Full Paper

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A clean industrial scheme for de-ketalization of EIDD-2801 intermediate in water to give molnupiravir (MK-4482) anti-COVID-19 agent (containing its pharmaceutical analytical analysis)

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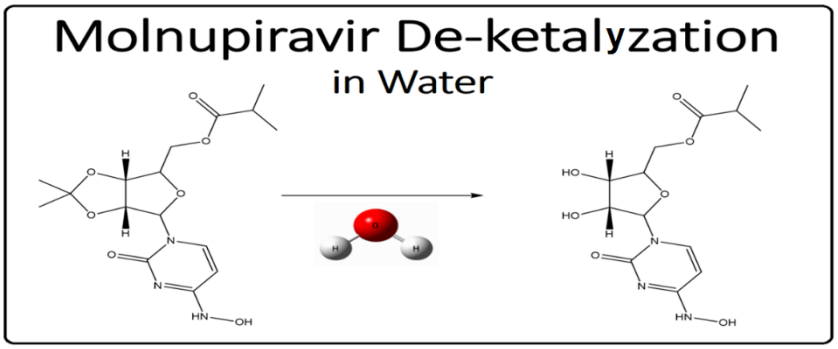

Abstract: Due to the need for molnupiravir (EIDD-2801, MK-4482) anti-COVID-19 agent, in the present report, we have systematically investigated the effect of different solvents, acids (as catalyst), temperature, and other parameters which play rolls in De-ketalization process of its key intermediate.

At the first glance, it might seem to be easy, but the complex nature of MK-4482 agent, and also the ultra-high purity of the crude (which is required for an active pharmaceutical ingredient (API)), make this process more complicated. As would be shown below, even a little change in the type of solvent, solvent ratio, the type or the amount of catalyst, and the temperature could directly change the reaction fate (it may lead to emergence of un-controlled impurity profile, or even it could block the reaction). However, in this work, we have been able to run this de-ketalization process only in water as the

whole of the system. Here, it was observed that the high energy water molecules have been able to hydrolyze the ketal intermediate of MK-4482.

Keywords: Molnupiravir, EIDD-2801, MK-4482, clean chemistry, COVID-19, De-ketalization in water

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Introduction

About three years have passed since the first outbreak of the mysterious *COVID-19* virus from *Wuhan*, China [1]. This shocking outbreak has practically changed all aspects of our lives, and it has led to global problems. As the human race tries to manage it, this tinny species changes itself to make more branches [2]. However, there are some vaccines that could protect most of people, from the last recent mutations [3].

Now, it seems that beside the global vaccination programs, the existence of harmless, but effective antiviral compounds are required. Indeed, revolutions are required both in improving the human immune system and in antivirals for handling such dangerous outbreaks [4].

Previous reports reveal that umifenovir, favipiravir, and remdesivir (Figure 1) are of the selected antivirals that have affected on *COVID-19* virus and its descendants. All of these four compounds are biologically active against a wide range of viruses. It is suggested that at least, in some cases, they prevent the viral replication via several kinds of mechanisms or physiology [5].

Now, after about two years, some of the healthcare scientists believe that the EIDD-2801 agent (MK-4482, or *molnupiravir*) could have significant effects on controlling the virus (see Figure 1) [6].

Molnupiravir, could be synthesized *via* a four-step procedure, started from uridine (or newly from Cytidine), which is a glycosylated pyrimidine-analog containing uracil [7]. This compound is commercially available for experts. Also, some reports show that the last step of this synthesis which leads to de-protection of the diol via a de-ketalization process, might be challenging. Somehow, different reports have revealed about different yields with various time-consuming workup procedures. Thus, unlike some new methods, the final yield of some previous total synthesis routes of this compound was depended on the de-ketalization step (Scheme 1) [8-10].

