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Exploratory Process Development and Kilogram-Scale Synthesis of a Novel Oxazolidinone Antibacterial Candidate

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Supporting Information

ABSTRACT: A concise, environmentally benign, and cost-effective route was developed for the large-scale preparation of **1**, a novel oxazolidinone antibacterial candidate. The key intermediate 2-(1-(2-fluoro-4-nitrophenyl)-1*H*-pyrazol-4-yl)pyridine **7** was prepared with high purity by mild deamination of the regioisomeric mixture **21**. The mixture was prepared from a nucleophilic SNAr reaction by selective C−N coupling of the secondary amine functionality of 4-(pyridin-2-yl)-1*H*-pyrazol-3-amine **14** with 1,2-difluoro-4-nitrobenzene **10** in optimized conditions with the primary amine group remaining intact. The gaseous nitrogen release rate and reaction mixture temperature of the deamination step can be well controlled by altering the feeding manner, thereby providing safety guarantees. The optimized synthetic strategy of **1** with an overall yield of 27.6%, including seven sequential transformations by only five solid−liquid isolations, significantly improved the product separation workup. The strategy bypassed time-consuming and laborious procedures for any intermediate involved as well as for the final API. This study presents a process enabling the rapid delivery of a multikilogram quantity of API with high purity.

INTRODUCTION

Linezolid (Figure 1) is the first representative of a new class of oxazolidinone antibacterials. It has successfully been used to treat serious Gram-positive infections in clinics since it was approved by the FDA in 2000.[1] A new member of the oxazolidinone antimicrobial candidates **1** (Figure 1) was found to be more active *in vitro* and *in vivo* and had a pharmacokinetic profile comparable to that of linezolid (with an apparent absolute oral bioavailability of 100%). Given these reasons, **1** was selected for preclinical and clinical studies.[2] Compound **1** was found through a medicinal chemistry project and required modest amounts of material for *in vitro* and *in vivo* pharmacological assessment and preliminary toxicity study. As biological results evolved, larger amounts were necessary to support the next phase of preclinical studies, and a synthetic route capable of delivering multikilogram quantities was investigated.

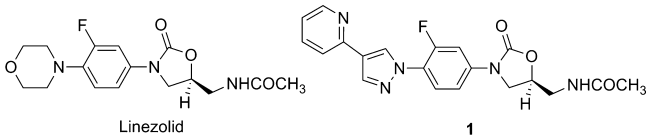

Figure 1. Structures of linezolid and compound **1**.

The original medicinal chemistry synthetic routes[2] were certainly able to deliver gram-scale products to support studies of SARs, preliminary toxicities, and physicochemical properties. However, the unstable intermediates and ineffective purification strategies made their application for a multikilogram campaign unpractical. Thus, reinvestigation of possible routes for the final compound **1** was necessary to expedite scale-up development and quick delivery for regulatory toxicity and preclinical studies.

Retrosynthetic analysis of compound **1** was carried out according to the general guidelines recommended by Warren[3] (Figure 2).

The most efficient disconnection of A occurrs in the most central area of the relevant starting molecule. This phenomenon leads to a highly convergent route to compound **1**, which meets our requirement of "scalable enabling technology" and affords fragments **2** and **3**. Fragment **3** was prepared according to published procedures[4] after minor modification but suffers disadvantages of low yield and inevitable chromatography procedures for purification. Fragments **2** and **3** were speculated to be combined via a C−N bond-formation reaction.[5] Disconnection of B gave fragments **4** and **5**, which could be coupled at a late convergent stage of the synthesis. Fragment **4** is commercially unavailable in large amounts, and its synthesis involves tedious workup. As shown in the disconnection of C, fragments **8** and **9** could function in oxazolidinone ring construction in the final step to yield **1**. Despite its linearity, disconnection of C is better than that of B because of the commercial availability of compound **8**.

We critically reviewed all three routes prior to making a final decision and found that all of these routes involve the common key building block **2**, 2-(1*H*-pyrazol-4-yl)pyridine (Figure 2). This building block could be facilely obtained through the reaction of 2-(pyridin-2-yl)malonaldehyde with hydrazine in gram scale according to the literature.[6] However, 2-(pyridin-2-yl)malonaldehyde is commercially unavailable and difficult to

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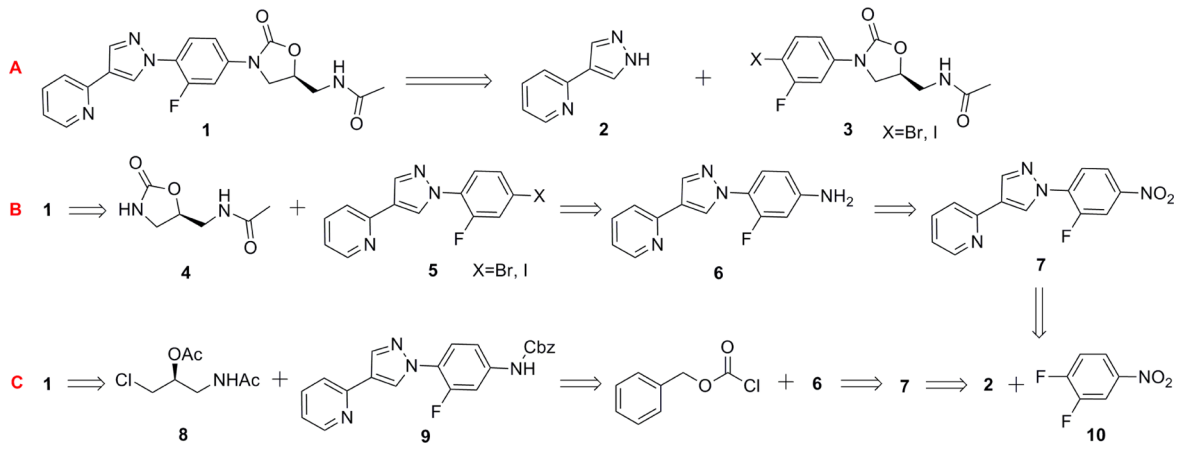


Figure 2. Retrosynthetic strategy of compound **1**.

