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Article

Development of a Green and Sustainable Manufacturing Process for Gefapixant Citrate (MK-7264) Part 1: Introduction and Process Overview

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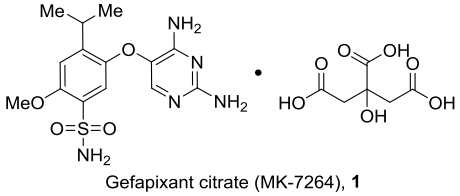
ABSTRACT: A robust, green, and sustainable manufacturing process has been developed for the synthesis of gefapixant citrate, a P2X3 receptor antagonist that is under investigation for the treatment of refractory and unexplained chronic cough. The newly developed commercial process features low process mass intensity (PMI), short synthetic sequence, high overall yield, minimal environmental impact, and significantly reduced API costs. The key innovations are the implementation of a highly efficient two-step methoxyphenol synthesis, an innovative pyrimidine synthesis in flow, a simplified sulfonamide synthesis, and a novel salt metathesis approach to consistently deliver the correct active pharmaceutical ingredient (API) salt form in high purity.

KEYWORDS: *P2X3 antagonist, flow chemistry, green chemistry, commercial process development*

INTRODUCTION

The prevalence of chronic cough, defined as a cough lasting longer than 8 weeks, is estimated at around 10% of adults globally, with a higher rate of diagnosis in industrialized countries.[1] Chronic cough can be very distressing for patients, as it causes physical, social, and psychological effects that negatively affect quality of life. Unfortunately, there are currently no approved therapies for the treatment of chronic cough. Gefapixant citrate (MK-7264, **1**), an antagonist of the purinergic receptor P2X3, has demonstrated significant efficacy in recent Phase 3 clinical trials in reducing the frequency of cough in patients with refractory chronic cough after 12 weeks of treatment compared to placebo (Figure 1).[2] In support of its development, we undertook the development of a commercial process for MK-7264.

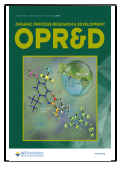
The ideal, green, and sustainable active pharmaceutical ingredient (API) manufacturing route has the aspirational goal of a "zero-waste" process. This goal is enabled by an innovative, green-by-design, development strategy to progress from initial route design through to a fully optimized and sustainable commercial manufacturing process. However, as highlighted recently, this goal is unachievable if chemists select a suboptimal route.[3a] In our experience, the greenest manufacturing processes require explicit design of all aspects, including starting with the synthetic route.[3b,4] Hence, the strategy commences with route exploration to identify the most direct method to convert commodity chemicals into API, in accordance with the principles of green chemistry.[4] Once the most direct route is prioritized, the application of new and enabling technologies and the discovery of new methods are often required as aspirational routes are rarely a sequence of well-known transformations. With the proof of concept for this route established, we turn to the core drivers of process development to translate this synthetic route into an efficient and robust process. In the following series of papers, the application of this strategy will be detailed for gefapixant citrate. This manuscript (Part 1) provides a high-level overview of the development of a commercial manufacturing process for gefapixant citrate. The subsequent manuscripts (Parts 2−6) describe in further detail the process development of each step in the commercial process.[5a]



Gefapixant citrate (MK-7264), **1**

Figure 1. Structure of gefapixant citrate 1.

