

Optimization of the Manufacturing Route to PF-610355 (1): Synthesis of Intermediate 5

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ABSTRACT: Tertiary carbinamine **5** is an isolated intermediate in the synthesis of a novel, inhaled β -2 adrenoreceptor agonist PF-610355. Process development for the key amide-formation and Ritter reactions, together with reaction understanding studies are discussed in context of the synthesis of **5**. The optimized process employed to manufacture 140 kg of **5** is described, and was shown to have superior metrics to the preliminary commercial route.

1. INTRODUCTION

Respiratory diseases such as asthma and chronic obstructive pulmonary disorder (COPD) are highly prevalent and affect millions of people across the globe. Common treatments include β -adrenoreceptor agonist inhalers, antimuscarinic inhalers, steroid inhalers, or combination treatments. Current marketed β -adrenoreceptor agonists salmeterol and formoterol possess a duration of action which is adequate for twice-daily administration.¹ A key focus area has been the identification and development of long acting β -2 adrenoreceptor agonists (LABAs) which would provide a single daily dose through a dry powder inhaler device. A summary of the discovery and synthesis of a range of β -2 adrenoreceptor agonists culminating in the identification of PF-610355 as a clinical candidate has recently been published.¹ The candidate progressed through the development phases with publications documenting the enabling chemistry² and alternative route investigations.³ This paper documents the development work performed to afford a synthetic process suitable for commercial scale manufacture of intermediate **5**.

2. RESULTS AND DISCUSSION

2.1. Background. Upon the identification of PF-610355 as a clinical candidate, enabling work performed led to the development of a synthetic process which built upon the medicinal chemistry route and developed effective syntheses of key building blocks.⁴ Although this provided the required quantity of material, the route was considered suboptimum for commercial scale manufacture in terms of processing and yield (36%). Process research investigations resulted in the nomination of a preliminary commercial route in which the API was constructed from three advanced starting materials. This process was employed to generate 35 kg of PF-610355 (Scheme 1) to support early clinical development.³ As the candidate progressed, continual development work was performed on the synthetic process and is discussed herein. This article focuses solely on the synthesis of **5**, the first isolated intermediate in the original process.

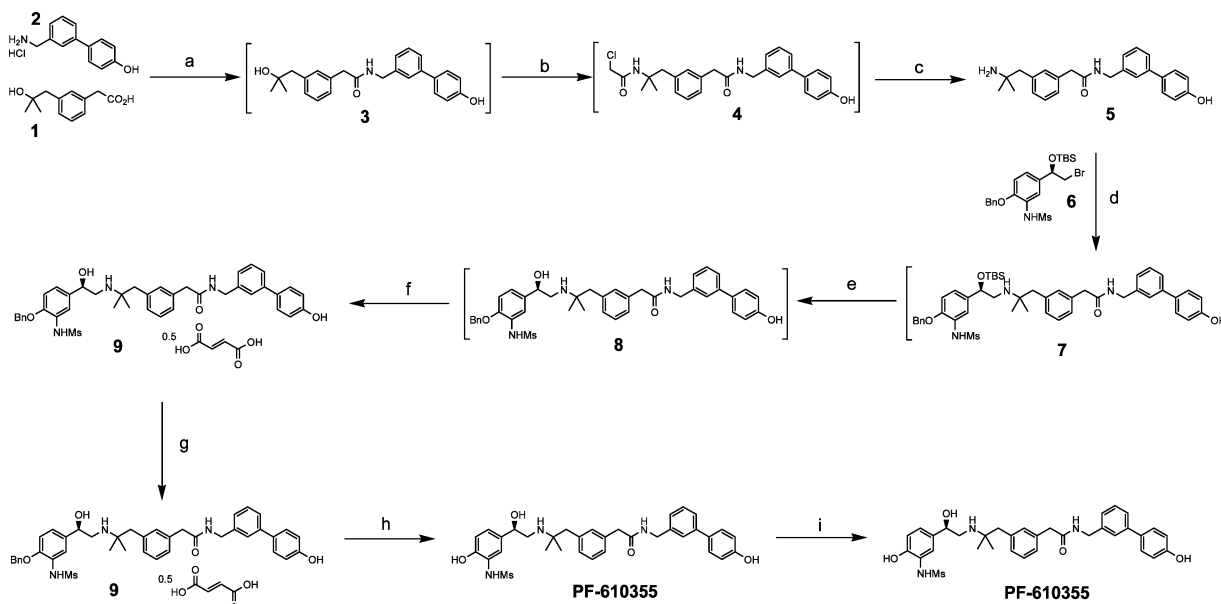
In the existing process, the synthesis of **5** was *via* a three-reaction sequence in which intermediates were not isolated but were carried through as solutions following workups. The sequence commenced with the amide coupling of [3-(2-

hydroxy-2-methylpropyl)phenyl]acetic acid **1** and the hydrochloride salt of 3'-(aminomethyl)biphenyl-4-ol **2** to give the tertiary alcohol **3** which, after an aqueous workup, was progressed as a solution into a Ritter reaction with chloroacetonitrile. This allowed the substitution of the alcohol function by an amine protected as the chloroacetamide.⁶ The resulting product **4** was again not isolated but progressed, after workup, through to the deprotection reaction as a solution in acetic acid. Removal of the chloroacetamide with thiourea generated the desired amine **5** which was isolated in a reasonable 58% yield (average) and high purity.