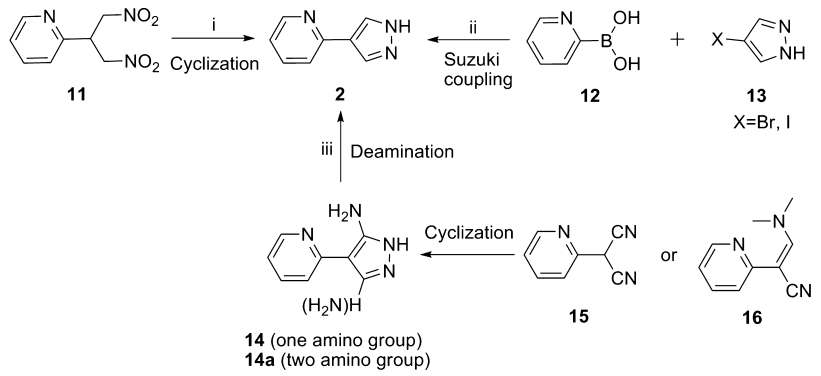
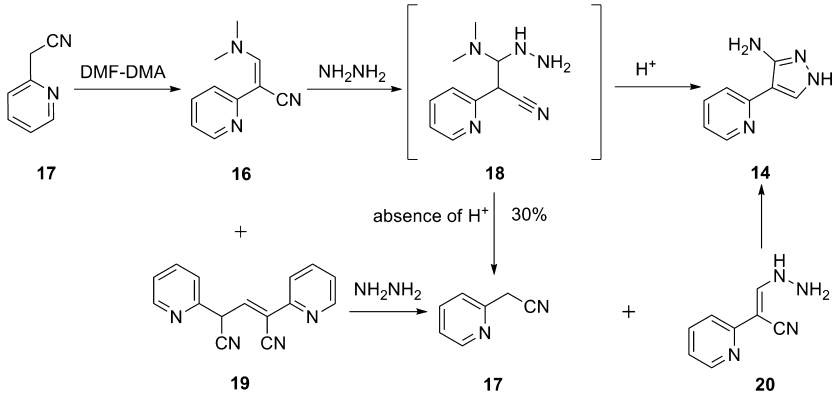


Figure 3. Three synthetic approaches of key intermediate **2**.

Scheme 1. Summary route to key building block 14 and proposed formation of impurity



produce on a large scale via a green procedure (see Supporting Information), which led us to investigate novel scalable methods to prepare compound **2**. This study describes our successful strategy for constructing key building block **2** from commodity components and an improved route to the key intermediate **7** in strategies B and C. The method considers the functional group addition (FGA) approach and adjusts the sequence of the reaction steps with the aim of addressing safety issues and tedious separation procedures for compound **2**. The remarkably improved route allowed the successful transition from gram-scale laboratory preparation to multikilogram production of **1** in a kilo laboratory.

RESULTS AND DISCUSSION

Figure 3 shows that key building block **2** could be produced using three approaches: (i) cyclization reaction of equivalent of 2-(pyridin-2-yl)malonaldehyde, 2-(1,3-dinitropropan-2-yl)-pyridine **11** with hydrazine; (ii) Suzuki−Miyaura reaction by C−C coupling of pyridin-2-ylboronic acid **12** with 4-bromo-1*H*-pyrazole or 4-iodo-1*H*-pyrazole **13**; and (iii) the FGA approach, i.e., addition of one or two amino groups on the pyrazole ring of compound **2**, resulting in different raw materials.

The first approach involved the discrete synthesis of the precursor 2-(1,3-dinitropropan-2-yl)pyridine **11** according to method reported by Roberto[7] with minor modifications; this method used 1,3-dinitropropane as a malondialdehyde

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synthetic equivalent to react with hydrazine and construct a pyrazole ring in refluxing ethanol.[8] However, the application of the reaction gave only trace amounts of **2**. In the second coupling approach, the hydrogen in the N-1 position of compound **13** should be substituted with an intact protecting group before being subjected to the basic Suzuki−Miyaura reaction conditions. These conditions involve a palladium catalyst, which is vulnerable to poisoning by nucleophilic attack. In addition, expenses associated with pyridin-2-ylboronic acid **12** also impede the implementation of this approach to produce compound **2** on a pilot scale.

Considering these issues, we investigated the FGA approach, which presented us with two options to access compound **2** after adding one or two amino groups to its pyrazole ring. First, for symmetry, two amino functionalities can be added in the pyrazole ring of compound **2** and reversely derived to 4-(pyridin-2-yl)-1*H*-pyrazole-3,5-diamine **14a**. This reverse step can be carried out by condensation reaction[9] of 2-(pyridin-2-yl)malononitrile with hydrazine. A key point here is the efficient synthesis of 2-(pyridin-2-yl)malononitrile. In the laboratory, production from 2-bromopyridine and malononitrile in suitable conditions is not difficult.[10] Nevertheless, this approach has several disadvantages, such as an expensive rare metal catalyst, high temperature, and unacceptable yields for further scale-up. In the second option, 4-(pyridin-2-yl)-1*H*-pyrazol-5-amine **14**, with one amino group addition, can be reversely derived to 3-(dimethylamino)-2-(pyridin-2-yl)-acrylonitrile. Its laboratory gram-scale synthesis can also be easily accomplished from 2-(pyridin-2-yl)acetonitrile **17** in a two-step sequence (Scheme 1) with moderate yield by microwave irradiation[11] or normal warm conditions. This synthetic sequence is more suitable for further optimization and scale-up because of its significant benefits in workups and acceptable yields as well as use of inexpensive starting materials and palladium catalyst. Given this analysis, precursor **14** was selected for further development.

