-chloropyrimidines and anilines could be found in the literature. A first approach was to use *p*-toluene sulfonic acid (*p*TsOH) in dioxane at reflux,[10a] and second 1 equiv 32% hydrogen chloride (HCl) in an alcohol at reflux was tried.[13] A small screen of reactions between compound **16** and *p*-aminobenzoic ester was set up. The use of *p*TsOH in dioxane generated only about 10% conversion, but the use of 37% HCl (2 equiv) in ethanol at reflux looked interesting with >40% conversion. Therefore, the higher boiling n-butanol (BuOH) was considered as solvent in combination with butyl 4-aminobenzoate (butamben). When a mixture of compound **16** and butamben in BuOH was heated at reflux with 37% HCl (1.05 equiv), >90% conversion was obtained. If the reaction was performed more concentrated 95% conversion was obtained after reacting overnight. Butamben is a cheap starting material with a melting point of 88−90 °C and it is also soluble in dilute acidic water. Therefore butamben (4 equiv) was considered as solvent by melting with compound **16** at 120 °C with 37% HCl (1.05 equiv). A clear solution was obtained, and within 5−6 h >97% conversion was

dx.doi.org/10.1021/op300365e | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

seen. Then 2 M HCl was added, and after filtration at 50 °C compound **17** could be isolated in 85% yield. The main features to investigate were the robustness prior to scale up and the filtration of compound **17** due to solidification of butamben in the receiver vessel during isolation. Butamben is fully soluble in EtOH, and if ethanol was charged in the receiver vessel before isolation no solidification was obtained. For the planned manufacture in the pilot plant, 4 equiv of butamben would have given a reaction volume under the minimum stirring volume of the intended reactor. Therefore amounts of butamben between 6−10 equiv were investigated. The use of 6 equiv of butamben proved to work satisfactorily, and in addition 10 equiv gave a somewhat slower reaction, and more degradation could be seen after reacting overnight. A reaction with 6 equiv of butamben gave >98% conversion overnight. A degradation of approximately 1−2% per day could be seen if the reaction mixture was left for several days. A good operating range for the amount of 37% HCl was 1.1 equiv ± 0.2 equiv, and the temperature was set to 110 °C. The reaction was scaled to 0.5 L, and compound **17** was isolated in 82% yield and 97% HPLC purity. Butamben was the largest impurity (∼2%), which was easily removed further downstream in the synthesis. Another advantage, in addition to the reaction being palladium free, is that butamben probably could be recycled in the longer term.

Ester Hydrolysis and Peptide Coupling. When performing the butyl ester hydrolysis in a mixture of EtOH and aqueous KOH at 50 °C, about 4% of the 5-ethoxy analogue, from displacement of fluoride by alkoxide, was formed as byproduct. To suppress this side reaction, EtOH was replaced with the more sterically hindered 2-propanol. Early in the hydrolysis, some trans-esterification to *i*-Pr-ester occurred, but at the end of the reaction >99.5% of the esters were converted to the carboxylic acid. The best procedure found for the hydrolysis was to heat **17** in a mixture of 2-propanol (8 relative volumes (rel vol mL/g) to the weight of **17**) and 4 M KOH (1.5 equiv) at 55 °C for about 6 h. Quenching the reaction mixture with 2 M HCl (1.5 equiv) diluted with water (6 rel vol) resulted in crystallization of the product which was isolated by filtration.

The formed carboxylic acid was then subjected to a peptide coupling with *N*-methylpiperazine as nucleophile to form compound **9**. The method of choice, due to very good knowledge in-house, was the two-phase system with 1-ethyl-3(3-dimethylaminopropyl)carbodiimide (EDCI) and a water solution of 1-hydroxybenzotriazole (HOBt, ∼20% w/w).[14] The reaction was performed in THF (6 rel vol) and water (2 rel vol) together with *N*-methylmorpholine as base at 45 °C, and within a few hours full conversion was obtained. After the reaction was completed addition of a second solvent was needed to enable an extractive work up. Several solvents were investigated, e.g., 2-MeTHF, isopropylacetate (*i*-PrOAc), and EtOAc. Due to precipitation of compound **9** during the extractions, only EtOAc showed good solubility of **9** at higher temperature. The extraction was performed at 55 °C followed by a brine wash. The free-base product could be made to crystallize from a solution of **9** at 55 °C by controlled addition of the antisolvent heptane, and high-quality **9** was isolated in 87% yield from compound **17**.