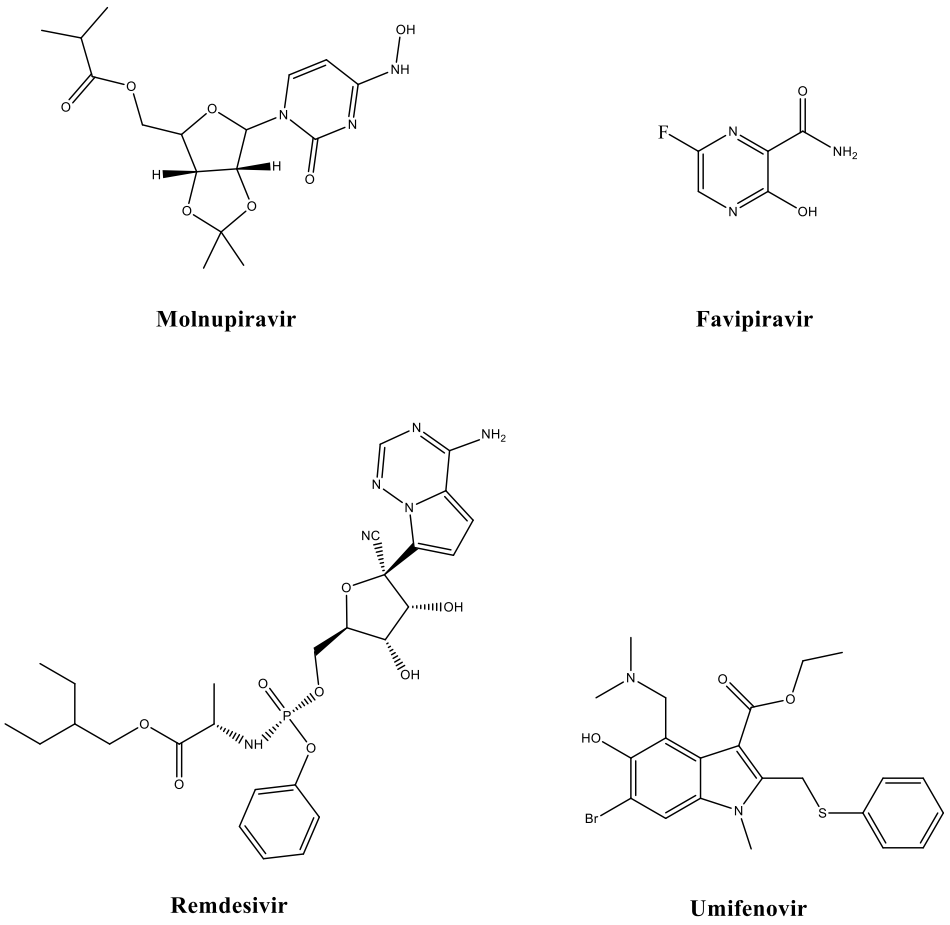


Fig. 1. The chemical structure of umifenovir, favipiravir, remdesivir, and molnupiravir.It is obvious that finding more facile, cheaper, or greener ways for synthesizing selected organic compounds has always been important for the experts [11-16]. Due to these, in the present project, first we have investigated the previous reports about that de-ketalization. Then, by designing a systematic scheme, the effect of the key parameters containing solvent, catalyst, time, and temperature on the process were investigated.