As depicted in Scheme 1, intermediate 3-(dimethylamino)-2-(pyridin-2-yl)acrylonitrile **16** was prepared by condensation of 2-(pyridin-2-yl)acetonitrile **17** and DMF−DMA without solvent and microwave irradiation as required in published procedures.[12] A small amount of fluorescent byproduct **19** formed in the first step was found by TLC under a UV lamp. This byproduct would convert back to starting material **17** and desired compound **14** through compound **20** (not isolated) by reacting with hydrazine in the second step. The reformed 2-(pyridin-2-yl)acetonitrile **17** can be easily recycled by suspending the compound **14** in water, filtering workup, and concentrating, thereby obtaining filtrates under reduced pressure. The chemical structure of fluorescent byproduct **19** was isolated and confirmed by ^{1}H NMR and MS spectra. Because fluorescent byproduct **19** cannot be conveniently removed in the first step and would partially convert to the desired product in the second step, purification of the crude intermediate **16** was necessary after conventional removal of excess reactant DMF−DMA in reduced pressure.

The second step for the synthesis of compound **14** gave us problems because of the absence of an acid catalyst in refluxing ethanol during our first kilogram campaign. Compound **14** was obtained with a lower chemical yield of 34% with a huge backward formation of 2-(pyridin-2-yl)acetonitrile **17**. Some studies suggest that moderate to good yields (50−80%) can be achieved if the appropriate acid catalyst is utilized. McCall[14] used acrylonitrile to react with hydrazine in the presence of 4 equiv of hydrobromic acid to give **14** with 78% yield. When an appropriate catalyst was applied, the protocol allowed the level of starting material **17** to be lowered to 5%, and the chemical yield was comparable with that reported. Several acids in different equiv ratios to the substrate were reported as catalysts that resulted in good reaction profiles.[13] However, this study determined a protocol maintaining a high level of atom efficiency and low corrosive effect to the environment. Several acids were screened to reduce corrosive effects on the equipment or environment. A laboratory improvement program was performed to determine whether the equivalents of acid and hydrazine used in the reaction could be reduced. Either a weak or strong acid, such as acetic, formic, or hydrochloric, resulted in high conversion (>90% HPLC peak area) to the desired **14** and low levels of 2-(pyridin-2-yl)acetonitrile **17** (<5%). Application of *p*-toluenesulfonic acid resulted in significantly decreased conversion. Moreover, crude **14** was obtained in ∼60% chemical yield, which mostly associated with 2-(pyridin-2-yl)acetonitrile **17** (∼10%) backward and unknown impurities (∼5%). Acetic acid was used for the process because formic and hydrochloric acids will result in more corrosive problems than acetic acid. Upon optimization, the second improvement was quickly observed. Only 1 equiv of acid and hydrazine for 12 h resulted in high conversion and a low level of impurities (Table 1).

Table 1. Product contents of crude intermediate 14 catalyzed with different equivalents of acids

		HPLC area %	
acid	equiv	**14**	**17**
formic acid	4	90.1	3.1
HCl	4	93.2	4.7
p-toluenesulfonic acid	4	82.2	12.4
acetic acid	4	92.8	3.5
acetic acid	1	93.6	3.6
acetic acid	0.1	87.0	7.3

Reappearance of starting material **17** could not be avoided in this process because it arose from both reactions of fluorescent byproduct **19** with hydrazine and the self-dissociation reaction of **18**. However, the level of **17** was successfully minimized without downstream difficulties. The sparingly soluble product **14** was purified by making a slurry of the crude product in water and filtering. Trace amounts of more soluble compound **17** were effectively partitioned into the water phase during workup such that the final filtered cake containing compound **14** was in relatively high purity (∼99% HPLC area %). While this process was telescoped, a two-step sequence was established for the preparation of up to 2 kg batches of **14**.

In accordance with the planned synthetic strategy, with an efficient and cost-effective preparation of **14**, we moved forward to the key intermediate **7** by direct deamination of compound **14** to obtain compound **2**, which was followed by C−N coupling with 1,2-difluoro-4-nitrobenzene. Alternatively, the fluorinated benzene ring was introduced to compound **14** to make the regioisomeric mixture **21**, which was followed by a deamination step to produce the key intermediate **7**. The differences between these two measures lay not only in the reversed synthetic sequence but in significant effects on the safety issues and separation workups as described below.

Initially, amine pyrazole **14** was directly subjected to the deamination step (Scheme 2). The use of hypophosphorous

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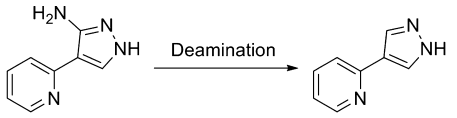
Scheme 2. Three conditions for the deamination of compound 14

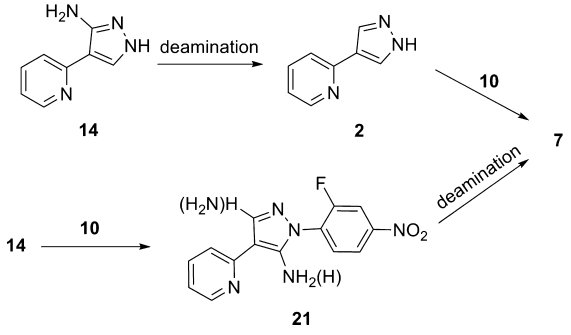


Condition 1: $NaNO_2$, HCl aq(37%), H_3PO_2, H_2O, 0-5 ℃
Condition 2: $NaNO_2$, HCl aq(37%), EtOH, reflux
Condition 3: Isoamyl nitrite, DMF, 55 ℃

acid is one of the conventional methods in the literature for this deamination in the presence of sodium nitrite.[14] The application of this acid resulted in a modest chemical yield (~60%), but the reaction suffered from tedious workup. This problem was mostly due to the very viscous and sticky reaction mixture, which could be resolved by using more volumes of water as solvent but would significantly decrease the process batch size. As depicted in Scheme 2, two more conditions for the deamination were specified.[15] Upon scaling up to 20 g of starting material **14**, these two conditions were used separately. Safety issues of a delayed sharp exothermic event and occurrence of N_2 release on this laboratory scale were observed, which are expected to present potential hazards during kilogram scale-up. Using isoamyl nitrite as the deamination reagent would produce more byproducts, which increases the isolation difficulty; however, we constructed the key building block up to 1 kg batches by this method. The preparation of **2** by the direction deamination method was still unsatisfactory for even larger-scale batches because of important safety issues or isolation difficulties.