Although the preliminary commercial route had provided the desired material of high purity on 35 kg scale, on commencing development work a number of areas were identified as targets for further optimization. First, the amide coupling between **1** and **2** utilized undesirable reagents *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl)/hydroxybenzotriazole (HOBt) and an undesirable solvent (dichloromethane) and involved a protracted aqueous workup.⁷ Second, the Ritter reaction utilized a large excess of the genotoxic chloroacetonitrile⁸ and trifluoroacetic acid. The reaction workup was again protracted, employed DCM and large volumes of concentrated aqueous ammonia, and delivered a solution of **4** that still contained several equivalents of chloroacetonitrile. As a result, a large excess of thiourea was required to cleave the chloroacetamide group to give the tertiary carbinamine **5**. This afforded significant quantities of solid waste products which were removed through a slow and problematic filtration. Amine **5** was isolated from the filtrate through a convoluted workup process utilizing DCM, expensive 2-MeTHF, and concentrated aqueous ammonia affording the point of highest dilution in the process (83 L/kg wrt **1**). From an environmental aspect the existing synthetic process generated a large quantity of waste (E-Factor = 302 [total waste {kg} per kg of **5**]) and employed large quantities of nonenvironmentally friendly reagents. Our goals were therefore to streamline the process, eliminate/minimize the use of undesirable reagents and solvents, and increase throughput, particularly in the workup stages.

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Scheme 1. PF-610355 preliminary commercial route^a

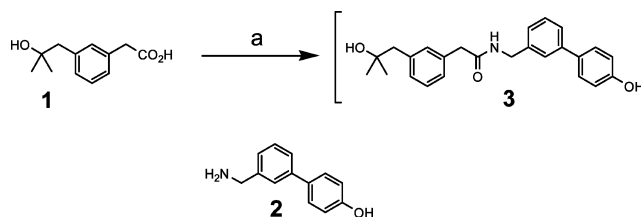
^aReagents and conditions: (a) EDC·HCl, HOBT, Et₃N, DCM, 20 °C then THF and 6 aq. washes. (b) ClCH₂CN, TFA, 50 °C, then DCM and 4 aq. washes. (c) (i) Thiourea, AcOH, 70 °C then byproduct filtration and 2-MeTHF and aq. washes (NH₃); (ii) Crystallization from MeCN, 58%. (d) NaHCO₃, *n*BuOAc, 125 °C then EtOAc and aq. wash. (e) Et₃N(HF)₃, *n*BuOAc, EtOAc, MeOH, 20 °C then 2 aq. washes (NH₃). (f) Fumaric acid, *n*BuOAc, MEK, 82%. (g) MeCN, 50 °C, 95%. (h) (i) THF/water, 2 aq. washes (NH₃); (ii) H₂, Pd/C; (iii) Crystallization from MeCN, 77%. (i) MeOH/water, 50 °C, 91%.

2.2. Development of the Amide Coupling. The first change made to the amide coupling reaction was to use the free-base form rather than the hydrochloride salt of **2** to avoid the need for an amine base. This change was facilitated by the identification of a new synthetic route to the free base outsourced to an external vendor.⁹

N,N-Carbonyldiimidazole (CDI) was rapidly identified as a suitable coupling agent, which led us to concentrate on using this reagent. This decision was derived from experience using the reagent, knowledge of the typical side reactions, and the opportunity to simplify the workup, as the imidazole byproduct is much easier to purge than those generated through an EDC·HCl mediated coupling.^{10,11} A range of solvents were screened with a large proportion disregarded based on solubility. The superior solvents were ethyl acetate and THF with the former selected due to lower water miscibility (facilitating the workup) and the fact a reaction concentration of 5 L/kg with respect to **1** could be employed.

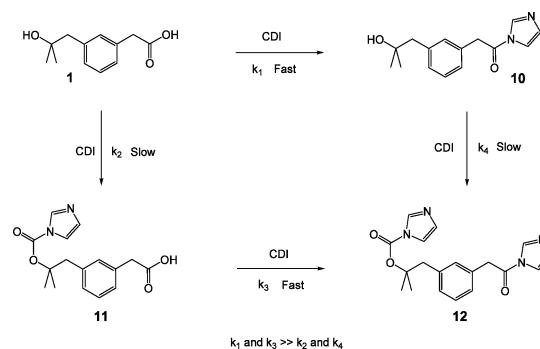
The new set of reaction conditions allowed the design of an aqueous workup which was superior to the protracted procedure employed in the initial route. The aim was to, in a minimum number of operations, remove the imidazole byproduct and any of the unreacted starting materials. After screening a number of approaches, a 2 M citric acid wash followed by a 1 M sodium hydrogen carbonate wash was implemented. The end product was a solution of the tertiary alcohol **3** in ethyl acetate (Scheme 2).