CONCLUSION

In summary, a new process for the manufacture of GSK3β inhibitor **9** was developed in our laboratories. This process relies on a new synthesis to an imidazole **14** with novel substitution pattern, a true application and scale-up of a Ziegler addition reaction and an environmentally friendly oxidative dehydrogenation of dihydropyrimidine **15** using copper catalysis and oxygen (O_2:N_2 5:95) as the stoichiometric oxidant. All of the major scale-up and quality issues with the early phase route have been addressed. The new route design and process development has resulted in removal of hazardous reaction mixtures and high energy intermediates **2** and **3**, expensive and low yielding fluorination chemistry, as well as avoiding Pd chemistry in the last synthetic step towards the API. Imidazole **14** was synthesized in four telescoped synthetic steps via the chloroimine **12** in 34% overall yield. Various classical methods for the transformation to **12** were tested, however triphosgene was found to give by far the best result regarding yield and byproduct formation. Two well working alternatives for aromatic amine coupling were developed for the pyrimidine **16**, one Pd catalyzed coupling using Buchwald-Hartwig conditions and another acid-mediated reaction using 37% HCl. The overall yield for the ten-step process, starting with 300 g of **10**, was 14%, which could be compared to the optimized medicinal chemistry process which gave 4% overall yield. The close collaboration between synthetic and process chemists, chemical engineers and analytical chemists greatly facilitated this process research and development.

EXPERIMENTAL SECTION

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer. HPLC analyses were performed on a Dionex P680 HPG, consisting of gradient pump with a Gynkotek UVD 170S equipped with a Symmetry Shield RP column (C18, 50 mm × 4.6 mm). The column temperature was set to +25 °C and the flow rate to 1.0 mL/min. UV detection was at 292 and 220 nm. A linear gradient was applied, starting at 90% A (A: 95:5 water/MeCN with 0.05% HCOOH buffer) ending at 80% B (B: 5:95 water/MeCN with 0.05% HCOOH buffer) over 12 min with 3 min hold at 90% A before next sample. GC analyses were performed on an Agilent HP6890 system equipped with an Ultra 2 (25 m × 320 μm, 0.25 μm) column. HRMS analyses were performed on a Waters Synapt G2 (Q-TOF), with mass resolution (fwhm) around 20000.

***N*-(Tetrahydro-2*H*-pyran-4-yl)-2,2,2-trifluoroacetamide (11).** Tetrahydro-2*H*-pyran-4-amine acetate, **10** (300 g, 1.86 mol), was mixed in toluene (2.4 L) at 25 °C. TEA (389 mL, 2.79 mol) was charged in one portion, followed by addition of ethyl trifluoroacetate (288 mL, 2.42 mol) over 30 min. The slurry reaction was left overnight. The reaction solution was washed with saturated $NaHCO_3$ (300 mL) and followed by water (300 mL). The organic phase was distilled to ∼1.7 L (6 rel vol towards compound **10**) of a solution of **11** in toluene that was telescoped directly in the next step. The crude product solution was sampled for GC analysis. GC analysis indicated ∼100% purity.

***N*-(Tetrahydro-2*H*-pyran-4-yl)-2,2,2-trifluoroacetimidoyl Chloride (12).** TEA (778 mL, 5.58 mol) was charged to the solution containing compound **11** (1.86 mol theoretical) in toluene at 50 °C. A solution of triphosgene (182 g, 0.61 mol) in toluene (800 mL) was charged over 4 h so that 50 °C was maintained and then left for an additional 4 h. The reaction mixture was cooled to 25 °C over 1 h and left stirring overnight. The crude product solution of **12** in toluene was sampled for GC analysis and telescoped directly in the next step. GC analysis indicated ∼85% purity, with approximately ∼4% of the unwanted carbamoyl chloride.

dx.doi.org/10.1021/op300365e | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

