Toward a Practical, Nonenzymatic Process for Investigational COVID-19 Antiviral Molnupiravir from Cytidine: Supply-Centered Synthesis

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ABSTRACT: A scalable four-step synthesis of molnupiravir from cytidine is described herein. The attractiveness of this approach is its fully chemical nature involving inexpensive reagents and more environmentally friendly solvents such as water, isopropanol, acetonitrile, and acetone. Isolation and purification procedures are improved in comparison to our earlier study as all intermediates can be isolated via recrystallization. The key steps in the synthesis, namely, ester formation, hydroxyamination, and deprotection were carried out on a multigram scale to afford molnupiravir in 36–41% yield with an average purity of 98 wt % by qNMR and 99 area% by HPLC.

KEYWORDS: COVID-19, antivirals, molnupiravir, EIDD-2801, MK-4482

INTRODUCTION

Molnupiravir (also known as EIDD-2801 and MK-4482) is a promising drug candidate for treating COVID-19. Merck licensed the compound from Ridgeback Biotherapeutics in 2020, and clinical results with outpatients advanced molnupiravir to Phase 3 clinical trials.1 Molnupiravir offers complementary advantages over remdesivir such as oral bioavailability and structural simplicity, thus reducing the manufacturing complexity.2,3 The original synthesis of molnupiravir developed by Painter utilizes uridine (1) and proceeds in five steps with a low overall yield (17% overall; two steps have assumed yields) with the aid of an acetonide-protecting group strategy (Scheme 1).4

Scheme 1. Discovery Route to Molnupiravir

As the above synthesis had a high step count accompanied by a low yield, an alternative synthesis of molnupiravir was necessary. In our original synthetic route, we found that Novozyme 435, a common lipase enzyme, could selectively esterify the primary hydroxy groups of cytosine derivatives without the need for acetonide protection, thus reducing the overall step count to two (Route I, Scheme 2).5a,b The order of this two-step sequence can be varied either by carrying out the hydroxyamination of cytidine (7) first followed by regioselective acylation or vice versa. Also, Kappe and co-workers in the year 2020 reported a high-yield synthesis of molnupiravir from uridine.6 In a recent preprint disclosure, Merck demonstrated a similar enzymatic strategy for molnupiravir using ribose 9 and uracil proceeding in 69% yield over three steps.7 Although the enzymatic routes are indeed attractive because of the low step count, we felt that demonstrating a scalable, nonenzymatic reaction sequence would still be valuable to ensure maximum global access to this important drug candidate.

Our preliminary results on a fully chemical route to molnupiravir (Route II, Scheme 2) were disclosed recently.5b The details of our acetonide approach to molnupiravir are shown in Scheme 3. The synthesis began with protection of 7 as its acetonide 10 in 94% yield using 2,2-dimethoxypropane in conjunction with acetone and sulfuric acid. Chemoselective
esterification was then accomplished using isobutyric anhy-
dride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in
acetonitrile to afford the ester in 78% isolated yield.
Hydroxyamination gave the penultimate intermediate 6 in
excellent yield (96%), and upon deprotection with formic acid,
molnupiravir was isolated in 42% overall yield in four steps.
Alternatively, we can reduce one step in this sequence by using
a solution of water/IPA (60/40), whereby molnupiravir is
obtained in a single step from 8 in an overall 39% yield (Step
3').

While this three-step approach appears attractive, challenges
foreseen to control the impurity profile of molnupiravir due to
telescoping the entire operation made it less favorable for
further development. Also, there is some safety and environ-
mental concerns related to hydroxylamine. It was reported that
hydroxylamine may explode on heating.8 It is also an irritant to
respiratory tract, eyes, skin, and other mucous membranes
making it a possible mutagen.9 However, hydroxylamine and
its derivatives are more safely handled in the form of salts. The
products from Steps 1 and 3 were isolated by crystallization;
however, column chromatography was used to isolate the
products of Step 2 and molnupiravir. This prompted us to
explore further optimization to avoid some of these drawbacks.

We now report herein an optimized, operationally simpler
process featuring chromatography-free isolation. The scal-
ability of the entire process has been demonstrated by
synthesizing multigram quantities of molnupiravir.