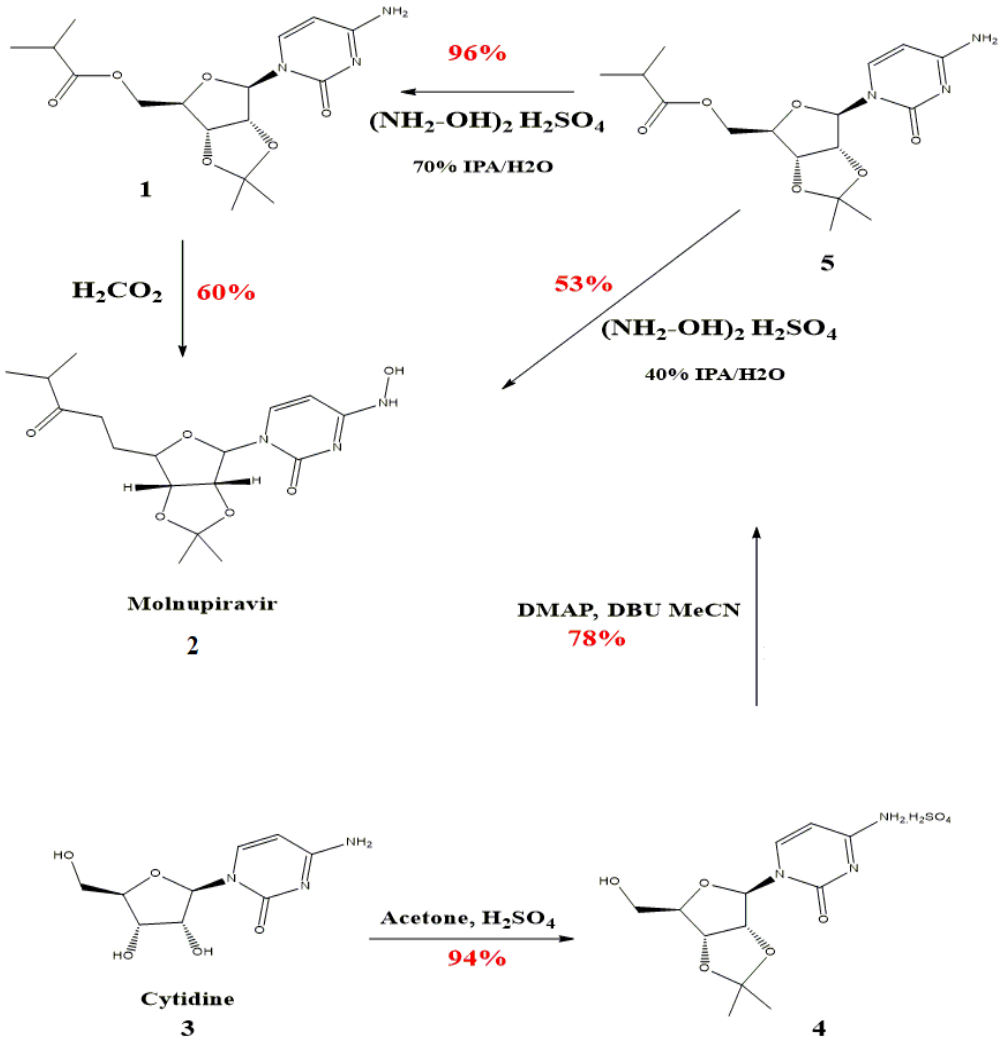
The results showed that the high energy water molecules could handle the de-ketalization process in a clean environment. Elimination of the time-consuming and costly extraction processes, and also, passing the OVI analysis test, are of the main advantages of this clean wet process.

Results and discussion

Synthesis section

As Table 1 shows, there are a few reports revealing about the exact synthesis procedures of molnupiravir *via* its de-ketalization process [17-20]. A survey on the presented data indicates that all de-ketalization processes of the medicinal compound need a type of

acid. Depend on the type of the solvent or acid, the type and the amount of molnupiravir or other impurities would change.



Scheme 1. The route of total synthesis of molnupiravir from Cytidine.

Our first choice for this reaction was organic acids such as Trifluoroacetic Acid (TFA), formic acid (FA), or acetic acid (AA) (both as solvent, and as catalyzing agent). Entry 1 shows that when using TFA as solvent (and catalyzing agent) for de-ketalization of 1 to molnupiravir, the reaction progress is good, but the cost of TFA, as well as the difficult workup process (several times evaporations of TFA with its high boiling point, before recrystallization in isopropanol-MTBE system) would make this process relatively difficult. Another choice for organic acids was FA (entries 2 to 4) which needs a 40 ºC heating for at least 24 hours. Like TFA, the boiling point of FA makes difficult the final evaporation processes of the reaction mixture.

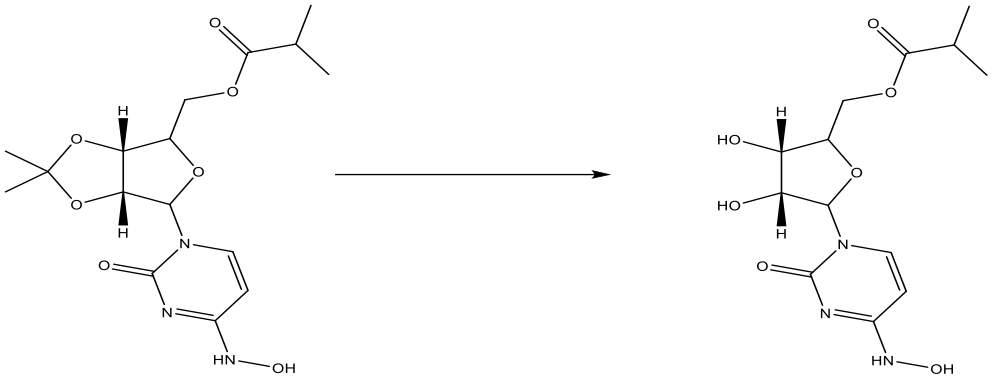
Entry 5 represents the use of toluene-4-sulfonic acid as the organic acid, and methanol as solvent. Experimenting of this system showed us that use of toluene sulfonic acid leads to emergence of variety of impurities, especially EIDD-1931. On the other hand, existence of trace amounts of toluene sulfonyl chloride in toluene sulfonic acid stock, may cause the emergence of other related byproducts. Also, the workup process of this scheme might be difficult.