***N*-(2,2-Dimethoxyethyl)-*Ń*-(tetrahydro-2*H*-pyran-4-yl)-2,2,2-trifluoroacetamide (13).** A solution of aminoacetaldehyde dimethyl acetal (293 g, 2.79 mol) in toluene (200 mL) was charged over 1 h to the solution containing compound **12** (1.86 mol theoretical) in toluene at 25 °C. The reaction mixture was left stirring at 25 °C overnight and then was washed with saturated $NaHCO_3$ (1 L). The toluene phase was concentrated under reduced pressure to a brown oil, which was stored at 5 °C. The crude product oil **13** was sampled for GC analysis and telescoped directly in the next step. GC analysis indicated ~81% purity.

1-(Tetrahydro-2*H*-pyran-4-yl)-2-trifluoromethyl-1*H*-imidazole (14). The oil containing **13** (1.86 mol theoretical) was dissolved in THF (1.5 L) at 20 °C. A solution of H_2SO_4 (121 mL, 2.23 mol, 98%) in THF (500 mL) was charged over 2 h so the temperature was maintained below 25 °C. The reaction solution was left for an additional 3 h at 25 °C and then cooled to 5 °C. Charged *i*-PrOAc (1 L), followed by saturated $NaHCO_3$ (1 L). The pH was adjusted to approximately pH 8 using 45% $NaOH_{(aq)}$. The water phase was separated, and the organic phase was washed with water (0.5 L). The organic phase was extracted with 4 M HCl (2 × 1 L). The acidic phases, containing the product, were combined and concentrated to remove remaining THF. The pH was carefully adjusted to approximately pH 8 using 45% $NaOH_{(aq)}$ at such a rate that the temperature was below 10 °C. During adjustment crystallization was obtained, but if the addition was too fast, oiling out could be seen. The crystallization was left stirring at 10 °C overnight. The solids were collected, washed with cooled water (500 mL), and dried to give the 2-CF_3-imidazole **14** (143.6 g, corrected for 98.4 wt % ^{1}H NMR assay, 0.641 mol) as an off-white sugar-like solid. The overall yield from **10** in four steps was 34.5%. MS (ESI) *m*/*z* 221 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) δ 1.84−1.89 (m, 2H), 1.96−2.08 (m, 2H), 3.49 (dt, 2H, *J* = 12.0 and 2.0 Hz), 3.96 (dd, 2H, *J* = 11.6 and 4.8 Hz), 4.34−4.44 (m, 1H), 7.13 (d, 1H, *J* = 1.2 Hz), 7.81 (d, 1H, *J* = 1.2 Hz); ^{13}C NMR (DMSO-d_6) 33.57, 53.51, 65.96, 119.15 (CF_3, $J_{C,F}$ = 267.2 Hz), 121.93, 128.61, 133.24 (C−CF_3, $J_{C,F}$ = 37.8 Hz); 99.5% GC purity. HRMS *m*/*z* found 221.0903 $[M + H]^+$, $C_9H_{12}N_2OF_3$ requires 221.0902.