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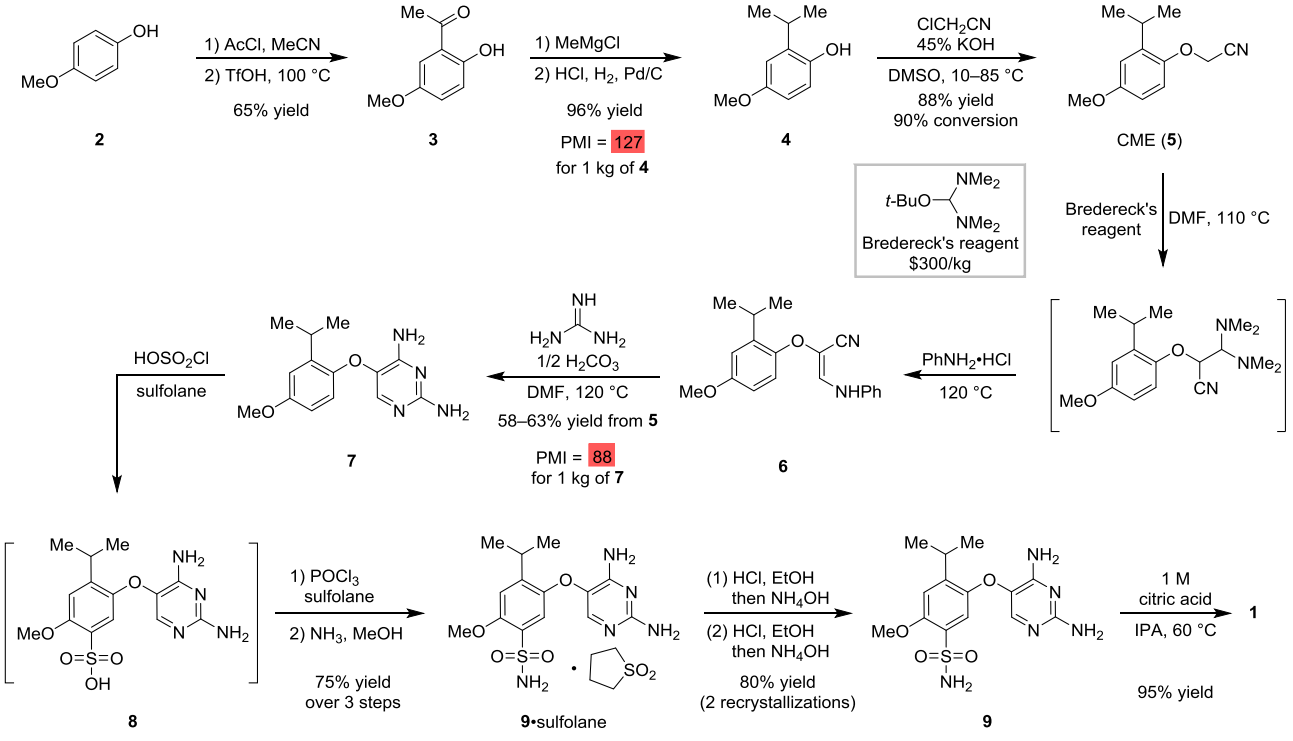


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Scheme 1. Supply Process for Gefapixant Citrate 1