There are potential side reactions associated with the use of CDI which can lead to impurity formation. The desired reaction is imidazolide **10** formation through reaction with the carboxylic acid function of **1**. In addition to the desired transformation, the CDI can also react with the tertiary alcohol function of **1** to give 1*H*-imidazole-1-carboxylate derivatives **11** and **12** which could potentially lead to carbamates upon

Scheme 2. Optimized amide coupling^a

^aReagents and conditions: (a) (i) CDI, EtOAc; (ii) **2**, 50 °C then 2 aq. washes.

reaction with the amine **2** (Scheme 3). However, we anticipated the compounds **11** and **12** would react in the Ritter reaction in

Scheme 3. Reactions of **1** and CDI

a similar way to **1** and the imidazolide alcohol **10** respectively. Furthermore, if any unreacted CDI is present upon the addition of **2**, the urea would rapidly form and it was known that this compound was difficult to purge in the downstream process. Therefore, the CDI charge is critical for controlling the desired

pathway and hence minimizing impurity formation. It was believed that the dual reactivity of **1** could provide an advantage in terms of controlling the CDI charge through the use of process analytical technology (PAT).

The *in situ* monitoring of the CDI activation of **1** was investigated using mid-IR. Two absorption peaks for CDI ($1406\text{--}1389\text{ cm}^{-1}$ and $880\text{--}860\text{ cm}^{-1}$) could be followed to assess the level present in the reaction. The portionwise addition of a slight excess of CDI allowed differentiation of the k_1 and k_4 reaction rates; the consumption of CDI slowed resulting in a different decay profile in the mid-IR compared to the substoichiometric charges (Figure 1). This is due to the

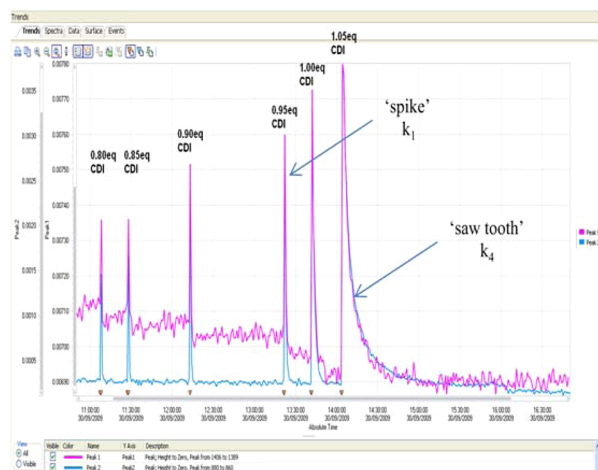


Figure 1. Mid-IR profile of CDI consumption.

slower reaction of the tertiary alcohol function with CDI becoming predominant following consumption of all the carboxylic acid groups. This experimental data allowed kinetic modeling using Dynochem¹² which suggested that the rate constants k_1 and $k_3 \gg k_2$ and k_4 , and it is these rate differences that account for the desired product being formed under normal conditions.

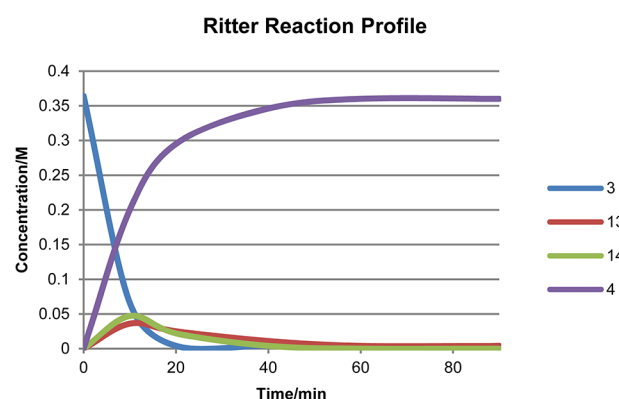
The change in shape of the mid-IR profiles on addition of the portions of CDI can be used to give an indication of when an excess of CDI has been added. This could allow maximization of conversion when considering variability in CDI potency and also avoid the need for a separate off-line reaction completion test. On a 25 kg batch size in our pilot plant, the CDI was added portionwise and acquired mid-IR data broadly reflected the lab observations shown in Figure 1.

2.3. Development of the Ritter Reaction. In the enabling process the conversion of the coupled product **3** had been performed with chloroacetonitrile (12 equiv) and trifluoroacetic acid (25 equiv) at $50\text{ }^\circ\text{C}$, and we wished to determine whether these conditions were optimum. A wide range of reagents and reaction conditions were screened and afforded the desired transformation.¹³ However, when considering the toxicity of reagents such as sulfonic acids, the requirement of a solvent such as acetic acid, and how the reaction could be integrated into the telescoped process, it was clear the alternative reaction conditions explored offered no significant advantage. Because a solvent was required for the Ritter reaction, the decision was made to focus on the development and optimization of the TFA/chloroacetonitrile conditions with chloroacetonitrile acting as both the reagent and the solvent. Furthermore, process safety investigations

showed that the conditions did not generate any violent exotherms associated with alternative systems such as sulfuric acid.¹⁴ A protocol was therefore developed to allow the solvent exchange of the solution of **3** in ethyl acetate to the high boiling chloroacetonitrile ($124\text{--}126\text{ }^\circ\text{C}$).