■ RESULTS AND DISCUSSION

Impurity Profiling in Four-Step Synthesis of Molnu-
piravir. Prior to further developmental work, we identified
the impurities in each step of our route either by direct isolation
from the reaction mixtures or by synthesis of authentic
materials for comparison with reaction in-process control data
(Figure 1). Step 1 is very clean and no impurities were
observed either during the reaction or after the isolation of the
product, whereas the key impurities generated in Step 2 were
the diacylated side compound 11 and the N-acylated
compound 12. For Step 3, the key impurities in the crude
reaction mixture were the starting material amine 8, molnupiravir, and the acetoneide-deprotected compound 13 of the starting material. For Step 4, the key impurities were 6, 8, EIDD-1931, 13, and uridine (1).

Step 1: Acetonide Protection—Impurity Profile and
Reaction Optimization. The acetonide protection of the
vicinal diol of cytidine was performed using 2,2-dimethoxy-
propane (5 equiv) in acetone mediated by sulfuric acid (2.3
equiv) to afford 10, which crystallized from the reaction
mixture as its sulfate salt and was isolated in 94% yield with 95
wt % purity based on quantitative nuclear magnetic resonance
(qNMR) spectroscopy. Purity by high-performance liquid
chromatography (HPLC) was 100%.
Step 2: Esterification—Impurity Profile and Reaction Optimization. A time profile for the acylation of 10 was recorded to determine the formation of product and impurities in this reaction (see Figure S1, Supporting Information). When the reaction was performed using isobutyric anhydride (1.1 equiv) and triethylamine (2.5 equiv) as the base in the presence of catalytic N,N-dimethylamino pyridine (DMAP, 20 mol %) in acetonitrile as a solvent at room temperature for 18 h, it was observed that within first 30 min, the reaction proceeded to more than 85% conversion and also that conversion quickly tapered off over the course of additional reaction time. When the reaction was stirred for additional 17 h of reaction period, only a marginal increase in product formation was observed along with the two side products, namely, over-acylated compound 11 and the N-acylated compound 12 (Figure 1) in 6.3 and 0.2 area % by HPLC (LCAP), respectively.

We were curious to know if 11 could be transformed to the desired product 6 of the subsequent step by transamination with hydroxylamine since this would eliminate the need for purging while providing a yield boost for the subsequent step. To probe this possibility, 11 was prepared from O-monoacylated 8 by reaction with iso-butyryl chloride (Scheme 4). Isolated 11 was treated with 3.2 equiv of hydroxylamine sulfate in 70% IPA-H₂O at 78 °C for 24 h. This reaction led to the formation of at least seven compounds by HPLC, of which the major constituents were 6 and molnupiravir in LCAP 21 and 31%, respectively. Although we were disappointed that this reaction did not lead to a higher level of the desired compound 6, it did provide some useful insights for Step 3. In particular, this reaction profile matches that seen for the hydroxamination step (Step 3), which suggests that the source of impurities in that reaction stems from side reactions arising from 11 (Scheme 4). This experiment clearly demonstrates that minimization of side product 11 in Step 2 is critical.

A systematic optimization of key variables in Step 2 was conducted to maximize the formation of the monoacylated product 8 and minimize the diacylation side reaction leading to compound 11. The results of this optimization are provided in Table 1. The optimization was performed using the base (2.1 equiv) in the presence of catalytic DMAP (20 mol %) in acetonitrile as a solvent over the period of 8 h reaction time. However, after screening some of the bases as shown in Table 1 (entries 1–5), it was observed that the reaction performed well with DBU as the base and gives a good yield of the desired product within 3 h of reaction time (entries 5–11).

Furthermore, the temperature and reaction concentration were studied (entries 5–11) using DBU as the base and it was observed that the most impactful result from this parameter screening is the role of the reaction concentration on the conversion of the starting material 10 to the product 8. Increasing the amount of the solvent from 2.5 to 10 V (entries 5–8) increased the LCAP of 8 from 89 to 94% and reduced the overall contribution from the impurities 10, 11, and 12 from 11 to 4.3%. Also, reaction temperature has a major effect on the formation of byproduct 11 and it was observed that decreasing the reaction temperature from 19 to 0 °C decreases the formation of byproduct 11 from 6.2 to 2.2% (entry 5 vs entry 9). Because the formation of byproduct 11 (major byproduct) requires two consecutive second-order reactions, here we reasoned that decreasing the reaction temperature would lead to a dramatic decrease in the rate of the second acylation reaction.