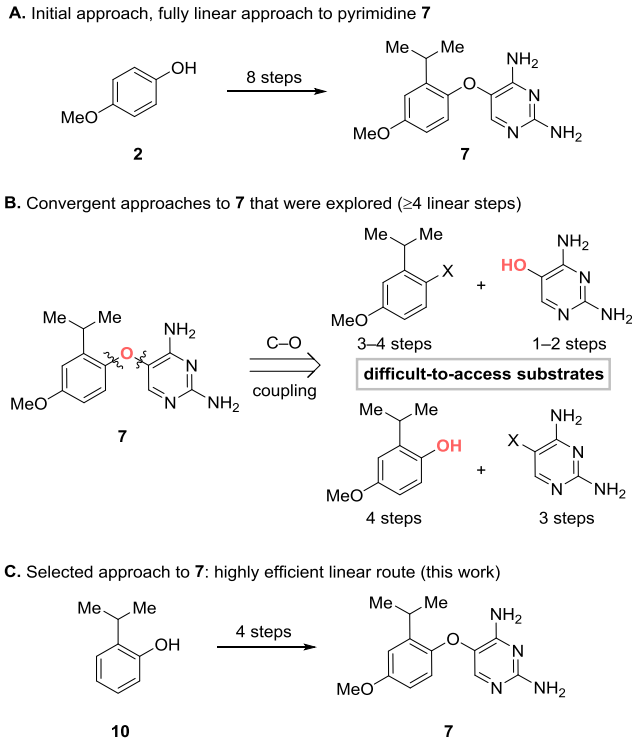


RESULTS AND DISCUSSION

The initial route utilized to provide gefapixant is shown in Scheme 1. As is often the case with initial scale-up routes, it was designed for sufficiency, meaning that little attention is paid to long-term measures of success and a premium is placed on speed of execution. While this approach is suitable for early preclinical toxicology studies and clinical supply, it does not meet our measures of success for a commercial manufacturing process in many ways including lead time, cost, process mass intensity (PMI), and robustness. The route contains a longest linear sequence of 11 steps, with a high PMI of 366, a low overall yield of 16%, and a high API cost.[6] The route also includes several reactions that are unsuitable for commercial manufacturing due to the hazardous reagents and conditions that are employed: (1) The Fries rearrangement used in the preparation of methoxyphenol **3** requires triflic acid as the reaction solvent at an elevated temperature (100 °C); (2) Installation of the cyanomethyl group in cyanoether **5** utilizes a high-temperature alkylation in dimethyl sulfoxide (DMSO), which is potentially hazardous due to the known risks of heating this solvent in the presence of base and alkylating agents;[7] (3) The subsequent preparation of the pyrimidine core requires multiple steps and the use of Bredereck's reagent,[8] an expensive and nonsustainable material; (4) Installation of the primary sulfonamide involves multiple steps, two of which require highly toxic and hazardous materials ($HOSO_2Cl$ and $POCl_3$); (5) After this sequence is complete, several recrystallizations of the product are necessary to deliver quality gefapixant free base **9**, which is first isolated as its sulfolane solvate; (6) Formation of the API salt, gefapixant citrate **1**, requires a slurry-to-slurry conversion with poor phase control.

For the long-term manufacturing process of gefapixant, we were particularly interested in exploring convergent approaches that disconnected the diaryl ether in intermediate **7** via C−O bond-forming reactions to avoid the long, linear synthesis in the supply route (Scheme 2A). However, while these convergent approaches were attractive on paper, due to the large number of steps required to synthesize the desired pyrimidine and phenol coupling partners from commodity chemicals, this strategy failed to shorten the longest linear sequence (Scheme 2B). Moreover, each of these proposed routes resulted in a much

Scheme 2. Comparison of Convergent and Linear Approaches to Pyrimidine 7



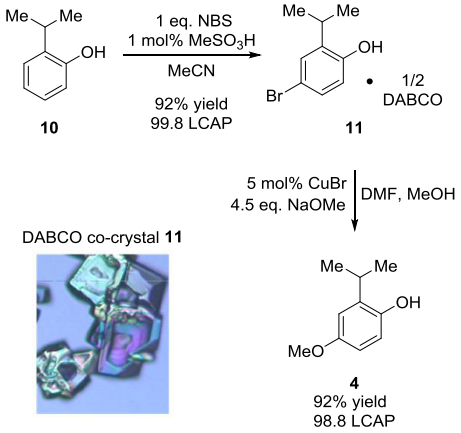
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greater total step count to access ether **7** (6−7 steps) than the highly efficient linear approach that was eventually chosen (four steps to ether **7** from a commodity starting material).[9] The added step count associated with this approach rendered the convergent route longer and less cost-effective than the linear strategy, and therefore, research efforts focused on the development of an efficient linear synthesis for gefapixant (Scheme 2C).

Our first challenge in approaching the synthesis of gefapixant was the synthesis of methoxyphenol **4**. An extensive literature survey showed that a four-step sequence for the synthesis of the key intermediate methoxyphenol **4** is the predominant approach in industry and academia (Scheme 1).[10] However, this approach uses the well-precedented four-step sequence to install the isopropyl group, providing the product in poor overall yield (<50%) and requiring the use of highly corrosive TfOH at an elevated temperature (100 °C). Ultimately, an efficient two-step route (Scheme 3) was developed to afford phenol **4** in high

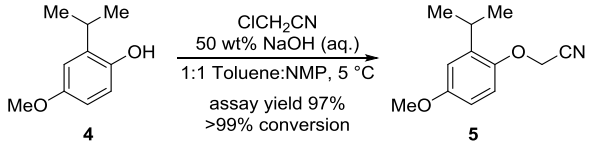
Scheme 3. Commercial Process for the Synthesis of Methoxyphenol 4



yield.[5a] Isopropylphenol **10** is a readily available commodity chemical and could be subjected to a highly para-selective bromination, followed by facile solation as its DABCO co-crystal **11**. The discovery of this crystalline solid was a key breakthrough that allowed for robust quality control of **11**, which we designate as the regulatory starting material, whereas the initial process notably lacked a solid phenol intermediate, obliging the isolation of compounds **3** and **4** as oils with no impurity rejection. A copper-catalyzed methoxylation of **11** readily provided methoxyphenol **4**, which was carried forward as a dimethylformamide (DMF) solution that was used directly in the subsequent alkylation step.