Entries 6 and 9, represent the use of mineral acids like $ZrCl_4$ in methanol, and isopropanol, respectively. The yields seem to be good, and those process not need negative temperatures. Entry 7 reveals about the use of NOVO enzyme-435 in methyltetrahydrofuran (2-MeTHF) at 40 ºC for this de-ketalization with a final yield of 39.8 % (for the purified powder) [21]. Entry 8 uses hydroxylamine sulfate in isopropanol-water system at 78 ºC for 17 hours, with 53% yield (which carries out two chemical reactions in one pot leading to production of molnupiravir crude) [22].

Entries 10 to 13 (Table 1) have used DCM as solvent. Due to low boiling point of DCM, the reaction temperature is usually room temperature (r.t), or lower. The advantage of using DCM as solvent is its aprotic nature which helps the reaction progress. While it causes the emergence of variety of impurities. On the other hand, use of DCM would need the costly and time consuming extraction process. Also, in the case of this de-ketalization process, only H_3PO_4 could be an acceptable case due to relatively higher purity compared to other acid-DCM systems. Use of ethyl acetate instead of DCM (by applying those mentioned acids; Entries 14-16), would lead to the same results. Thus, instead of higher reaction rate, we could not use acids like TFA, H_2SO_4, and H_3PO_4, at least when using solvents like DCM, or ethyl acetate.

In this work (Table 2), we have used some solvents containing methanol, ethanol, isopropanol, butanol, TFA, FA, AA, and water. We have also used those mentioned acids, and also water-acid, as catalyzing agents. Our results state that using alcohols as solvent in presence of HCl, or H_2SO_4 as acid catalysts (entries 6 to 11) lead to emergence of high percentage of byproducts in parallel with molnupiravir. Also, use of pure (water-free) alcohols especially use of isopropanol without H2O could not give molnupiravir even in high temperatures (lower than 70 ºC). On the other hand, when using organic acids like TFA, FA, or AA, the reaction progress needs higher temperatures (at least 40 ºC). Obviously, the reaction rate, and the impurity profile increase along with increasing the acidity (AA < FA<TFA). Somehow, when using AA, the reaction progress is very low, even with the aid of heating. All three acids face us with a difficult workup process including several times evaporations in parallel with other solvent additions. Because, due to the high acid ratio, the neutralization process is harder than evaporation.

Table 1. A comparison between the previous reports and the examples of the present work.



1 **2**
Molnupiravir

Entry	Catalyst	Solvent	Temperature (ºC)	Time (h)	Yield (%)	Type of workup
1	TFA	TFA	-	-	85*	[20]
2	FA	Ethanol/MTBE	r.t	20	64.8	[19]
3	FA	FA (16 v)	r.t	4	30.7[a]	[20]
4	FA	FA (16 v)	r.t	5	60.0	[20]
5	toluene-4-sulfonic	Methanol	45	0.17	93.1	[23]
6	$ZrCl_4$	Methanol	-	-	79*	[20]
7	NOVO enzyme-435	2-methyltetrahydrofuran	40	20	39.8	[21]
8	hydroxylamine sulfate	isopropanol-water	78	17	53	[22]
9	$ZrCl_4$	Isopropanol (70%)	-	-	85*	[20]
10	HCl	DCM	-	-	10*	[20]
11	TFA	DCM	-	-	15*	[20]
12	H_2SO_4	DCM	-	-	55*	[20]
13	H_3PO_4	DCM	-	-	75*	[20]
14	TFA	Ethyl Acetate	-	-	10*	[20]
15	H_2SO_4	Ethyl Acetate	-	-	45*	[20]
16	H_3PO_4	Ethyl Acetate	-	-	75*	[20]

*above mentioned data are approximately extracted from screening of conditions for de-protection of the acetonide group designed by reference [20]. a) 68 % yield for crude (single recrystallization from EtOAc/ MeCN 1/1, 98 wt%) 82 % yield (combined three pots of recrystallization from EtOAc/ MeCN 1/1, 97 wt%).