5-Fluoro-4-[1-(tetrahydro-2*H*-puran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-chloride (16). 2-CF_3-imidazole **14** (120.0 g, 0.55 mol) was dissolved in THF (1080 mL) and cooled to −25 °C. The reactor was inerted by evacuation and refilled with N_2. Hexyllithium (2.47 M, 243 mL, 0.60 mol) was charged over 35 min so the temperature was maintained below −15 °C. 2-Chloro-5-fluoro-pyrimidine (80.2 g, 0.60 mol) dissolved in THF (360 mL) was charged over 30 min so the temperature was maintained below −15 °C. The reaction solution was left at −25 °C for 1 h. A solution of HOAc (47 mL, 0.82 mol) in EtOAc (480 mL) was charged over 30 min, and during the charging the temperature was increased to 0 °C. Water (720 mL) was charged, and the temperature was set to 20 °C. The water phase was separated off, and the organic phase was washed with brine (1 L). A solvent swap from THF to MeCN was performed to a final volume of approximately 1.8 L of MeCN solution containing compound **15** with precipitation at 10 °C. $Cu(OAc)_2$ (5.44 g, 27.8 mmol) and TEA (76 mL, 0.55 mol) were added. A mixture of 5% oxygen in nitrogen was bubbled through at a flow rate of 300 mL/min overnight (approximately 50% conversion after 5 h), and a clear-brown solution was obtained when the reaction had finished. The organic solution was concentrated under reduced pressure to approximately 900 mL (7.5 rel vol towards **14**) and adjusted to 20 °C. NH_3 in water (5%, 900 mL) was charged over 1.5 h to initiate precipitation. The slurry was cooled to 0 °C over 2 h and left for 1 h. The solids were collected, washed with MeCN/H_2O (1:1, 300 mL), and dried at 40 °C with vacuum to give the pyrimidine **16** (117.1 g, 60.5% yield, corrected for 98.7 wt % ^{1}H NMR assay) as a yellow-beige solid. MS (ESI) *m*/*z* 351 and 353 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) δ 1.93 (dd, 2H, *J* = 12 and 2 Hz), 2.21−2.33 (m, 2H), 3.41 (dd, 2H, *J* = 11.6 and 10.4 Hz), 4.00 (dd, 2H, *J* = 11.6 and 4.4 Hz), 4.87−4.97 (m, 1H), 7.78 (d, 1H, *J* = 3.2 Hz), 9.09 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR (DMSO-d_6) δ 31.89, 56.71, 66.67, 118.78 (CF_3, $J_{C,F}$ = 267.9 Hz), 126.54 (C−C, $J_{C,F}$ = 2.4 Hz), 134.55 (C−H, $J_{C,F}$ = 9.6 Hz), 137.79 (C−CF_3, $J_{C,F}$ = 38.8 Hz), 146.27 (C−C, $J_{C,F}$ =12.4 Hz), 149.77 (C−H, $J_{C,F}$ = 25.5 Hz), 153.52 (C−Cl, $J_{C,F}$ = 3.8 Hz), 154.48 (C−F, $J_{C,F}$ = 264.1 Hz); 99.6% HPLC purity. Reaction monitoring (**14**, t_R ~3.77 min; **15**, t_R ~5.22 min; **16**, t_R ~6.96 min) was conducted by HPLC analysis with UV detection at 220 nm. HRMS *m*/*z* found 351.0635 $[M + H]^+$, $C_{13}H_{12}N_4OF_4Cl$ requires 351.0636.

Butyl 4-({5-Fluoro-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl] pyrimidin-2-yl}-amino)benzoate (17). *Method A.* Butamben (127.5 g, 0.66 mol) and compound **16** (40.0 g, 0.11 mol) were neat combined and heated to 85 °C over 60 min. Concentrated HCl (10.1 mL, 0.12 mol, 37%) was added dropwise over 30 min to the clear-brown solution. The reaction solution was heated at 110 °C overnight and then cooled to 100 °C over 30 min, before controlled addition of 2 M HCl (230 mL). The resulting precipitate was stirred for about 30 min at 100 °C before cooling to 50 °C over 1 h and was left an additional 2 h at 50 °C. The solids were collected at 50 °C, washed with 2 M HCl (230 mL), and dried at 40 °C with vacuum to give the butyl-ester **17** (51.0 g, 82% yield, corrected for 89.7 wt % ^{1}H NMR assay) as a yellow-brown solid. 96.6% HPLC purity. **Caution!** Add EtOH (230 mL) in the receiver vessel during isolation of **17** to avoid solidification of butamben in the filtrate.