We next aimed to develop improved alkylation conditions to avoid the potential hazards inherent in the conditions in the supply route. Cyanomethyl ether **5** was obtained via alkylation with concentrated base and alkyl halides in DMSO, presenting a severe safety risk due to the exothermic nature of this reaction in addition to the known thermal instability of such mixtures at the high temperatures necessary for high conversion.[7] A safe, streamlined, and high-yielding synthesis of the cyanomethyl ether **5** was developed by simply switching from DMSO as solvent to an NMP/toluene mixture and replacing concentrated KOH with aqueous NaOH. This improved protocol also overcame the incomplete conversion issues observed in the initial procedure. An additional benefit of the NMP/toluene system is that it provides a unified solvent to bridge from methoxyphenol **4** to the pyrimidine-forming step. This solvent system was key for enabling the combination of these three steps on scale and, thus, enabled significantly decreased cycle time and PMI, and increased productivity (Scheme 4).

Scheme 4. Optimized Process for the Synthesis of Cyanomethyl Ether 5



We next turned our attention to the synthesis of the pyrimidine core. The original process for the production of compound **7** had several major drawbacks, including a lengthy eight-step synthesis from mequinol, stoichiometric use of the expensive Bredereck's reagent, and the potential mutagenic impurities introduced by the aniline intermediate **6**.[11] Since the aniline moiety is not part of gefapixant, we strove to eliminate its use in the commercial process and identified ethyl formate as the ideal formylating reagent. We initially developed an efficient and direct two-step, batch-mode synthesis of pyrimidine **7** from ether **5** using ethyl formate, potassium *tert*-butoxide, and guanidine (Scheme 5A).[5b] However, due to competing side reactions, all of these reagents were required in excess, and the process generated toxic CO gas. Further development led us to carry out the formylation reaction in flow, while running the subsequent cyclization in batch mode as before, resulting a greener, lower-PMI reaction that no longer generated significant amounts of carbon monoxide (Scheme 5B). The final process has been demonstrated successfully on an ∼1 MT scale with good isolated yield and robust impurity control.[5c]

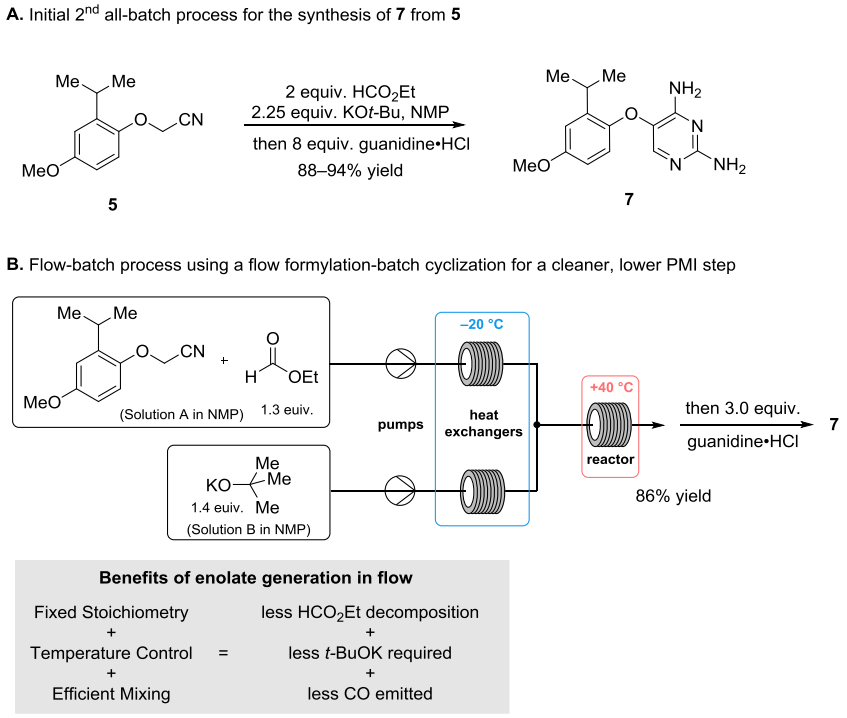
Following the successful development of the flow-based process, efforts were then focused on the conversion of pyridimide **7** into gefapixant free base **9**.[5d] Although sulfonamides such as compound **9** are most commonly synthesized from the reaction of arylsulfonyl chlorides with amines (in our case, ammonium hydroxide),[12,13] we hypothesized that a direct sulfonamidation of arene **7** would provide a more expeditious route to sulfonamide **9** that would bypass the corresponding reactive sulfonyl chloride intermediate. Therefore, an aspirational goal was set to develop a direct sulfonamide formation for the synthesis of gefapixant free base **9** (Scheme 6). Leveraging high-throughput experimentation (HTE), we identified and developed a Lewis acid-catalyzed Friedel−Crafts-type sulfonamidation reaction using sulfamoyl chloride **12** and $AlCl_3$ in dichloroethane (DCE), which gave gefapixant free base **9** directly from arene **7** in 70% isolated yield. This reaction was successfully performed in the laboratory to provide the free base **9**. While this transformation was appealing on paper, there were challenges associated with handling the smoky semisolid sulfamoyl chloride **12** on scale. In addition, the high cost of sulfamoyl chloride **12** and the need to use DCE, a toxic class I solvent, rendered this a nonviable commercial process. Thus, efforts were taken to develop a more practical and cost-effective method for the synthesis of gefapixant free base **9**.