Table 2. Optimization of de-ketalization process of intermediate **1** to molnupiravir.

Entry	Catalyst	Solvent	Temp (ºC)	Time (h)	Yield (%)	Type of workup
1	FA /H_2O	FA	25	24	20	Evaporation
2	FA /H_2O	FA	45-50	24	70 (87% purity)	Evaporation
3	TFA/H_2O	TFA	40	24	60	Evaporation
4	AA /H_2O	AA	60	48	trace	-
5	AA	AA	60	48	trace	-
6	HCl (37%)	Methanol	rt	10	By product	-
7	HCl (37%)	Ethanol	rt	10	By product	-
8	HCl (37%)	1-Butanol	rt	10	By product	-
8	H_2SO_4	Isopropanol	rt	2	decompose	-
9	HCl (37%)	Isopropanol	rt	10	By product	-
10	HCl (37%)	Isopropanol	50	5	By product	-
11	HCl (37%)	Isopropanol/H_2O	rt	5	23	precipitation
12	-	water	100	13	93	precipitation
13	HCl (37%) (0.05 w/w)	water	50	20	trace	-
14	HCl (37%) (6ml / 10g)	water	rt	2	60 (containing byproducts)	-

The interesting issue which made use wondered, was the role of hot water molecules in destruction of C-O bonds of ketal intermediate. Somehow, the fresh distillated water (without any acid addition) has run this de-ketalization process. One of the other interesting point of the reaction was that; the pure water de-ketalization progresses at 95 °C or upper temperatures (entry 12) to give above 90%. While, the reaction does not progress in lower temperatures even in the presence of acids (entry 13). Of course, it should be noted that by using higher acid volumes (like 6ml of HCl 37% for 10 g of intermediate) the reaction could be run even without any heating (entry 14). However, it might lead to emergence of byproducts. The outcome of the experiments showed that ultra-hot water molecules are able to handle the de-ketalization process even without acid catalysts.

Pharmaceutical analytical section

At the first step, the HPLC system was applied both for pharmaceutical analytical identification (*via* comparison with the retention time (RT) of the molnupiravir standard), and for assaying the purity percentage of the synthesized sample. Where, the mobile phase A was 20mM dibasic potassium phosphate buffer at pH 3.0; the mobile phase B was 100% ACN; and the diluent was (mobile phase A:B)(90:10). The flow rate was 1.0 ml min^{-1}. The column oven was 35ºC, and the spectrum is recorded at 235 nm. Also, the injection volume was 20 µl. Table 3, would shows the gradient of the elution. The retention time (RT) of the main peak (molnupiravir (by this method is about 11.5 min.

Table 3. The used gradient of the elution for the HPLC analysis of the API of molnupiravir.

time	Flow rate (ml min^{-1})	phase A %	phase B %
0	1.0	95	5
2	1.0	95	5
17	1.0	60	40
22	1.0	30	70
28	1.0	30	70
29	1.0	95	5

As shown in Figure 2, the purity of the purified sample was 99.75%, and the amount of each impurity of was about 0.05%, showing that the API was satisfying in view of related impurity analysis. By using this HPLC method, the peak of cytidine, and N (4)-hydroxycytidine, appear about 2.7 min, and 3.9 min, respectively (due to the high polar nature of those two, comparing with molnupiravir. While the peak of the ketal-intermediate appeared at 18 min which confirmed the nonpolar nature of it, compared to molnupiravir (Figure 2).

At the next step, the sample goes under Karl-Fischer titration analysis (KF) for determination of its water content percentage (KF%). The KF analysis could give us some important information, especially about the residual water or even the crystal water of an API. The pharmaceutical polymorph of molnupiravir must have not crystal trapped water, and the total water of it must be lower than 1%. The KF% of the synthesized sample is less than 0.8% which would show that the product crystals are not in a water solvated form. Also, the ash sulfate analysis (>0.1%), shows that the NaCl salt has not remained in the crude.