After optimization of the key reaction variables for the regioselective acylation of 10, we found the optimal conditions for the formation of 8 in a high yield to be isobutyric anhydride (1.1 equiv) and DBU (2.1 equiv) in CH₃CN (10 V) at 0 °C for a reaction time of 3 h (entry 9). Although DBU was found to be the optimal base for this reaction, its removal from the reaction mixture is challenging. In our first study, chromatographic separation was used to isolate the pure compound, but this will be costly on scale. Given the large pKₐ difference between DBU (∼12.5) and the cytidine amine functionality (∼4.2), we reasoned that a mild acidic workup could potentially remove DBU from the organic layer without extraction of the product 8. The reaction mixture was concentrated to remove acetonitrile and then dissolved in dichloromethane. Several aqueous acid washes were performed for DBU removal, including 10% ammonium chloride, 10% acetic acid, 10% sulfuric acid, and 85% H₃PO₄. It was observed that using 10% acetic acid resulted in the maximum recovery of the ester 8 and extraction of DBU into the aqueous layer. The

![Scheme 4. Synthesis of Diacylated Side Product 11 and Its Subsequent Hydroxyamination Products](image1)

### Table 1. Optimization of Regioselective Acylation of 10

| entry | base | temp (°C) | solvent (V) | LCAP (%) |
|-------|------|----------|-------------|----------|
| 1     | Et₃N | 19       | 10          | 59       |
| 2     | Bu₃N | 19       | 10          | 52.6     |
| 3     | DIPEA| 19       | 10          | 60.4     |
| 4     | lutidine | 19 | 10         | 34.5     |
| 5     | DBU  | 19       | 10          | 93.5     |
| 6     | DBU  | 19       | 2.5         | 89.3     |
| 7     | DBU  | 19       | 5           | 89.4     |
| 8     | DBU  | 19       | 7           | 92.5     |
| 9     | DBU  | 0        | 10          | 94.7     |
| 10    | DBU  | 40       | 10          | 88.7     |
| 11    | DBU  | 56       | 10          | 85.5     |

*Reaction conditions: isobutyric anhydride (1.1 equiv), base (2.1 equiv), DMAP (20 mol %), and CH₃CN. *Reaction time: 8 h for entries 1–4 and 3 h for entries 5–11. *LCAP at 260 nm.
acid wash was followed with a saturated sodium bicarbonate wash to remove the residual acetic acid. The product was then isolated by concentrating the organic layer to dryness. The purity of the final product was found to be 84 wt % by qNMR in chloroform-d, and LCAP was 94.7% for 8, 2.1% for 11, and 0.6% for 12.

A comparison of HPLC data for an in-process control versus the organic layer post 10% acetic acid and bicarbonate workup showed that the relative ratios of cytosine-containing materials were relatively unaffected by the extraction conditions. A trace amount of DBU was detected (0.5 area%) in the final product 8 (Figure S2, Supporting Information).

**Step 3: Hydroxyamination—Impurity Profile and Reaction Optimization.** In our preliminary study, the transamination of 8 using hydroxylamine sulfate resulted in 96% yield (94 wt % purity) of 6. Unreacted hydroxylamine sulfate was removed by filtration after dissolution of 6 in a minimal amount of acetonitrile. However, in our previous study, the starting material for this reaction had been purified by column chromatography. Conducting the same transamination reaction with ester 8 (84 wt % purity) that was obtained using our optimized acetic acid workup gives a mixture of the product 6, molnupiravir, and some unreacted starting material (Scheme 5). A typical distribution of products at the end of 20 h of the reaction period with an internal reaction temperature of 73 °C is 86% product 6, 6% of starting material 8, 3% molnupiravir, and ~1% of the acetonide-deprotected ester 13 by HPLC. After isolation, this translated to 89% average-adjusted isolated yield with 73 wt % purity from duplicate runs before removal of unreacted hydroxylamine sulfate.