In view of this result, we decided to investigate the use of a sulfonyl chloride intermediate in the conversion of arene **7** to sulfonamide **9**. The synthesis of arylsulfonyl chlorides has been dominated by the tedious preparation via oxidation of aryl

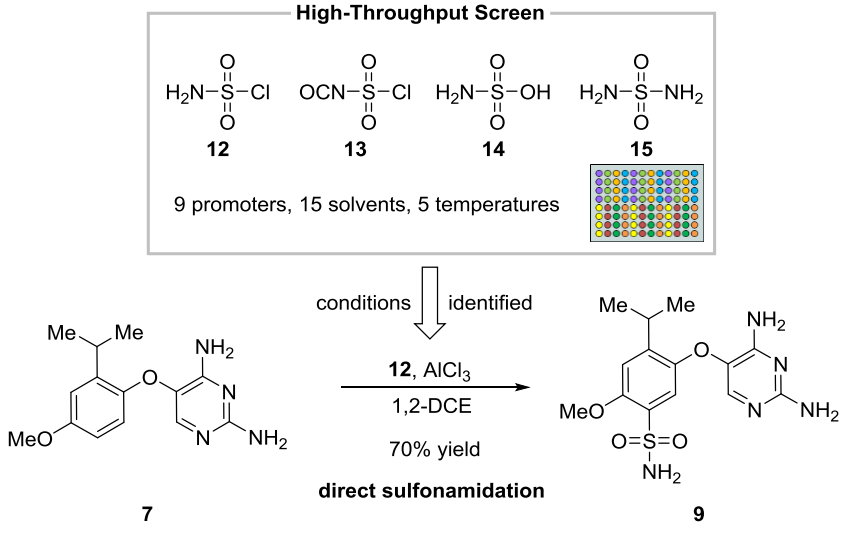
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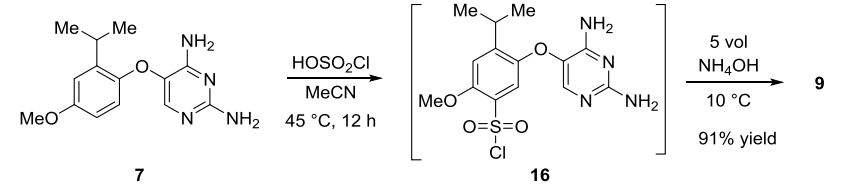
Scheme 5. Optimized Synthesis of Pyrimidine 7 Using Ethyl Formate