Method B. Butamben (63.7 g, 0.32 mol) and compound **16** (111.4 g, 0.31 mol) were mixed with THF (500 mL) and the slurry stirred at room temperature. K_2CO_3 (61.3 g, 0.44 mol) was charged, followed by THF (580 mL). The mixture was purged with N_2. A solution of $Pd(OAc)_2$ (0.86 g, 3.76 mmol) and (*R*)-BINAP (4.83g, 7.52 mmol) in THF (150 mL) was added to the slurry, and the vessel was inerted by evacuation and refilling with N_2. The mixture was heated to 60 °C with rapid stirring overnight. The mixture was cooled to 30 °C. EtOAc (1100 mL) and HOAc (25 mL, 0.44 mol) were added, followed by water (330 mL), and a solution was obtained. The lower water phase was separated off, and the organic phase was washed with 5% NaCl in water (300 mL) and then concentrated under reduced pressure until reaching half of the original volume. EtOH (1.5 L) was added, and the distillation was continued to half of the original volume (~1 L). The slurry was heated to 80 °C and stirred until a solution was obtained. The solution was cooled to 65 °C over 2.5 h and left for 1 h before cooling was continued to 5 °C with 10 °C/h. The solids were collected, washed with cooled EtOH (200 mL), and dried at 50 °C with vacuum to give the butyl-ester **17** (131.0 g, 81% yield, corrected for 97.8 wt % ^{1}H NMR assay) as a light-brown solid. MS (ESI) *m*/*z* 508 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) δ 0.92 (dd, 3H, *J* = 7.6 and 7.2 Hz), 1.36−1.45 (m, 2H), 1.63−1.71 (m, 2H), 1.88−1.94 (m, 2H), 2.10−2.18 (m,

dx.doi.org/10.1021/op300365e | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

2H), 3.23 (t, 2H, J = 11.4 Hz), 3.80 (dd, 2H, J = 11.4 and 3.8 Hz); 4.23 (t, 2H, J = 6.6 Hz), 4.76−4.87 (m, 1H), 7.57 (d, 1H, J = 2.0 Hz), 7.80 (d, 2H, J = 8.8 Hz), 7.90 (d, 2H, J = 8.8 Hz), 8.84 (d, 1H, J = 1.6 Hz), 10.25 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.57, 18.72, 30.29, 32.03, 55.97, 63.91, 66.43, 118.14, 118.89 (CF_3, $J_{C,F}$ = 267.9 Hz), 122.72, 127.41, 130.06, 132.46 (C−H, $J_{C,F}$ = 5.5 Hz), 136.47 (C−CF_3, $J_{C,F}$ = 38.3 Hz), 144.23 (C−C, $J_{C,F}$ = 12.5 Hz), 144.42, 147.94 (C−H, $J_{C,F}$ = 24.2 Hz), 150.27 (C−F, $J_{C,F}$ = 252.0 Hz), 155.70 (C−N, $J_{C,F}$ = 3.0 Hz), 165.43; 99.4% HPLC purity. Reaction monitoring (**17**, t_R ∼10.15 min) was conducted by HPLC analysis with UV detection at 292 nm. HRMS m/z found 508.1972 $[M + H]^+$, $C_{24}H_{26}N_5O_3F_4$ requires 508.1972.

[4-[5-Fluoro-4-[3-tetrahydropyran-4-yl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-yl]-aminophenyl]-(4-methylpiperazin-1-yl)-methanone (9). *Ester Hydrolysis.* The butyl-ester **17** (130 g, 0.25 mol) was mixed in 2-propanol (1040 mL) at 25 °C. KOH (4 M, 95 mL, 0.37 mol) was charged, and the reaction mixture was heated at 55 °C for 6 h. HCl (2 M, 189 mL, 0.38 mol) diluted with water (780 mL) was charged to the reaction solution over 45 min, while 55 °C was maintained. The slurry was cooled to 15 °C over 2 h and left for 1 h. The solids were collected, washed with water (380 mL), and dried at 55 °C with vacuum to give the butyl acid (122.8 g, 98% yield, corrected for 98.5 wt % ^{1}H NMR assay) as a yellow solid. MS (ESI) m/z 452 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) δ 1.88−1.94 (m, 2H), 2.10−2.18 (m, 2H), 3.23 (t, 2H, J = 11.4 Hz), 3.81 (dd, 2H, J = 11.6 and 4.0 Hz), 4.77−4.84 (m, 1H), 7.57 (d, 1H, J = 2.0 Hz), 7.78 (d, 2H, J = 8.8 Hz), 7.88 (d, 2H, J = 8.8 Hz), 8.83 (d, 1H, J = 1.6 Hz), 10.22 (s, 1H), 12.61 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 32.02, 55.96, 66.43, 118.08, 118.89 (CF_3, $J_{C,F}$ = 267.9 Hz), 123.66, 127.43, 130.24, 132.45 (C−H, $J_{C,F}$ = 5.4 Hz), 136.48 (C−CF_3, $J_{C,F}$ = 38.2 Hz), 144.08, 144.21 (C−C, $J_{C,F}$ = 12.6 Hz), 147.94 (C−H, $J_{C,F}$ = 24.4 Hz), 150.22 (C−F, $J_{C,F}$ = 251.9 Hz), 155.76 (C−N, $J_{C,F}$ = 3.1 Hz), 167.01; 99.8% HPLC purity. Reaction monitoring (*acid*, t_R ∼7.25 min) was conducted by HPLC analysis with UV detection at 292 nm. HRMS m/z found 452.1345 $[M + H]^+$, $C_{20}H_{18}N_5O_3F_4$ requires 452.1346.