Consequently, the synthesis of key intermediate **7** by preparing the planned **2** followed by coupling with 1,2-difluoro-4-nitrobenzene **10** was not an ideal strategy. To address the aforementioned issues, we wondered whether or not reversion of the two-step synthetic sequence would provide us a more attractive alternative leading to the key intermediate **7** (Scheme 3).

Scheme 3. Synthetic routes of compound 7



In the gram-scale synthesis of regioisomeric mixture **21**, 1.0 equiv of 1,2-difluoro-4-nitrobenzene **10** and K_2CO_3/DMSO at various temperatures (25, 45, and 75 °C) were used arbitrarily. The reaction progress was monitored by HPLC. The different temperatures gave similar reaction profiles, which were high conversion but low HPLC purity with a level of 10−20% byproduct of **22** (Figure 4). The formation of **22** was mostly attributed to a strong polarization effect of DMSO, which activated the C−F bond in 1,2-difluoro-4-nitrobenzene **10**.

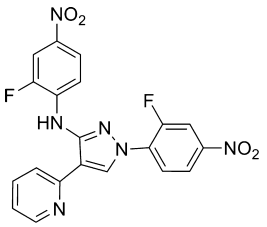


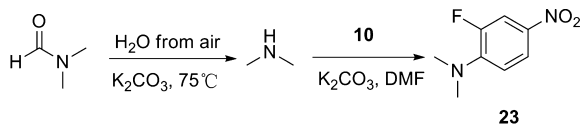
Figure 4. Chemical structure of byproduct **22**.

Thus, its electrophilic reactivity was enhanced and resulted in nonselective electrophilic attack of the secondary as well as the primary amine functionality in compound **14**. This unacceptable nonselectivity triggered screening for a less polar solvent with suitable base to synthesize compound **7** with high purity.

Screening of conditions was performed using microscale high-throughput experimentation strategy. As we expected, the use of less polar solvents gave no impurity **22**, which was detected in the reaction when DMSO was used as solvent.

Initial attempts to identify the reaction temperature were performed using DMF solvents and K_2CO_3 as base. Reactions under temperatures of 25 and 45 °C were not ideal with low to moderate conversion of compound **10**; conversion was as high as 95% at 75 °C. Thus, the following development work was carried out at 75 °C. This high conversion was not reproduced when DMF was used as solvent in the first batch of screening, which did not progress beyond 70% conversion. A byproduct **23** was also produced, the chemical structure of which was elucidated by NMR and MS spectra (see Supporting Information). This byproduct **23** arose from the coupling reaction of 1,2-difluoro-4-nitrobenzene **10** with dimethylamine, which was supposed to arise from hydrolysis of DMF in the presence of moisture at 75 °C (Scheme 4). To address this

Scheme 4. Proposed route to the formation of impurity 23



issue resulting from water, N_2 atmosphere was charged in our subsequent development work. In the second batch of screening, the reaction, which was charged with N_2 using DMF as solvent, provided high conversion with no byproduct **23** detected.

Figure 5 shows that the efficiency of formation of **21** was found to be highly dependent on the polarity of solvent as well as the strength of the employed base. Experimental results suggested that the solvents with high polarity gave better conversions. For example, reactions in dioxane or acetone showed slow conversion rates and stalled at less than 90% conversions, whereas reactions in ACN or DMF demonstrated high conversion rates of >95% for 5 h at 75 °C when Cs_2CO_3 was used as the base for deprotonation of **14**. Similar trends were observed for the strength of the employed bases, i.e. the stronger base produced higher conversions compared with its weaker counterparts. Notably, among these screened bases, potassium and cesium were both better counterions for deprotonation than sodium. However, when K_2CO_3 was used as base, the reaction conversion in ACN significantly decreased (95.6% to 53.1%), whereas DMF resulted in a good conversion

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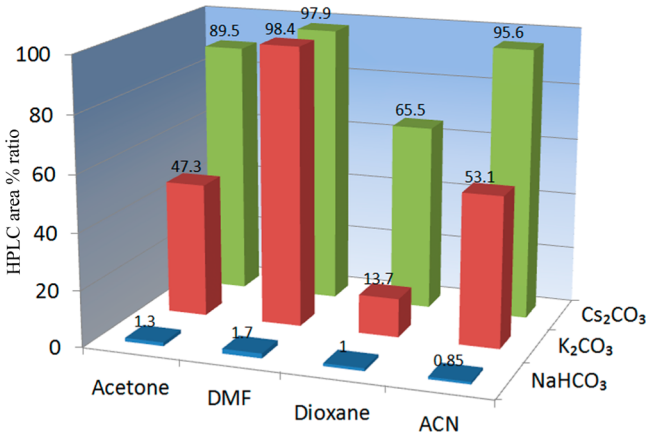


Figure 5. HPLC results of the C−N coupling reaction in different conditions at 75 °C.

of 98.4%. Meanwhile, considering the cost and hygroscopic property of Cs_2CO_3, K_2CO_3 was selected as the base promoter.

More repetitions of this reaction were performed in gram scales. Optimal conditions were found and confirmed by using 1.2 equiv of 1,2-difluoro-4-nitrobenzene **10** and 1.5 equiv of potassium carbonate in DMF at 75 °C. Using these conditions, a kilogram batch was performed, and compound **21** yielded 96% without contaminants. The product was notably a mixture of 3-amino and 5-amino regioisomers in a ratio of about 3:1 by ^{1}H NMR (Figure 6). Separation of the isomeric mixture was not necessary because the amino groups would be removed in later steps.