Scheme 6. Direct Sulfonylation of Functionalized Arenes



Scheme 7. Synthesis of Gefapixant Free Base 9 via Direct Chlorosulfonylation

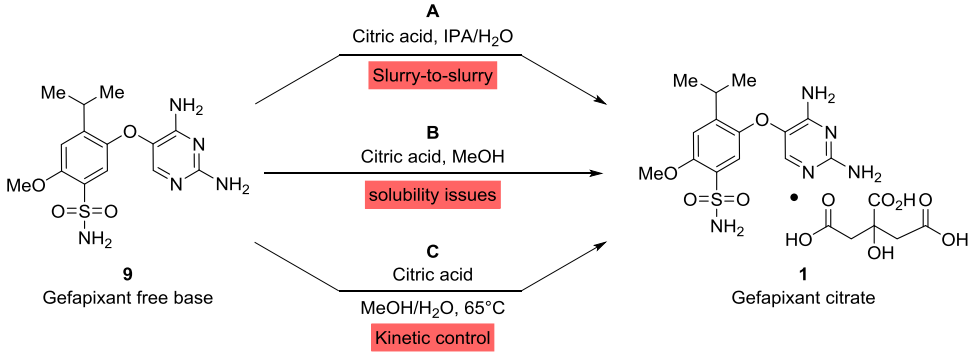


sulfide.[14] Alternatively, sulfonyl chlorides have been made from aryl halides or diazoniums, but this typically involves the use of unstable intermediates, gaseous reagents, and transition-metal catalysts.[15] Chlorosulfonic acid has proven to be a highly efficient reagent in sulfonylating electron-rich arenes.[16] However, as was seen in the initial clinical supply route, the most common products of these reactions are not sulfonyl chlorides but sulfonic acids such as compound **8**, despite the use of excess chlorosulfonic acid (Scheme 1). This intermediate must then be converted to the desired sulfonyl chloride with $POCl_3$, followed by amidation to give the desired sulfonamide **9**. Eager to avoid a three-step sequence to introduce the

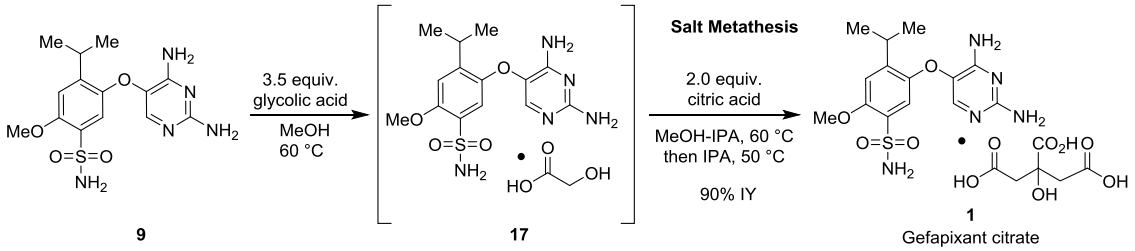
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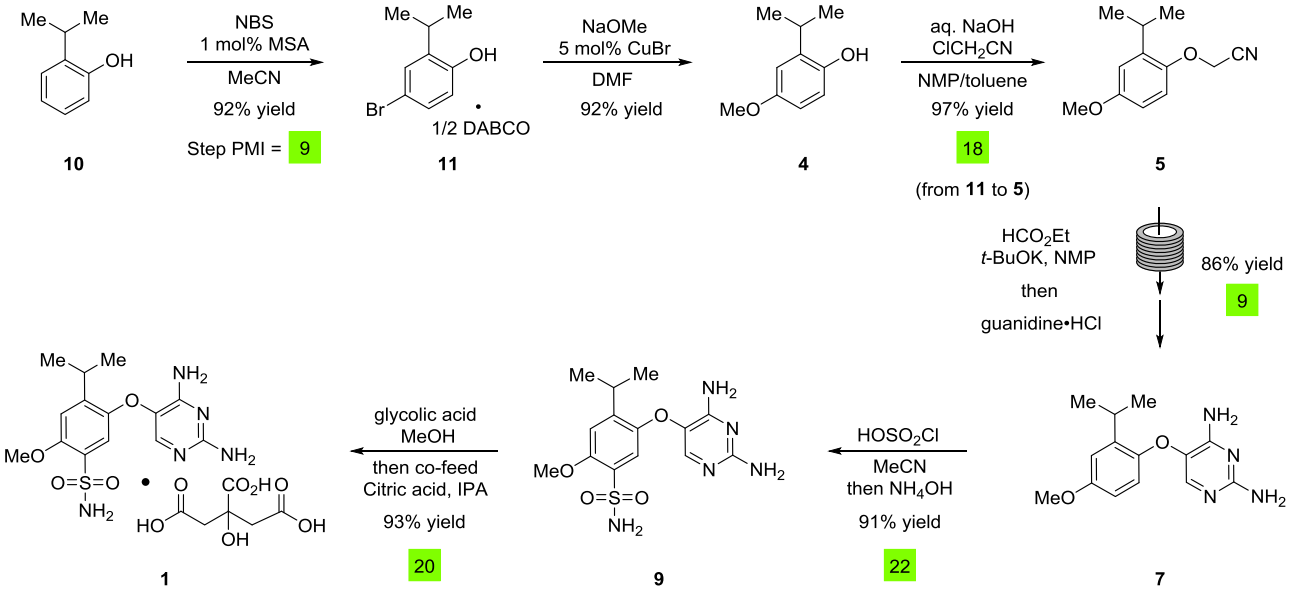
Scheme 8. Challenges with the End-Game Citrate Crystallization