Qualitative solubility studies were carried out using different solvents (Figure S3, Supporting Information) for purification of the product 6 (Table 2) and two methods were identified. The first method (Method A) involves recrystallization of crude 6 (73 wt % purity) from 2.5 V of isopropyl acetate. The mass recovery using this method is 66% and the purity is 98 wt % by qNMR in acetone-d$_6$, and more 6 was present in the mother liquor from Method A. In the second purification method (Method B), recrystallization of the crude 6 (73% purity) from 2.5 V of acetonitrile provided 64% adjusted isolated yield of 6 with a purity of 96 wt % by qNMR. Additional product 6 (second crop) from Method B was isolated by concentrating the mother liquor and recrystallizing the remaining solid in 2.5 V of acetonitrile. This secondary isolation affords an additional 11% mass yield of material with a purity of 90 wt % by qNMR.

The two methods described above afford the Step 3 product 6 of ≥96% purity. More notably, the amount of 13 was reduced by postpurification by either of these methods from 1.7 area% to 0.1 area% (see the HPLC trace in Figure S4, Supporting Information, a peak at a retention time of 4.998 min). The key impurities in 6 obtained by either of these methods were molnupiravir and 8 (2.6 area% and 0.3 area% by Method A and 2.1 area% and 0.5 area% by Method B). Method A was preferred for scale up as it provided 6 with a higher purity.

**Step 4: Acetonide Deprotection—Impurity Profile and Optimization.** With access to a relatively pure 6 from Step 3, screening of conditions for deprotection of the acetonide group in 6 was next performed (see Figure S5, Supporting Information). Most protic acids such as sulfuric acid, phosphoric acid, hydrochloric acid, or Lewis acids such as zirconium tetrachloride provided molnupiravir in low to modest yields (<50%) (as estimated by HPLC area% purity). For example, increased formation of 8 and 13 under some reaction conditions (TFA in EtOAc, TFA in DCM or HCl in DCM, and H$_2$SO$_4$ in DCM) possibly indicates a self-oxidation reduction, previously reported with aryl hydroxylamines. Of all the acids screened, neat formic acid and trifluoroacetic acid provide conversions to molnupiravir in >90% yield. Finally, formic acid was selected for further development as it gave consistent results over different scales during the development of molnupiravir.

A range of recrystallization conditions was evaluated to purify molnupiravir (Table 3). Using 10 volumes of 1:1 EtOAc/acetonitrile, the condition used for purification, the enzymatic route, an 82% mass recovery of molnupiravir was obtained in three crops with 97 wt % purity (HPLC area % purity of the product was 97.8% and area% purity of known impurities 6 and 8 was 0.4 and 0.3%, respectively). Improved purity could be obtained by crystallization from five volumes of 1:1 n-BuOH/water with 99.7 wt % purity (the HPLC area % purity of the product was 99.7%, and area% purity of the known impurity 8 was 0.2%, entry 4) or two volumes of water with 98.5 wt % purity (the HPLC area% purity of the product was 98.6% and area% purity of known impurities 6 and 8 were 0.3 and 0.8%, respectively, entry 3) although with reduced mass.
recovery. With two volumes of n-BuOH/water (1:1), precipitation of the product was observed with a lower purity. Based on the balance of purity of molnupiravir and its recovery, water was selected as the final crystallization solvent.

**Scalability.** A preliminary evaluation of the scalability of the entire sequence was conducted at 100 g scale. Acetonide protection proceeded smoothly to afford the product of Step 1 in an excellent yield and purity (>95%) on a 100 g scale (Table 4). The optimized Step 2 conditions resulted in >90% isolated yield with good purity on a 150 g scale. At a 130 g scale, the reaction by filtration and washing, whereas compound 8 from Step 2 is obtained directly by washing the organic layer with 10% acetic acid. The pure compound 6 from Step 3 is obtained by recrystallization of the crude from isopropyl acetate, and molnupiravir from Step 4 is obtained by recrystallization from water. We have demonstrated comparable overall yields to our previous study and we have also been able to substitute column chromatographic purification with simple purification procedures that can be performed at a large scale.