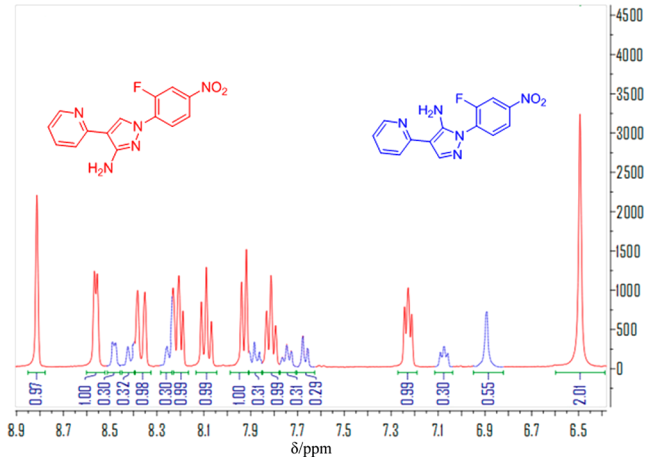
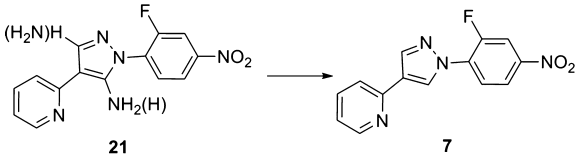


Figure 6. Component ratio determination of regioisomers of **21** by ^{1}H NMR.

Thus, the key intermediate 2-(1-(2-fluoro-4-nitrophenyl)-1*H*-pyrazol-4-yl) pyridine **7** could be synthesized by deamination of the corresponding regionisomeric mixture **21** as depicted in Scheme 5.

To find an effective and efficient condition suitable for a safer deamination process of **21**, conditions used for deamination of **14** to give **2** were again investigated in this step. Condition 1 resulted in a similar reaction profile stated in the reaction of deamination of **14**, which also suffered from a delayed sharp exothermic event and nitrogen release. The application of condition 2 on this reaction resulted in the absence of sticky and viscous materials. However, a tedious and time-consuming

Scheme 5. Different reaction conditions for deamination to make key intermediate 7



Condition 1: $NaNO_2$, HCl aq(37%), H_3PO_2, H_2O, 0-5 ℃
Condition 2: $NaNO_2$, HCl aq(37%), EtOH, reflux
Condition 3: Isoamyl nitrite, DMF, 55 ℃

workup was still involved, where large amounts of solvent and repetitions of the extraction procedure were needed to warrant major isolation of the products from the aqueous phase. In condition 3, an altered feeding manner guaranteed a good safety with mild nitrogen release and no delayed sharp exothermic event with an adiabatic temperature rise value of <17.5 °C after the completion of feeding the amine compound **21**. In previous attempts, amine substrate **21** was charged in the reactor and dissolved in DMF. Then, isoamyl nitrite was added in one portion (slow addition made the product quite impure), which resulted in uncontrollable nitrogen release and increased reaction temperature. When the anhydrous DMF was heated to 55 °C, isoamyl nitrite was poured into the reactor in one portion with vigorous agitation. After heating, the solid amine **21** was then added in batches. The feeding speed was controlled to ensure a mild gaseous release, and a period of 40 min was appropriate on a scale of 2 kg of solid amine **21**. The obtained product was of high purity, and this reaction feeding manner was suitable for scalable synthesis. The aforementioned optimized feeding manner was successfully applied in the preparation of key intermediate **7** up to 2.1 kg in one batch.

All reasonable endeavors for the key intermediate **7** exhibited good results. The following steps (Scheme 6) were implemented according to conventional reaction conditions although some major improvements had also been made during our development.

Reduction of **7** with iron powder in the presence of concentrated hydrochloric acid at reflux in EtOH cleanly afforded **6** in 67% yield. This reaction condition was not suitable for industry because of its significant environmental effect from the iron slurry. The alternative for preparing **6** involved reduction of **7** with $FeCl_3{\cdot}6H_2O$ and hydrazine in the presence of activated carbon at reflux. Notably, the safety issue of potential pressure hazard that was caused by evolution of N_2 was minimized by the slow hydrazine feeding rate and favorable agitation speed. The reaction mixture was warmly filtered through a short pad of silica to remove $FeCl_3$ and activated carbon powder, with the filtering cake washed with hot ethanol. After evaporation workup, the residue was dissolved in anhydrous acetone, with a small amount of hydrazine hydrochloride remaining at the bottom, which could be removed by decantation. The acetone solution of compound **6** was used directly in the following *N*-acylation reaction to give intermediate **9**.

N-acylation of **6** with benzyl chloroformate (Cbz-Cl) in the presence of K_2CO_3 at 25 °C in DCM afforded **9** in a yield around 90%. Although this condition resulted in a high yield, extraction workup was needed, and that suffered from a significant emulsification problem which was time- and solvent-consuming. The product was also contaminated with colored