EDCI Coupling. The butyl acid (112.6 g, 0.24 mol) was mixed in THF (675 mL) at 25 °C. *N*-Methyl-piperazine (29.3 mL, 0.26 mol), NMM (41 mL, 0.37 mol), and HOBt as a water solution (17 mL, 24.4 mmol, 19.4%) were added to the reaction solution. EDCI (72.7 g, 0.34 mol) dissolved in water (220 mL) was added over 10 min. The reaction mixture was heated at 45 °C for 1 h. EtOAc (675 mL) was added, and the reaction solution was heated at 55 °C. The lower water phase was separated off, and the organic phase was washed with 5% NaCl in water (225 mL), and then the organic solution was left stirring at 55 °C. Heptane (675 mL) was added over 1.5 h to initiate crystallization. The slurry was cooled to 5 °C over 8 h and left for at least 2 h. The solids were collected, washed with a cooled mixture of EtOAc and heptane (1:1, 600 mL), and dried at 60 °C with vacuum to give compound **9** (120.8 g, 89% yield, corrected for 96.1 wt % ^{1}H NMR assay) as a light-yellow solid. MS (ESI) m/z 534 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) δ 1.86−1.93 (m, 2H), 2.08−2.18 (m, 2H), 2.19 (s, 3H), 2.23−2.38 (m, 4H), 3.22 (t, 2H, J = 11.4 Hz), 3.34−3.68 (m, 4H), 3.80 (dd, 2H, J = 11.4 and 3.8 Hz), 4.77−4.88 (m, 1H), 7.35 (d, 2H, J = 8.8 Hz), 7.57 (d, 1H, J = 2.4 Hz), 7.70 (d, 2H, J = 8.8 Hz), 8.05 (d, 1H, J = 1.6 Hz), 10.04 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 32.01, 45.57, 54.49 (piperazine), 55.96, 66.44, 118.65, 118.90 (CF_3, $J_{C,F}$ = 267.8 Hz), 127.53, 127.89, 129.08, 132.39 (C−H, $J_{C,F}$ = 5.6 Hz), 136.42 (C−CF_3, $J_{C,F}$ = 38.3 Hz), 141.07, 144.06 (C−C, $J_{C,F}$ = 12.5 Hz), 147.96 (C−H, $J_{C,F}$ = 24.7 Hz), 150.02 (C−F, $J_{C,F}$ = 251.2 Hz), 156.04 (C−N, $J_{C,F}$ = 2.9 Hz), 168.89; 99.6% HPLC purity. Reaction monitoring (**9**, t_R ∼2.90 min) was conducted by HPLC analysis with UV detection at 292 nm. HRMS m/z found 534.2250 $[M + H]^+$, $C_{25}H_{28}N_7O_2F_4$ requires 534.2241.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Erika Lindberg and Erica Tjerneld for engineering support, David Aslan and Marie Berzelius for analytic support, Hefeng Pan for the HRMS analyses, Mats Ridemark and Tommi Ratilainen for the development of the Mid-IR analysis, and Ann-Britt Fransson for chemistry production in 5-L scale. We also thank Jim Brennan and Tobias Rein for helpful suggestions and guidance during the course of this work.

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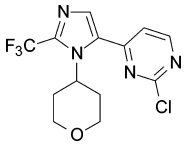

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