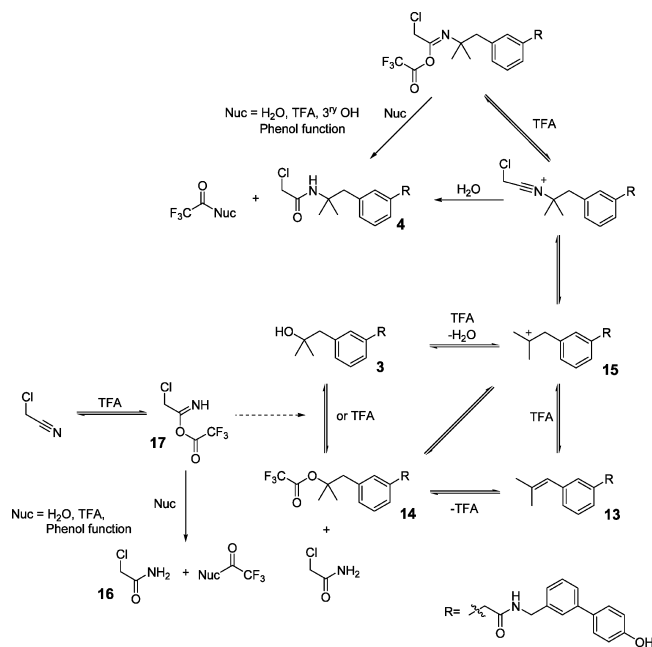
With the reagents for the Ritter reaction selected, attention was focused on increasing the reaction understanding in order to optimize the conditions used in the transformation. In doing so there was a particular emphasis on reducing the quantities of the chloroacetonitrile and TFA employed. The original reaction conditions of 12 equiv of chloroacetonitrile and 25 equiv of TFA at $50\text{ }^\circ\text{C}$ were scrutinized using HPLC monitoring over the course of the reaction to develop a better understanding of the reaction profile, kinetics, and any transient species formed (Chart 1).

Chart 1. Ritter reaction profile



The consumption of the starting material was very rapid, affording not only the desired product chloroacetamide **4** but also two other species, the alkene **13** and the trifluoroacetate ester **14**. Note that styrene **13** undergoes the Ritter reaction and that **14** appears unstable and eliminates to afford the styrene. Scheme 4 shows the desired transformation following the readily accepted S_N1 mechanism; also depicted are a number of pathways for which evidence was collated. Protonation of the alcohol **3** and subsequent loss of water lead to the formation of the tertiary carbocation **15**. Following the standard mechanism of nitrile trapping and addition of water to the nitrilium ion, the desired chloroacetamide **4** is produced. The styrene **13** is observed in the reaction and is formed by elimination from either the alcohol or the derived TFA ester and undergoes the Ritter reaction after protonation of the double bond to afford **4** allowing conversion of the transient styrene species into the desired product. This mechanism raised the possibility of forming a regioisomer of **4** through chloroacetonitrile trapping of a benzylic carbocation; however, even when starting from pure **13**, investigations failed to identify this potential impurity in the reaction mixture or isolated material. The synthesis of the chloroacetamide from **13** raised an additional issue around the reaction mechanism, the source of the oxygen atom of the product chloroacetamide. Unlike alcohol **3**, water, the most likely source, is not generated on formation of the carbocation, and analysis of the reagents suggested the water levels were too low to allow the observed level of conversion. Evidence for an alternative or additional source came from the identification of an impurity formed in the reaction, 2-chloroacetamide **16**, the hydrolysis product of chloroacetonitrile. Further experiments suggested that the TFA

Scheme 4. Ritter reaction mechanistic pathways



reacts with the chloroacetonitrile to form acylating species 17. This can react with a range of nucleophiles such as TFA to form the anhydride, the tertiary alcohol 3, to afford the observed transient ester species 14 or the phenolic oxygen of the R group, all of which liberate 2-chloroacetamide. This mechanism could account for the hydrolysis of the nitrilium ion along the desired pathway which affords compound 4 when starting from either the alcohol 3 or alkene 13.¹⁵

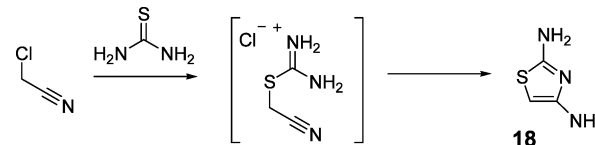
Building on the initial findings further work was performed to understand how the telescoped nature of the process influenced the reaction. It was found that the presence of water reduced the reaction rate, presumably by shifting the equilibrium of carbocation formation. This supported the selection of ethyl acetate over THF as the amide coupling solvent, since it would minimize the potential carryover of water into the solution of 3 in chloroacetonitrile.

The focus was then turned toward the optimization of the reagent quantities. By considering the accepted $\text{S}_{\text{N}}1$ mechanism for the Ritter reaction, where the rate should depend solely on the concentration of 3, it was confirmed that the reduction of the chloroacetonitrile charge from 12 to 6 equiv was possible with a negligible effect on the rate of the Ritter reaction for a given charge of TFA. Importantly, this reduced charge still maintained stirrable solutions in chloroacetonitrile's second role as a solvent. Reducing the TFA charge had a more profound effect, slowing the reaction and resulting in increased levels of the alkene and TFA adduct intermediates during the course of the reaction. Although the reduction in reagent charges resulted in a slower reaction (completion after 2 h, previously 1 h), the advantage of reducing their quantities with only a relatively small time extension was a significant overall improvement to the process. Concentrating the reaction with respect to the chloroacetonitrile charge appeared to be limited by the solubility of 3 and also the volume required to ensure an efficient solvent exchange from the solution of 3 in EtOAc from the amide coupling stage. From the investigation the conditions selected for the Ritter reaction were to use chloroacetonitrile (6 equiv) and TFA (16 equiv) at 50 °C affording a reaction time

of 2 h to give a solution of the desired product 4 in chloroacetonitrile and TFA. Attention then focused on the optimum approach to progress the chloroacetamide 4 to the target molecule 5.