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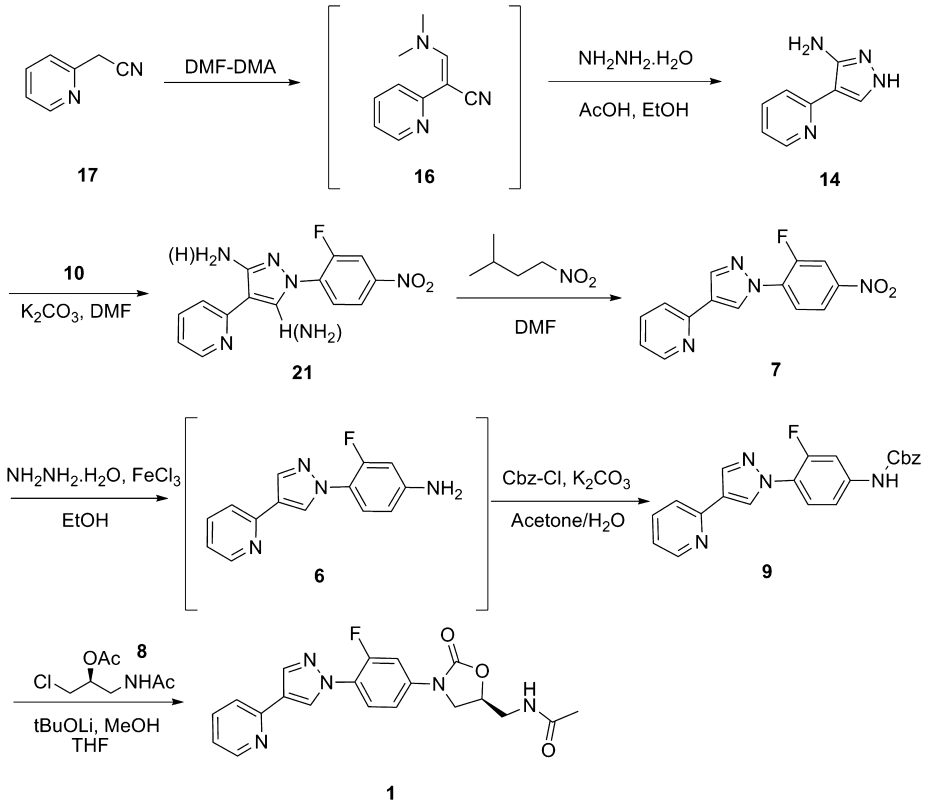
Scheme 6. Final process synthetic route of compound 1



impurities, which were difficult to remove by crystallization regardless of solvent. When the resultant colored material was directly carried into the next step, it presented the same downstream difficulties. Thus, after careful development, the conditions of the Schotten–Baumann acylation modification were finally used for the synthesis of **9**. These conditions with dilute aqueous K_2CO_3 in acetone required 2.0 equiv of Cbz-Cl. When the reaction was complete, a concise solid–liquid separation removed most of the impurities, including a small amount of unreacted **7**, (carried over from the previous step), amine **6**, and inorganic salts. The filtered cake was resuspended in water to remove the trace amounts of attached inorganic salts. Crystallization from 50% ethanol allowed the removal of excess Cbz-Cl, and the isolated product was consistently pale white with no colored impurity. After drying in an oven to a constant weight at 80 °C, the water content, which would consume lithium *tert*-butoxide in the subsequent chemical reaction, was 0.8% as determined by Karl Fischer titration. This content met our practical demand.

Finally, application of the literature conditions to convert compound **9** gave expected yields and high conversions to the oxazolidinone.[16] Significant impurities were not observed as reported by studies,[17] and unknown minor impurities were removed by crystallization. We attempted various solvent systems, but with minimal success, except for the EtOH and H_2O (3:1) mixture, which removed most of the colored impurities and lithium salt. Final active pharmaceutical ingredient (API) **1** with desired polymorph was obtained by straightforward solid–liquid separation with a high isolated chemical yield of 82%. This material was of pharmaceutically acceptable purity (99.9 HPLC area %) and met all the required specifications. Thus, the final synthetic route for API was established as shown in Scheme 6.

CONCLUSION

In summary, the key building block **14** was successfully prepared using a catalyst of 1 equiv of acetic acid. This compound was produced on a large scale and high yield after the proposed mechanism was telescoped. The key intermediate 2-(1-(2-fluoro-4-nitrophenyl)-1*H*-pyrazol-4-yl)pyridine, **7**, leading to the API was made by reversing the two-step reaction sequence from the key building block **14**, thereby providing safety guarantees and facile solid–liquid separation workups. The merits of the environmentally benign synthetic strategy of **1** are highlighted by its acceptable cost because of its readily available starting materials, only five isolation procedures for seven sequential transformations, and no laborious separation work-ups involved throughout the route. This study presents a process that allows rapid delivery of a multikilogram quantity of API with pharmaceutically acceptable purity and an overall yield of 27.6%.

EXPERIMENTAL SECTION

All solvents and reagents were purchased from the suppliers and used without further purification. ^{1}H NMR spectra were recorded on a Bruker Avance (Varian Unity Inova) 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 with Me_4Si (TMS) as an internal standard. Mass spectra were recorded on a Waters Q-TOF Premier mass spectrometer. HPLC analyses were performed on a Waters Alliance system (Waters Corp., Milford, MA, U.S.A.), which was equipped with a performance PLUS inline degasser along with an autosampler and a 2998 photodiode array detector. LC/MS analyses were carried out using a Shimadzu LC-20AD interfaced to an Agilent AB SCIEX 3200 Q TRAP mass spectrometer equipped with an electrospray ionization (ESI) source. Separation was achieved using an

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XBridge BEH C_{18} XP column (75 mm × 2.1 mm, 2.5 μm) from Waters. This column has a mobile phase consisting of methanol and an aqueous solution of formic acid (0.01%, v/v) at a flow rate of 0.3 mL/min. The MS analysis was performed in Q1MS mode.

(*E*)-3-(Dimethylamino)-2-(pyridin-2-yl)acrylonitrile (16). A reactor was charged with 2-pyridylacetonitrile (**17**, 2 kg, 16.93 mol) and DMF−DMA (3.31 L, 24.89 mol). The reaction mixture was heated to reflux for 3 h. The progress of the reaction was monitored by HPLC for the complete absence of starting material **17**. When the reaction was completed (conv. >99%), the solution was evaporated to dryness under reduced pressure at 60 °C. The solid residue was used without further purification in the next step (100% yield of **17** was assumed for calculations). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 4.4 Hz, 1 H), 8.06 (s, 1 H), 7.58 (t, J = 7.7 Hz, 1 H), 7.39 (d, J = 8.1 Hz, 1 H), 6.98−6.91 (m, 1 H), 3.31 (s, 6 H); ESI-MS m/z 174.4 (M + H$^+$).