### EXPERIMENTAL SECTION

**General.** For all compounds, 1H and 13C NMR spectra were recorded using a Bruker Avance III 600 MHz spectrometer. Chemical shifts were measured relative to the residual solvent resonance for 1H and 13C NMR (CDCl3 = 7.26 ppm for 1H and 77.0 ppm for 13C, DMSO-d6 = 2.50 ppm for 1H and 39.5 ppm for 13C, CD3OD = 3.31 ppm for 1H and 39.5 ppm for 13C, and D2O = 4.79 ppm for 1H). Coupling constants J are reported in hertz (Hz). The following abbreviations were used to denote signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; dd, doublet of doublet; dt, doublet of triplet; ddt, doublet of triplet; dtt, triplet of triplets; m, multiplet; and br, broad. Reactions were monitored by HPLC using the methods indicated. Quantitative NMR measurements were done using either mesitylene or 1,3,5-trimethoxybenzene as the internal standard. Glassware was oven-dried at 120 °C, assembled while hot, and cooled to an ambient temperature under an inert atmosphere. Unless otherwise noted, reactions involving air-sensitive reagents and/or requiring anhydrous conditions were performed under a nitrogen atmosphere.

Cytidine 7 was purchased from Chem-Impex. All other reagents and solvents were purchased from Aldrich Chemical Company, Fisher Scientific, Alfa Aesar, Acros Organics, Oakwood, or TCI. Liquid reagents were purified by distillation when necessary. Unless otherwise noted, solid reagents were used without further purification.

Acronyms: DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), MTBE (methyl tert-butyl ether), CPME (cyclopentyl methyl ether), DMAP (N,N-dimethylanilinoipridine), LCAP (Area % by HPLC), qNMR (Quantitative NMR in the presence of an internal standard), DCM (chloroform), and IPA (isopropanol).

**4-Amino-1-((3aR,4R,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)pyrimidin-2(1H)-one (1) Sulfuric Acid Salt.** To the mechanically stirred 2000 mL three-neck round-bottom flask, cytidine 1 (100 g, 0.41 mol, 1 equiv) and anhydrous acetonitrile (1300 mL) were added followed by 2,2-dimethoxypropane (251.9 mL, 2.055 mol, 5 equiv) under a nitrogen atmosphere. Neat sulfuric acid (50.7 mL, 0.94 mol, 2.3 equiv) was added to the above suspension and left for stirring for 15 h. The insoluble residue was filtered, and the solid precipitate was washed multiple times with aceton (1000 mL) followed by MTBE (400 mL). The solid was left for drying under vacuum for a day to obtain 155 g (94% corrected yield, 95 wt % purity by NMR in DMSO-d6) of compound 10 as an off-white solid.

Data matched with those previously reported.6

(3aR,4R,6R,6aR)-6-(4-Amino-2-oxypyrimidin-1(2H)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl isobutyrate (8). To the mechanically stirred 2000 mL three-neck round-bottom flask, compound 10 (150 g, 95 wt % purity, 0.37 mol, 1 equiv) and dry acetonitrile (1500 mL) followed by DMAP (9.13 g, 0.075 mol, 0.2 equiv) and DBU (117.4 mL, 0.78 mol, 2.1 equiv) were added at room temperature. The reaction mixture was stirred for 10 min and isobutyric anhydride (65.11 mL, 0.39 mol, 1.05 equiv) was added dropwise at 0 °C in two equal portions at half hour intervals each and the reaction mixture was maintained for 2 h at the same temperature. The reaction mixture was then directly concentrated under a reduced pressure to afford a waxy solid. The resultant material was redissolved in dichloromethane (600 mL) and washed with 10% acetic acid (1000 mL) once. To the organic layer in a 2000 mL three-neck round-bottom flask was then added a clear solution of saturated sodium bicarbonate (1000 mL) dropwise with stirring until effervescence ceased. The layers were then separated, and the dichloromethane layer was dried over