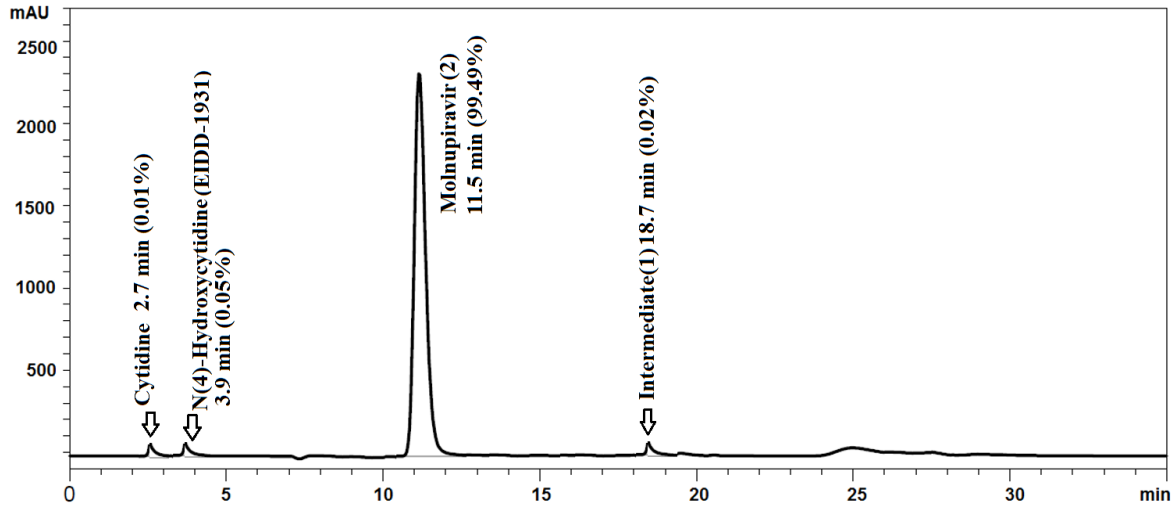


Fig. 2. The chromatogram of the related impurity analysis, prepared by the reverse phase HPLC system.

On the other hand, the OVI analysis of the sample showed that there is not any out of limitation solvent residue. It is believed that use of water as the solvent of the last step of synthesis would lead to elimination of unpleasant solvent residues in the API.

Materials and methods

Reagents and instrumentations

All of the chemical reagents and solvents were obtained from commercial sources and were used without further purifications. All of the analytical thin layer chromatography (TLC) analyses were performed on Silica Gel 60 F254 pre-coated plates. The melting points were corrected. The 1H NMR spectrum was taken in the commercial deuterated solvents on a multinuclear spectrometer (Varian, *INOVA*400MHz). All of the chemical displacements (of 1H NMR), were being reported in parts per million (ppm) relative to internal tetramethylsilane (TMS, ppm 0.0) (and) or with the solvent reference relative to TMS which was used as the internal standard (DMSO-D6, 2.500 ppm). Data (chemical shifts) were reported as follow: (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), broad (br), and multiplet (m)], coupling constants [Hz], and integration). The 13C NMR spectrum was taken on a multinuclear spectrometer (400 MHz), applying diluted solutions of the resulting compound in DMSO-d6 as the solvent. Also, the chemical shifts were reported in ppm (ppm unit) downfield from tetramethylsilane as the internal standard (CDCl3, ppm 77.0). The mass spectra was prepared utilizing the electron impact (EI) at an ionizing potential of 70 eV. The experiments for OVI analysis have be carried out using a gas chromatography-flame ionization detector (GC-FID) system (CP-3800, GC Varian, equipped with CTC Combi-Pal headspace auto sampler injection

containing an incubator. A capillary column (the Agilent J&W CP-Select 624 CB, length 30m, internal diameter 0.53 µm, and film thickness 3.0 µm GC column, with an optimized G43 stationary phase) has been used for separation of the gaseous specious. The carrier gas was nitrogen, and the flow rate was 6 ml min^{-1} [24].