4-(Pyridin-2-yl)-1*H*-pyrazol-3-amine (14). The aforementioned residue (2.33 kg, 13.45 mol) was dissolved in EtOH (11.5 L) in a 50 L reactor. The mixture was heated to reflux for 30 min and cooled to 25 °C. Then, acetic acid (759 mL, 13.25 mol) and hydrazine hydrate (805 mL, 16.6 mmol) were added successively into the reaction mixture with stirring. The mixture was heated to reflux for 12 h. The progress of the reaction was monitored by HPLC for the complete absence of **16**. When the reaction was completed, the mixture was evaporated to form a thick slurry. The resultant slurry was then transferred into a separate vessel, and water (2 L) was added under constant stirring. The mixture was filtered under vacuum. The solid collected was then washed with water (1 L × 3) and air-dried on the filter under suction and then dried to a constant weight in an oven at 60 °C. The result was a solid beige **14** (1.68 kg, two steps, 63%), which was used in the next step without further processing. The HPLC purity was over 98.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.78 (br s, 1 H), 8.43 (d, J = 4.8 Hz, 1 H), 7.91 (br s, 1 H), 7.66 (t, J = 7.6 Hz, 1 H), 7.55 (d, J = 8 Hz, 1 H), 7.00 (t, J = 5.6 Hz, 1 H), 5.96 (br s, 2 H); ESI-MS m/z 161.4 (M + H$^+$).

Regioisomeric Mixture of 1-(2-Fluoro-4-nitrophenyl)-4-(pyridin-2-yl)-1*H*-pyrazol-3(5)-amine (21). A reactor was charged with **14** (1.58 kg, 9.86 mol), K_2CO_3 (2.1 kg, 14.79 mol), and DMF (32 L), and the resulting mixture was stirred for 30 min at 25 °C. Then 1,2-difluoro-4-nitrobenzene (**10**, 1.33 kg, 11.83 mol) was added into the reaction mixture in one portion. After the reactor was degassed under vacuum, the atmosphere was exchanged with nitrogen. The mixture was heated to 75 °C and stirred for about 5 h. The progress of the reaction was monitored by HPLC for the complete absence of **14**. When coupling was completed as indicated by HPLC (conv >99%), water (64 L) was added into the slurry with stirring. Then, the resulting slurry was stirred for 10 min, cooled to 25 °C, and filtered. The filtered cake was washed with deionized water to remove base substance and dried to constant weight in an oven at 80 °C to give **21** (2.83 kg, 96% yield) as a yellow solid. The HPLC purity was over 97.9%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.56 (d, J = 4.8 Hz, 1 H), 8.48 (d, J = 4.8 Hz, 0.3 H), 8.41 (d, J = 10.4 Hz, 0.3 H), 8.37 (d, J = 12.8 Hz, 1 H), 8.26 (s, 0.3 H), 8.21 (t, J = 10.0 Hz, 1 H), 8.09 (t, J = 8.8 Hz, 1 H), 7.93 (D, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 0.3 H), 7.81 (t, J = 7.6 Hz, 1 H), 7.75 (t, J = 8.0 Hz, 0.3 H), 7.67 (d, J = 8.0 Hz, 0.3 H), 7.23 (t, J = 6.4 Hz, 1 H), 7.07 (t, J = 6.4 Hz, 0.3 H), 6.89 (s, 0.6 H), 6.49 (s, 2 H); ESI-MS m/z 300.0 (M + H$^+$).

2-(1-(2-Fluoro-4-nitrophenyl)-1*H*-pyrazol-4-yl)-pyridine (7). A 50-L reactor was charged with DMF (30 L) and heated to 55 °C, and 3-methyl-1-nitroso-oxybutane (2.43 L, 18 mol) was added in one portion. The solid **21** (2.7 kg, 9 mol) was then added to the mixture in batches to stabilize the nitrogen release rate (on this scale, 40 min was required to complete the addition). During addition of **21**, the temperature was maintained below 75 °C (the addition was exothermic). The reaction mixture was slowly cooled to 55 °C and stirred for 2 h. When HPLC analysis indicated complete conversion, the water (90 L) was charged with stirring. The resulting slurry was cooled to 25 °C, allowed to stand for more than 1 h, and filtered. The filtered cake was washed with water (3 L × 3) and dried to constant weight in an oven at 80 °C to give **7** (2.1 kg, yield 81.9%) as a brown solid. The HPLC purity was over 98.8%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1 H), 8.69 (d, J = 5.2 Hz, 1 H), 8.62 (s, 1 H), 8.50 (dd, J = 11.6 Hz, J = 2.4 Hz, 1H), 8.30−8.21 (m, 2 H), 7.50−7.46 (m, 2 H), 7.11 (d, J = 8.8 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.61, 150.02, 145.99, 141.33, 137.52, 133.12, 130.25, 126.45, 124.59, 122.61, 121.33, 120.71, 114.13, 111.37; ESI-MS m/z 285.13 (M + H$^+$).

3-Fluoro-4-(4-(pyridin-2-yl)-1*H*-pyrazol-1-yl)aniline (6). Compound **7** (2.0 kg, 7.04 mol), $FeCl_3$ (400 g), EtOH (20 L), and activated carbon were added consecutively to a reactor. The mixture was heated to reflux and stirred vigorously. To this solution was dropwise added hydrazine hydrate (2.82 kg, 56.28 mol; on this scale, 80 min was required to complete the addition) with stirring while maintaining reflux. The progress of the reaction was monitored by HPLC for the complete absence of **7**. When coupling was completed as indicated by HPLC (conv. >99%), iron salts and activated carbon powder were removed by filtration through a pad prepared from silica gel (1 kg). The pad was then rinsed with ethanol (1 L), and the filtered cake was washed with ethanol (2 L × 2). The filtrate was then concentrated (partial vacuum and jacket temperature <60 °C) to dryness to give crude **6**, a pale-brown solid containing hydrazine hydrochloride. This obtained product was directly used in the next step without further purification (100% yield of **7** was assumed for calculations). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.89 (s, 2 H), 9.48 (s, 1 H), 8.88 (s, 1 H), 8.73 (d, J = 6 Hz, 1 H), 8.58−8.54 (m, 1 H), 8.46 (d, J = 8.4 Hz, 1 H), 7.84 (t, J = 6.8 Hz, 1 H), 7.66 (t, J = 8.4 Hz, 1 H), 7.04 (d, J = 12.8 Hz, 1 H), 6.95 (d, J = 8.8 Hz, 1 H); ESI-MS m/z 255.16 (M + H$^+$).