Scheme 9. Gefapixant Citrate Isolation via Innovative Salt Metathesis and Intermediate Glycolate 17



Scheme 10. Gefapixant Citrate Commercial Manufacturing Process



sulfonamide group, we again turned to high-throughput experimentation and identified the use of MeCN as solvent as unique in directly yielding the sulfonyl chloride **16**, obviating the need of additional chlorinating reagents (Scheme 7). When the sulfonyl chloride **16** was quenched into aqueous NH_4OH, the desired API free base sulfonamide **9** was obtained. This process has been demonstrated on ~400 kg scale in 91% yield with robust impurity control and is described in greater detail in Part 5.[5d]

Form control was a major challenge in the formation of API citrate salt **1**. Our initial process (Method A, Scheme 8) adopted a slurry-to-slurry conversion with IPA and H_2O (Scheme 8). However, disproportionation of free base was a great concern given that as much as 10% of free base was observed in some isolated citrate batches. Extensive polymorph screening indicated that methanol would be an optimal solvent for the formation and isolation of the citrate salt (Method B, Scheme 8). However, the free base showed low solubility in pure MeOH (<3 mg/mL), and large volumes of MeOH would have been required to dissolve the free base prior to the pure-pocket filtration and final crystallization. The unacceptably high amount of MeOH was expected to cause low productivity and unnecessarily high process mass intensity. Thus, a 9:1 $MeOH/H_2O$ solvent mixture was adopted to overcome the low-solubility issues of free base in pure MeOH (Method C, Scheme 8). However, further investigation of the citrate phase diagram revealed that the 9:1 $MeOH/H_2O$ solvent mixture led

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to a kinetically controlled crystallization process that presented a risk for the development of a robust process.

(A) Slurry-to-slurry conversion prevents pure-pocket filtration, and isolated citrate **1** is contaminated with 10% of free base **9**. (B) Low solubility of free base **9** and citrate **1** in MeOH results in poor volumetric efficiency. (C) Using a mixture of MeOH and water (9:1) results in a kinetically controlled process that is not robust.

To overcome the low-solubility issues of free base **9** in MeOH, an innovative salt metathesis approach was developed (Scheme 9).[5e] By first forming a highly soluble transient glycolate salt **17** in situ, a homogeneous solution in MeOH was obtained and productivity was greatly improved. Next, salt metathesis with citrate, followed by addition of the antisolvent, isopropyl alcohol, afforded the desirable citrate salt **1** in 90% yield. In addition, this innovative salt metathesis approach also provided an opportunity for a highly productive pure-pocket filtration, robust form control, and complementary impurity rejection.

CONCLUSIONS

The commercial manufacturing route to gefapixant citrate **1** has a much improved overall PMI of 78 from commodity raw materials (Scheme 10).[17] This result represents a 5-fold reduction compared to the clinical supply route. In addition, a significantly higher overall yield (16 → 60% yield) and a 6-fold reduction in API raw material costs were realized. Furthermore, the hazardous alkylation, as well as two highly toxic and hazardous chemicals have been replaced, rendering this a safer and more robust process. The key innovations are (1) the implementation of a highly efficient two-step methoxyphenol synthesis; (2) an innovative diaminopyrimidine synthesis using a hybrid flow-batch process; (3) a simplified direct sulfonamide synthesis; and (4) a novel and robust salt metathesis approach to consistently deliver the correct API salt form in high purity. The entire process has been successfully demonstrated to make >300 kg gefapixant citrate.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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