The Agilent 1260 HPLC system (Agilent Technology) equipped with a G1311BLC pump, a G1316A column oven, and a G4212B UV-Vis detector, were used for all analysis. Also, a C18, end-capped (15×4.6) mm, 5µm liquid chromatography column was applied for the related substance analysis of the API. The mobile phase A was 20mM dibasic potassium phosphate buffer at pH 3.0; the mobile phase B was 100% ACN; and the diluent was (mobile phase A:B)(90:10). The flow rate was 1.0 ml min^{-1}. The column oven was 35ºC, and the spectrum is recorded at 235 nm. Also, the injection volume was 20 µl [24,25].

Synthesis procedure

Representative Procedure for the clean synthesis of molnupiravir via de-ketalization reaction in water:

About 100 g (271 mmol) of **1** should be dissolved in 500 ml of water. Then, the temperature must be increased up to 95°C-100°C. The reaction proceeds for about 8 hours. After monitoring the reaction progress by TLC (acetone:toluene:ethanol:ammonia) (45:45:7:3), it could be observed that the reaction is completed during 8 hours (check by TLC). After the reaction completion, the temperature should be decreased down to 0°C and 2 g of NaCl must be added to the mixture. Then, it must be left for about two hours. The white precipitates of molnupiravir forms (yield= %93; 60.5 g).

The melting point for the product is about 266ºC. The mobile and the stationary phases for the TLC test were (acetone:toluene:ethanol:ammonia)(45:45:7:3), and the Silica gel 60 F_{254} TLC plates, respectively. The NMR spectra of molnupiravir ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.99 (s, 1H, OH^{11}), 9.49 (s, 1H, NH^{8}), 6.79 (dd, J = 8.3, 2.9 Hz, 1H, CH^{5}), 5.69 (dd, J = 5.5, 3.1 Hz, 1H, CH^{22}), 5.57 (dd, J = 6.9, 3.8 Hz, 1H, CH^{23}), 5.33 (s, 1H, OH), 5.18 (s, 1H, OH), 4.18 (dt, J = 11.6, 2.8 Hz, 1H, CH^{16}), 4.11 (dd, J = 11.9, 4.9 Hz, 1H, CH^{3}), 3.98 (t, J = 4.9 Hz, 1H, CH^{2}), 3.90 (dd, J = 4.6 Hz, 2H, $CH_2{}^{17}$), 2.53 (m, 1H, CH^{20}), 1.07 (d, J = 2.9 Hz, 3H, CH_3), 1.06 (d, J = 2.9 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO) δ 176.56, 150.04, 143.92, 130.48, 99.34, 88.34, 81.29, 72.58, 70.52, 64.44, 33.77, 19.36, 19.33. Also, the mass spectrum MS (m/z) for the product is 330.1302 [17,18,21].

Representative Procedure for the clean synthesis of molnupiravir via de-ketalization reaction in water-Isopropanol-HCl system:

About 10 g (27.1 mmol) of **1** should be dissolved in a mixture of (water:isopropanol), with a ratio of (15ml:35ml). Then, the temperature must be increased up to 40 °C. The reaction proceeds for about 10 hours. After monitoring the reaction progress by TLC, it was observed that the intermediate was finished during 10 hours (check by TLC). After the reaction completion, the mixture should be concentrated by rotary to 1/3 volume. Then, the temperature should be decreased down to 0 °C. Then, it must be left for about five hours. The white precipitates of molnupiravir forms (yield= %23; 2.05 g).

Conclusion

After a systematic investigation on the effect of the key parameters of the de-ketalization process (including the type and the ratio of solvent, the type and concentration of catalyst, and the reaction temperature), we found out that this process could be carried out only in water as solvent, and without any catalysts. Indeed, in a pure and clean environment, the hot and high energy molecules of water could handle this de-protection only by the aid of heating at 100 °C, without intervention of catalyst molecules. After the reaction completion, by decreasing the temperature (and addition of trace amounts of sodium chloride (salting out)), white precipitates of molnupiravir appear. Also, the ash sulfate analysis (>0.1%), shows that the NaCl salt has not remained in the crude.

Absence of acids (which cause the difficult workup process, and also lead to emergence of high percentage impurities), elimination of the time-consuming and costly extraction process, and easily passing the OVI analysis test, are of the main advantages of this clean watery process.

Conflict of interest

The authors declare that there is no conflict of interest.

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