Benzyl 3-fluoro-4-(4-(pyridin-2-yl)-1*H*-pyrazol-1-yl)-phenylcarbamate (9). The previously mentioned crude **6** (1.79 kg, 7.04 mol) was dissolved in acetone (11 L) with undissolved hydrazine hydrochloride remaining at the bottom. The supernatant was decanted to a reactor, and the hydrazine hydrochloride was discarded. The reactor containing a solution of **6** in acetone (11 L) was charged with potassium carbonate solution (1.46 kg K_2CO_3/7 L H_2O) with agitation. The resulting mixture was cooled to 5 °C and stirred for 1 h. To this solution was dropwise added Cbz-Cl (1.68 L, 13.9 mmol) with stirring, and the temperature of the reaction mixture was maintained under 15 °C. When the addition was completed (on this scale, 80 min was required to complete the addition), the temperature of the reaction was cooled to 25 °C and stirred for 12 h. The HPLC analysis of a reaction aliquot indicated >99% conversion of raw material **6**. The resulting slurry was

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filtered, and the filtered cake was washed with water to remove the base substance. The obtained solid was suspended in 50% EtOH (5 L) and heated to reflux for 1 h. The resulting slurry was cooled to 20 °C, filtered, and dried in an oven to a constant weight at 45 °C. The result was a solid, pale-white compound **9** (1.83 kg, two steps, 68%). The HPLC purity was more than 99.0%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J = 4.8 Hz, 1 H), 8.48 (d, J = 2 Hz, 1 H), 8.21 (s, 1 H), 7.82 (t, J = 8.8 Hz, 1 H), 7.72−7.68 (m, 1 H), 7.64 (d, J = 12.8 Hz, 1 H), 7.54 (d, J = 8 Hz, 1 H), 7.43−7.36 (m, 4 H), 7.17−7.14 (m, 1 H), 7.09 (dd, J = 8.8 Hz, J = 1.2 Hz, 1 H), 6.86 (s, 1 H), 5.23(s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.55, 153.08, 151.37, 149.68, 138.96, 138.04, 137.96, 136.75, 135.69, 129.06, 129.00, 128.67, 128.51, 128.37, 124.92, 124.62, 123.48, 121.54, 119.92, 114.46, 107.00, 67.36; ESI-MS m/z 389.19 (M + H$^+$).

(*S*)-*N*-((3-(3-Fluoro-4-(4-(pyridin-2-yl)-1*H*-pyrazol-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (1). In a 50-L reactor, **9** (1.8 kg, 4.64 mol) and **8** (1.79 kg, 9.27 mol) were dissolved in THF (12.6 L) at −5 °C. The reaction mixture was degassed by purging with N_2. Then, methanol (375 mL, 9.27 mol) was added to the mixture under N_2 atmosphere. After stirring for about 10 min at −5 °C, lithium *tert*-amylate (1.11 kg, 13.91 mol) was added to the mixture in one portion with an exotherm from −5 to 17 °C. The resulting solution was cooled to −5 °C, yielding a thick slurry, and stirred for about 1 h and stirred again at 25 °C for about 15 h. The slurry was cooled to 10 °C. The reaction was quenched by adding acetic acid (525 mL, 9.27 mol) in one portion and stirred for 30 min. The reaction mixture was then evaporated to dryness at 30 °C. The solid residue was allowed to soak for 3 h in water (30 L), stirred, filtered under reduced pressure, and washed with water (10 L × 3). The solid filtered cake was suspended in ethyl acetate (10 L). The resulting suspension was heated to reflux for 2 h, cooled to 25 °C, and filtered under reduced pressure. The collected solid was resuspended in a mixture of EtOH and water (6 L/2 L) and heated to reflux for 2 h. The slurry was cooled to 25 °C, filtered under reduced pressure, and washed with EtOH (3 L × 2). The filtered cake was dried in an oven to a constant weight at 45 °C. The final product was an off-white solid **1** (1.5 kg, isolated yield of 82%). The HPLC purity was over 99.9%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 4 Hz, 1 H), 8.52 (d, J = 6.8 Hz, 2 H), 8.22 (s, 1 H), 7.94 (t, J = 8.8 Hz, 1 H), 7.77−7.69 (m, 2 H), 7.55 (d, J = 8 Hz, 1 H), 7.27−7.26 (m, 1 H), 7.18−7.15 (m, 1 H), 6.06 (t, J = 6 Hz, 1 H), 4.86−4.80 (m, 1 H), 4.11 (t, J = 9.2 Hz, 1 H), 3.86−3.82 (m, 1 H), 3.78−3.62 (m, 2 H), 2.04 (s, 3 H); ^{13}C NMR (DMSO-d_6): δ 170.51, 154.47, 152.94, 151.26, 149.94, 139.70, 139.15, 137.43, 129.96, 125.61, 125.19, 123.42, 122.19, 120.38, 114.52, 106.68, 72.29, 47.70, 41.84, 22.91; ESI-MS m/z 418.08 (M + Na$^+$).

■ ASSOCIATED CONTENT

Supporting Information

Analytical methods for the intermediates and API, synthetic methods for 2-(pyridin-2-yl)malonaldehyde in laboratory scale and spectral data of process-related impurities. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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