### Table 4. Scale Up of the Four-Step Sequence to Molnupiravir

| step | scale (g) | LCAP of producta | wt % purityb | yield (%)c |
|------|-----------|------------------|--------------|------------|
| 1    | 100       | 99.1             | 95.0         | 94         |
| 2    | 100       | 99.2             | 95.5         | 92         |
| 3    | 150       | 98.6             | 89.0         | 92         |
| 4    | 130       | 94.0             | 85.8         | 95         |
| 5    | 120       | 97.3             | 94.0         | 70         |
| 6    | 80        | 98.7             | 95.0         | 76         |
| 7    | 100       | 98.6             | 98.5         | 59         |
| 8    | 100       | 99.6             | 97.6         | 61         |

aLCAP at 260 nm. bBy qNMR. cYield adjusted to purity.
anhydrous sodium sulfate and concentrated under a reduced pressure to obtain 136.5 g (91.9% corrected yield, 89.3 wt % purity by NMR in DMSO-d$_6$) of compound 8 as a white foamy solid.

$^1$H NMR (600 MHz, CD$_3$OD). δ 7.90 (s, 1H), 7.63 (d, J = 7.4 Hz, 1H), 5.86 (d, J = 7.4 Hz, 1H), 5.71 (d, J = 6.9 Hz, 1H), 5.03 (dd, J = 4.7, 1.6 Hz, 1H), 4.84 (dd, J = 6.3, 3.4 Hz, 1H), 4.31 (m, 1H), 2.55 (septet, J = 7 Hz, 1H), 1.53 (s, 3H), 1.34 (s, 3H), 1.13 (ddd, J = 3.2, 1.8, 1.3 Hz, 6H) ppm.

Data matched with those previously reported.$^{2b}$

$^{13}$C NMR (151 MHz, CD$_3$OD). δ 178.46, 168.32, 158.13, 145.15, 115.32, 97.21, 96.25, 87.04, 86.71, 83.36, 65.86, 35.35, 27.74, 25.75, 19.75, 19.60, 19.52 ppm.

Data matched with those previously reported.$^{2b}$

To the mechanically stirred 2000 mL three-neck round-bottom flask, compound 8 (130 g, 89.3 wt % purity, 0.33 mol, 1 equiv) and hydroxylamine sulfate (172.7 g, 1.05 mol, 3.2 equiv) followed by 70% IPA (1300 mL) were added and the resultant solution was heated to an internal temperature of 72−73 °C for 19 h at which time HPLC showed the formation of a product in addition to the starting material and molnupiravir. At this juncture, the two layers were filtered and the wet solid was washed with MTBE (210 mL) and dried under vacuum to obtain 136.5 g (91.9% corrected yield, 89.3 wt % purity by NMR in DMSO-d$_6$).

$^1$H NMR (600 MHz, CD$_3$OD). δ 6.85 (d, J = 8.2 Hz, 1H), 5.69 (d, J = 2.2 Hz, 1H), 5.57 (d, J = 8.2 Hz, 1H), 4.97−4.99 (dd, J = 6.4, 2.2 Hz, 1H), 4.79−4.81 (dd, J = 6.3, 4.8 Hz, 1H), 4.26 (d, J = 5.3 Hz, 2H), 4.21 (q, J = 4.9 Hz, 1H), 2.60 (septet, J = 7 Hz, 1H), 1.53 (s, 3H), 1.34 (s, 3H), 1.15−1.17 (dd, J = 7, 1.8 Hz, 6H) ppm.

$^{13}$C NMR (151 MHz, CD$_3$OD). δ 178.61, 141.52, 146.49, 134.21, 115.73, 99.73, 94.53, 85.62, 85.58, 82.87, 65.54, 35.36, 30.97, 27.79, 25.82, 19.61, 19.58 ppm.

Data matched with those previously reported.$^{2b}$

$^{2b}$

## ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at [https://pubs.acs.org/doi/10.1021/acs.oprd.1c00219](https://pubs.acs.org/doi/10.1021/acs.oprd.1c00219).

Reaction optimization, experimental details, copies of $^1$H and $^{13}$C NMR spectra of all new compounds, and HPLC method (PDF)

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Notes
The authors declare no competing financial interest.

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