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Concise synthesis of antiviral drug, molnupiravir by direct coupling of fully protected D-Ribose with cytosine

Tanmoy Sahoo [a,b], B.V. Subba Reddy [a,*]

[a] Fluoro-Agrochemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad, India
[b] Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, UP, India

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ABSTRACT

A four step synthetic process has been developed for the synthesis of orally active ribonucleoside molnupiravir (MK-4482 & EIDDD-2801), starting from a readily available D-ribose. The synthesis involves the formation of acetonide from secondary hydroxy groups of the ribose, isobutrylation of primary and anomeric hydroxy groups, ribosylation of cytosine and one-pot hydroxyamination of cytosine ring along with the hydrolysis of acetonide. It is an effective process that can replace the high cost starting materials like uridine or cytidine that are being used in previous synthetic routes for MK-4482. The use of low cost starting materials with less number of synthetic steps is expected to expand access to molnupiravir.

Introduction

During this Covid pandemic time, several drugs have been repurposed to treat COVID-19 patients [1]. Among them, Remdesivir and Favipiravir are widely used anti-viral drugs to combat with COVID-19 [2]. Globally, several efforts have been made to develop novel antiviral drugs that are effective against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. In addition to novel vaccines [4], the development of simple and a direct acting antiviral drug to treat patients with COVID-19 is in high demand to end the pandemic [5]. Indeed, molnupiravir was found to exhibit a broad-spectrum of antiviral activity against SARS-CoV-2 [6]. It is structurally simple compared to remdesivir and it can easily be made from readily available precursors. It is a first orally active and direct-acting antiviral drug that is highly effective in reducing nasopharyngeal SARS-CoV-2 infectious virus and viral ribonucleic acid (RNA) levels (Figure 1) [7].

In 2020, Merck & Co. has initiated further studies to develop molnupiravir in collaboration with Ridgeback Biotherapeutics. The reported route for making this API involves 10 steps starting from ribose en-route to uridine with an overall yield of less than 10%. The original route developed by Emory University involves five steps from uridine with an overall yield of 17% [8]. Subsequently, several approaches have been reported for the synthesis of molnupiravir (MK-4482 & EIDDD-2801) either from uridine[9] or cytidine [10]. Recently, an excellent two step process has been reported to molnupiravir from cytidine using enzymatic esterification and hydroxyamination of cytidine, which avoids the protection and deprotection of hydroxy groups [11]. Later on, a two-step process has been reported for molnupiravir involving the hydroxyamination of cytidine followed by the esterification of primary hydroxyl group [12]. However, most of these previous syntheses require either uridine or cytidine as nucleoside building block for making molnupiravir. More recently, Merck has developed a short three steps route to molnupiravir starting from ribose by means of enzymatic approach [13] (Scheme 1).

Results and discussion

We herein report a concise method for the synthesis of antiviral drug, Molnupiravir starting from D-Ribose (Scheme 2).

Accordingly, we began the synthesis of molnupiravir from D-Ribose. The protection of secondary hydroxy groups of the ribose with acetone using a catalytic amount of H_2SO_4 at 25 °C over 2 h

* Corresponding author.
E-mail address: basireddy@iict.res.in (B.V. Subba Reddy).

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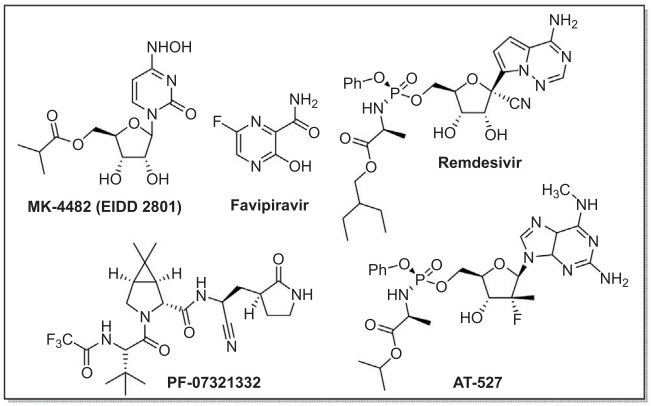
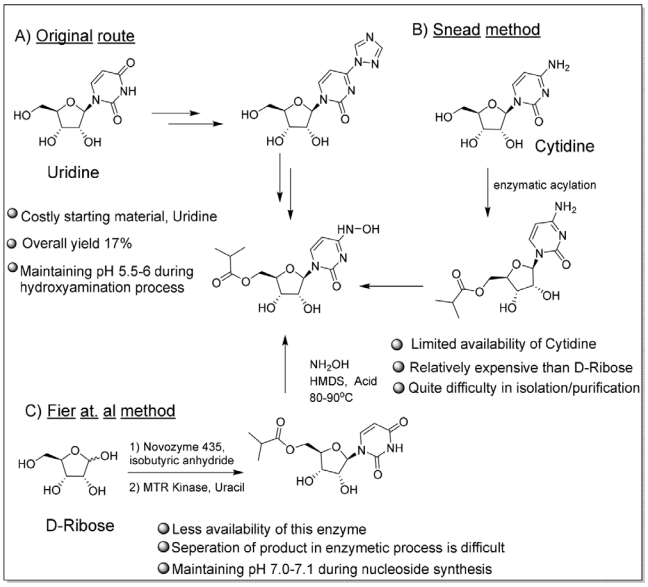