A major drawback of the preliminary commercial route was the use of a large thiourea excess (4.2 equiv employed) in the chloroacetamide deprotection step. This was necessary to achieve completion of the desired transformation due to the competing reaction of thiourea with the chloroacetonitrile carried over from the Ritter reaction. This side reaction afforded the potentially genotoxic¹⁶ diaminothiazole 18 (Scheme 5) which was removed, together with some of the

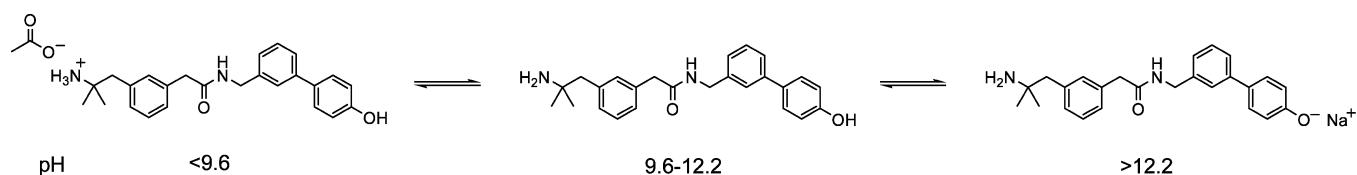
Scheme 5. Undesirable side reaction of chloroacetonitrile and thiourea



pseudothiohydantoin 20 generated as a byproduct from the desired reaction (Scheme 6), through a time-consuming filtration upon completion of the reaction. This generated approximately 3.9 kg of solid waste per kg of target compound 5, and so there was a significant waste stream to minimize. Work therefore focused on the optimum method for the removal of chloroacetonitrile from the system prior to the deprotection stage in order to allow a reduced thiourea charge and minimize waste generation.

At this point the optimum solvent for the deprotection reaction had been identified as 2-butanol (see section 2.4.); the first area of investigation was a solvent exchange of the chloroacetonitrile/TFA solution into 2-butanol. Exploratory practical investigations of this solvent exchange by distillation demonstrated that TFA could be easily removed but complete removal of chloroacetonitrile was not possible. Computer modeling-based prediction of the distillation characteristics for this solvent system was employed to help identify a more efficient process. Initially binary parameters for each solvent pair were studied along with a ternary diagram for the trisolute mixture (Figure 2).⁵ Note that T-x (blue) and T-y (green) are the liquid and vapour phase boundaries respectively.

The diagrams illustrate that the TFA pairings are the most problematic because of a maximum boiling azeotrope near the end of TFA removal from both 2-butanol and chloroacetonitrile. This is further demonstrated in the ternary map for the combination of all three solvents where the contour lines all tend toward the maximum boiling azeotrope of TFA and chloroacetonitrile. Furthermore, because chloroacetonitrile has a higher boiling point than 2-butanol, and the relative volatility between them is low, the distillation is inefficient heading towards the 2-butanol boiling point. The results suggested that the most efficient approach to maximize the removal of chloroacetonitrile was to remove as much TFA as possible in an initial concentration by distillation and then to remove the chloroacetonitrile by successively adding 2-butanol. Models were constructed and compared to evaluate the concentration–dilution–concentration and constant volume distillation modes; however neither offered a process that was of the efficiency desired, and so an alternative protocol was sought.

Scheme 7. Amphoteric behavior of **5**

and solved the problem of chloroacetonitrile carryover into the next stage of the process. Whilst the introduction of an isolation stage into a previously telescoped process could be viewed as a step backwards in terms of cost and process efficiency, the advantages that it gave in terms of process robustness, throughput, and product quality significantly outweighed these perceived disadvantages and resulted in its inclusion for scale-up.

2.4. Development of the Deprotection Reaction. In the initial exploratory commercial route the use of a solution of **4** resulted in a number of species, impurities, residual solvents, and excess reagents, such as chloroacetonitrile, entering the deprotection reaction step. The conditions employed for the desired reaction required an excess of thiourea (4.2 equiv) in neat acetic acid (11 L/kg wrt **1**) at 70 °C, conditions that were not ideal for large scale manufacture.³ This was in addition to the problematic workup involving filtration of the solid side-product **18** (diaminotiazole) and byproduct **20** (pseudothiohydantoin) as discussed earlier. The isolation of **4** as a crystalline solid eliminated the problem associated with the carryover of chloroacetonitrile, and this allowed the thiourea charge to be lowered to 1.2 equiv and simplified the workup considerably through the minimization of waste. There was also a strong desire to avoid the use of acetic acid as the solvent because managing this solvent contributed to the high volume of the reaction workup. In order to develop a more efficient process for the deprotection reaction, gaining a better understanding of the reaction and workup was the initial focus.

The desired transformation is depicted in Scheme 6 and illustrates the intermediacy of the thiourea adduct **18** and the formation of the pseudothiohydantoin **20** byproduct that needs to be purged during the workup. A literature review for chloroacetamide deprotection reactions highlighted the optimum solvent system as being an ethanol/acetic acid 4:1 volume ratio.⁶ Initial investigations confirmed the use of alcoholic solvents provided an increased reaction rate over acetic acid for the initial nucleophilic attack of thiourea on **4**. However, the reactions stalled at the thiourea adduct stage, **19**, unless acetic acid was present in the reaction mixture, in which case the desired product **5** was formed as the acetate salt. Significantly, the laboratory data confirmed that acetic acid could be employed as a reagent rather than solvent to guarantee complete reaction conversion.

Attention was then focused on the identification of the optimum solvent. The reaction could be successfully performed in a range of solvents, primarily alcohols but also THF, 2-MeTHF, and MEK. However, the solvent also had to provide solubility for both the acetate salt and free base of **5** as well as a good phase separation during an aqueous workup. After significant experimentation and evaluation, 2-butanol was selected since it was the solvent that most closely matched the requirements. With the solvent selected and very different reaction conditions developed, the reaction workup required redesigning. The key goals were to efficiently generate the free

base of **5** and to maximize the purge of the pseudothiohydantoin **20**, which is a potentially genotoxic compound¹⁶ and hence needed to be controlled to low levels.

The salt break of the acetate salt of **5** was not straightforward since this compound is amphoteric by virtue of the structure containing both an amine and a phenol group. The salt break was investigated with 2 M sodium hydroxide, using ¹H NMR to determine the optimum pH window for generating the neutral species. As can be seen in Scheme 7, the desired range was pH 9.6–12.2 with a target for the process set at pH 10.8 at 25 °C. This evaluation and pH target selection was later validated through further experimentation and Dynochem modeling.¹² The model, based on estimated pK_a values, identified that pH 10.6 was optimum to achieve the optimum ratio of free base. However, based on the equilibria the model suggested that a maximum of only 95% of **5** could exist in the desired free base form.

Although conditions for the salt break had been identified, the workup procedure was complicated by the presence of the reaction byproduct pseudothiohydantoin **20**. This byproduct exhibited some water solubility which provided encouragement that the desired purge could be achieved; however it precipitated on cooling the reaction mixture to 25 °C, and solids remained during the salt break and phase separation. To overcome this problem, two modifications were made to the workup. First the reaction solvent system was changed from neat 2-butanol to 2-butanol/water whilst maintaining the same concentration. This change did not significantly impact the reaction rate, but it prevented precipitation of the pseudothiohydantoin on cooling the reaction mixture. Second the aqueous workup was performed at 40 °C to prevent solids from precipitating during the aqueous washes and so maximized the partition of **20** into the aqueous phase. Two further water washes ensured pseudothiohydantoin purged to acceptable levels.

The isolation developed in the preliminary commercial route involved a cooling crystallization from acetonitrile following a solvent exchange from the workup solvent. After evaluation of alternative strategies for the isolation of **5**, such as formation and crystallization of a salt, crystallization after azeotropic drying of a solution, and cooling crystallizations with a range of solvents, the acetonitrile approach was retained. Therefore, the process that needed to be developed for the crystallization was an exchange from 2-butanol to acetonitrile before seeding to initiate crystallization.

Crystallization and solubility studies were completed to identify the optimum acetonitrile/2-butanol composition from which to isolate **5** based on yield and purity. This was shown to be 90/10% w/w acetonitrile/2-butanol. Solutions richer in acetonitrile were found to be less effective for purging impurities, although yields were slightly higher. Further investigation indicated that the presence of water had a negative impact on nucleation by increasing the metastable zone width. Above a water level of 5% w/w, self-nucleation

would not occur on cooling. This was important since the solution of **5** in 2-butanol generated following the water-washing stage contained high and variable levels of water (44–59% w/w). Thus the water content had to be controlled and reduced as much as possible to achieve the target solvent composition for crystallization. The best opportunity to remove water was through distillation in the initial concentration operation of the solvent exchange process, in order to utilize the water/2-butanol azeotrope. Analysis of the 2-butanol/water phase diagram showed that a water content greater than 28% w/w would, during any initial concentration, result in the vapor phase actually containing a greater composition of 2-butanol effectively increasing the water content of the bulk solution (Figure 3).

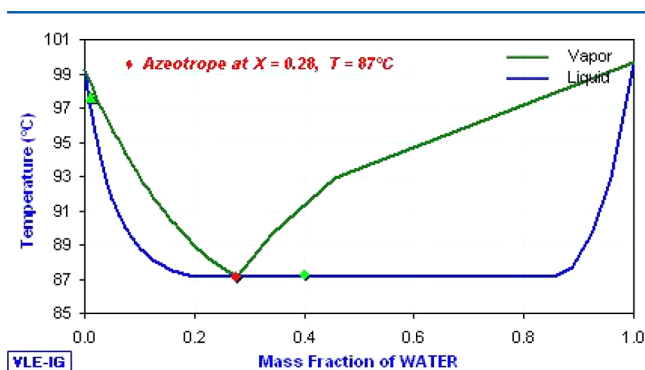


Figure 3. Phase diagram for 2-butanol/water.

Thus it was essential to ensure that the water content of the initial 2-butanol solution was below the level of 28% w/w. The simplest and most efficient way to achieve this was to partially dry the organic phase by the introduction of a brine wash as the final step of the aqueous workup. This guaranteed the water content to be below the 28% w/w target, allowing its efficient removal through the solvent exchange process, to finally achieve the seeding solvent composition of approximately 80:20% w/w acetonitrile/2-butanol necessary for crystallization. This solution was seeded (1% w/w) to induce a controlled crystallization prior to dilution with additional acetonitrile antisolvent to achieve the desired 90:10% w/w isolation solvent composition and maximize the yield and purity on cooling. Across numerous trial runs in the laboratory the maximum water content observed at the seeding point was 0.2% w/w affording **5** in a typical yield of 85% (Scheme 8).

2.5. Transfer to the Pilot Plant. The process, developed as outlined as above, was transferred to the pilot plant to generate 140 kg of **5**. Four batches of **4** were produced in the pilot plant with no deviations from the laboratory process, producing 203 kg with a reproducible 86–88% yield. The crystallization process of the highly crystalline, granular form of chloroacetamide **4** observed in the laboratory was replicated in

the pilot plant for the four batches and consequently filtered and dried rapidly on 50 kg scale. The isolated intermediate **4** was progressed as four separate batches through the deprotection stage with no deviations from the expected process to afford 140 kg of the amine **5** in excellent yield (84–88%) and again with high reproducibility. The overall yield for the synthesis of **5** from **1** was 74%, an increase of 16% on the 58% obtained from the previous process. The purity of the isolated product was extremely high with a maximum total impurity level in any batch of 0.16% and was suitable for progression into the downstream process for the manufacture of the PF-610355 API.

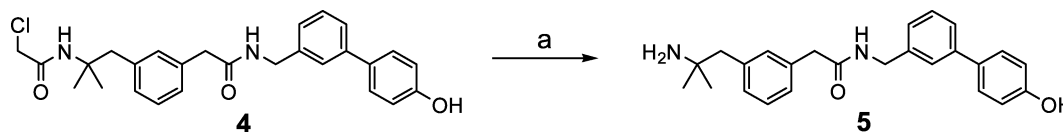
3. CONCLUSION

A new process for the manufacture of **5** has been developed that overcomes many of the issues associated with the original process. Process optimization focused on elimination/minimization of the use of undesirable materials, reproducibility, time reduction, throughput increase, waste minimization, and yield optimization. The key change made to the process was the introduction of the isolation of the chloroacetamide **4**. The seeded crystallization of **4** from 2-butanol/chloroacetonitrile allowed the isolation of a highly crystalline, granular form that provided a number of advantages. Of primary significance was the purge of chloroacetonitrile which prevented carryover to the deprotection reaction and avoided the production of 3.9 kg per kg of **5** of side-product waste. This in turn allowed the reduction of the maximum volume of the step by 61% from 83 L/kg to 32 L/kg (wrt **1**) through simplification of the chloroacetamide deprotection step and workup. This dramatic reduction in volume swing allowed each step to be performed in a single reactor. The rapid filtration of the intermediate, and the streamlining of the process to reduce unnecessary unit operations, afforded a 33% reduction in cycle time from 180 to 120 h. All of the improvements contributed to an overall yield increase from 58% to 74% and vastly superior green metrics. The E-factor (total waste [kg] per kg of **5**) was reduced from 302 to 91 with a significant proportion of the reduction attributed to the optimization of the aqueous workups (aqueous waste was reduced by 100 kg per kg of **5**). The new process was demonstrated on scale to be robust, leading to the manufacture of 140 kg of **5**.

4. EXPERIMENTAL SECTION

General. The starting materials **1** and **2** were synthesized by external vendors following procedures developed and supplied by Pfizer. All reagents and solvents were used as received from commercial suppliers. ^1H NMR was performed using either a Bruker Avance III spectrometer at 600 MHz or a Bruker Ultrashield Plus spectrometer at 400 MHz. ^{13}C NMR was performed using either a Bruker Avance III spectrometer at 150 MHz or a Bruker Ultrashield Plus spectrometer at 100 MHz.

Scheme 8. Optimized deprotection process^a



^aReagents and conditions: (a) (i) Thiourea, acetic acid, 2-butanol, water, reflux; (ii) 2 M NaOH, 2 water washes and a brine wash; (iii) Crystallization from MeCN, 85%.

Mass spectrometry was performed on a Bruker MaXis QTOF under positive ion conditions. Combustion analyses were performed by Warwick Analytical Service, University of Warwick Science Park, The Venture Centre, Sir William Lyons Road, Coventry, UK, CV4 7EZ.

2-Chloro-N-{2-[3-(2-[(4'-hydroxybiphenyl-3-yl)methyl]amino)-2-oxoethyl]phenyl}-1,1-dimethylethyl}acetamide 4. [3-(2-Hydroxy-2-methylpropyl)phenyl]acetic acid **1** (30 kg, 144 mol) was dissolved in ethyl acetate (150 L) at 25 °C. 1,1'-Carbonyldiimidazole (24.1 kg, 144 mol) was added to the solution, and the reaction was left to proceed for 1 h. 3'-(Aminomethyl)biphenyl-4-ol **2** (31.6 kg, 159 mol) was added, and the resulting slurry was heated to 50 °C. After 3 h the reaction mixture was cooled 20 °C and was washed with 2 M aqueous citric acid (158 L) and 1 M aqueous sodium bicarbonate solution (150 L). The organic layer was diluted with chloroacetonitrile (56.1 L), and the solution was distilled at atmospheric pressure; the end point was when the internal temperature reached 110 °C. The chloroacetonitrile solution was cooled to 50 °C, and trifluoroacetic acid (168 L) was charged over 90 min. The reaction was allowed to proceed at this temperature for an additional 2 h. The solution was subjected to a reduced pressure (−0.950 barg) to allow the distillation of trifluoroacetic acid, maintaining a temperature of 50 °C. Upon completion of the distillation, 2-butanol (225 L) was added to the reaction and the solution was warmed to 60 °C. Seed crystals of **4** (0.67 kg, 1% w/w based on 100% conversion) were added, and the slurry was held at 60 °C for 1 h. Cyclohexane (150 L) was added whilst maintaining the 60 °C temperature. The slurry was allowed to cool from 60 to 20 °C at a rate of 0.5 °C/min and stirred at 20 °C for 4 h. The solid was collected by filtration, washed with cyclohexane (2 × 90 L), and dried *in vacuo* at 45 °C to give **4** (58.7 kg, 87.6% yield) as a white solid. Mp 157–159 °C. ¹H NMR (600 MHz, *d*₆-DMSO) δ 1.22 (s, 6H), 2.96 (s, 2H), 3.48 (s, 2H), 4.00 (s, 2H), 4.34 (d, *J* = 5.9 Hz, 2H), 6.87 (m, 2H), 7.00 (dt, *J* = 7.5 and 1.5 Hz, 1H), 7.06 (t, *J* = 1.5 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 3H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.42 (m, 4H), 7.60 (s, 1H), 8.58 (t, *J* = 5.9 Hz, 1H) and 9.56 (br s, 1H). ¹³C NMR (150 MHz, *d*₆-DMSO) δ 26.7, 42.3, 42.4, 43.3, 43.4, 53.5, 115.7, 124.4, 124.8, 125.3, 126.8, 127.6, 127.7, 128.5, 128.8, 130.8, 131.2, 135.9, 137.8, 139.9, 140.3, 157.2, 165.5, and 170.2. HRMS (ESI): calcd (M + H)⁺ 465.1939, found 465.1950. Anal. Calcd for C₂₇H₂₉ClN₂O₃: C, 69.74; H, 6.29; N, 6.02. Found: C, 69.64; H, 6.31; N, 5.99.

2-[3-(2-Amino-2-methylpropyl)-phenyl]-N-[(4'-hydroxybiphenyl-3-yl)methyl]acetamide 5. 2-Chloro-N-{2-[3-(2-[(4'-hydroxybiphenyl-3-yl)methyl]amino)-2-oxoethyl]phenyl}-1,1-dimethylethyl}acetamide **4** (55 kg, 118 mol) was added to a stirred solution of 2-butanol (248 L) and water (275 L) at 20 °C forming a slurry. Acetic acid (14.9 L, 260 mol) and thiourea (10.8 kg, 142 mol) were added, and the reaction was heated at reflux. After 5 h the solution was cooled to 40 °C. The pH was adjusted to 10.8 ± 0.2 (at 25 °C) using 2 M NaOH, and the layers were then separated. The organic layer was diluted with additional 2-butanol (165 L) before washing with water (2 × 248 L) and brine (248 L). The organic layer was distilled down to a volume of 143 L at atmospheric pressure. Acetonitrile (242 L) was then added, and the solution was distilled down to a volume of 180 L. Acetonitrile (198 L) was then added. The solution was cooled to 70 °C at which point seed crystals of the title compound were added (0.4 kg, 1% based on 100% yield of the title compound), and the

resulting slurry was stirred at 70 °C for 1 h. The slurry was diluted with additional acetonitrile (275 L) before cooling to 20 °C at 0.3 °C/min where it was left to stir for 4 h. The slurry was diluted by the addition of acetonitrile (121 L). The solid was collected by filtration, washed with acetonitrile (2 × 121 L), and dried *in vacuo* at 50 °C to give **5** (39.8 kg, 86.7% yield −85.7% when corrected for H₂O content) as a white solid. Mp 144 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 0.96 (s, 6H), 2.54 (s, 2H), 3.48 (s, 2H), 4.33 (d, *J* = 4 Hz, 2H), 6.85 (d, *J* = 8 Hz, 2H), 7.06 (d, *J* = 8 Hz, 1H), 7.11–7.23 (m, 4H), 7.32 (t, *J* = 8 Hz, 1H), 7.38–7.44 (m, 4H), and 8.57 (bs, 1H). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 30.0, 42.2, 42.5, 49.7, 50.5, 115.7, 124.3, 124.7, 125.2, 126.5, 127.5, 127.6, 128.4, 128.7, 130.7, 131.0, 135.8, 138.8, 139.9, 140.2, 157.3, and 170.2. HRMS (ESI): calcd (M + H)⁺ 389.2224, found 389.2223. Anal. Calcd for C₂₅H₂₈N₂O₂·0.25 H₂O: C, 76.50; H, 7.33; N, 7.13. Found: C, 76.44; H, 7.18; N, 7.15.

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Notes

The authors declare no competing financial interest.

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