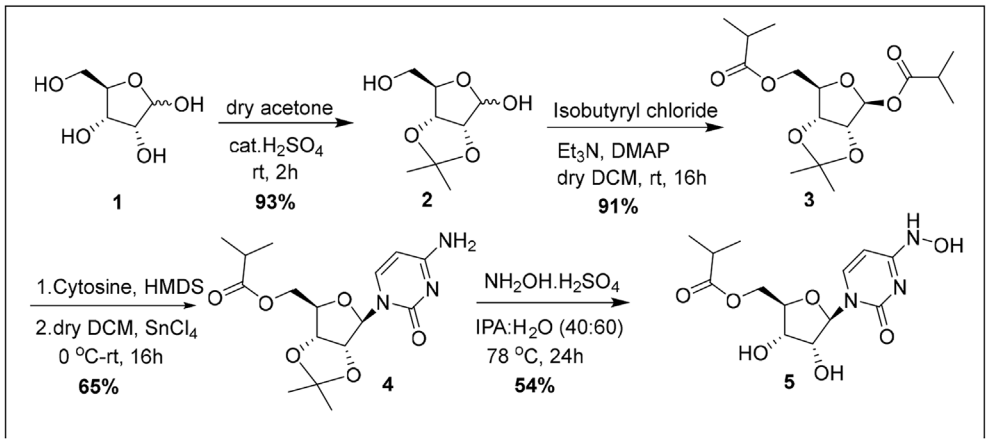
Figure 1. Examples of antiviral drugs for COVID-19.



Scheme 1. Previous methods for Molnupiravir.

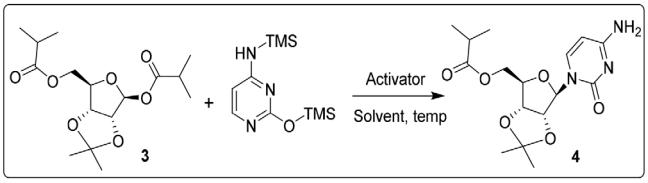
afforded the acetonide **2** in 93% yield. Subsequent one-pot isobutyrylation of primary and anomeric hydroxy groups of **2** with isobutyryl chloride using Et_3N in the presence of DMAP in DCM at 25 °C for 16 h gave the diester **3** in 91% yield. Following silylation of cytosine using HMDS in the presence of TMSCl at 140 °C and subsequent removal of the excess silylating agent under reduced pressure afforded the silylated cytosine, which was then added to a solution of diester **3** in DCM under the several reagents condition (Table 1). The reaction did not proceed with molecular iodine, $B(C_6F_5)_3$, and $Ph_3P.HBr$ (entries 1, 2, 3, Table 1). Only a trace amount of **4** was obtained when the reaction was carried out with 1 equiv of silylated cytosine using 1.2 equiv of TMSOTf in DCM at 25 °C (entry 4, Table 1). A slight improvement of yield was observed when the reaction was conducted with 2 equiv of silylated cytosine and 1.5 equiv of TMSOTf in DCM at 40 °C (entry 5, Table 1). No further improvement was observed even by increasing the quantity of TMSOTf to 2 equiv. (entry 6, Table 1). Therefore, the reaction was then carried out with a conventional Lewis acid, $SnCl_4$. Surprisingly, a trace amount of product **4** was obtained when the reaction was performed using 1.2 equiv of $SnCl_4$ in DCM at 0 °C (entry 7, Table 1). Interestingly, the desired product **4** was isolated in 35% yield when the reaction was performed at 25 °C using 1.5 equiv $SnCl_4$ (entry 8, Table 1). By increasing the quantity of $SnCl_4$ to 2.5 equiv. the desired product was obtained in 65% yield (entry 9, Table 1), which is consistent with a previous report on the coupling of compound **3** with *N*-hydroxycytosine [14]. No further improvement was observed even by increasing the quantity of $SnCl_4$ to 3.5 equiv (entry 10, Table 1). However, the reaction did not proceed with conventional Lewis acid like $BF_3.OEt_2$ (entry 12, Table 1).

A tentative reaction mechanism for the silyl-Hilbert-Johnson reaction is presented in Scheme 2. Initially, the compound **3** is likely activated by $SnCl_4$ to provide the oxo-carbenium ion **B** [15]. The preferential pseudo axial attack of the silylated cytosine on oxo-carbenium ion would give the major product **4** (Scheme 3).



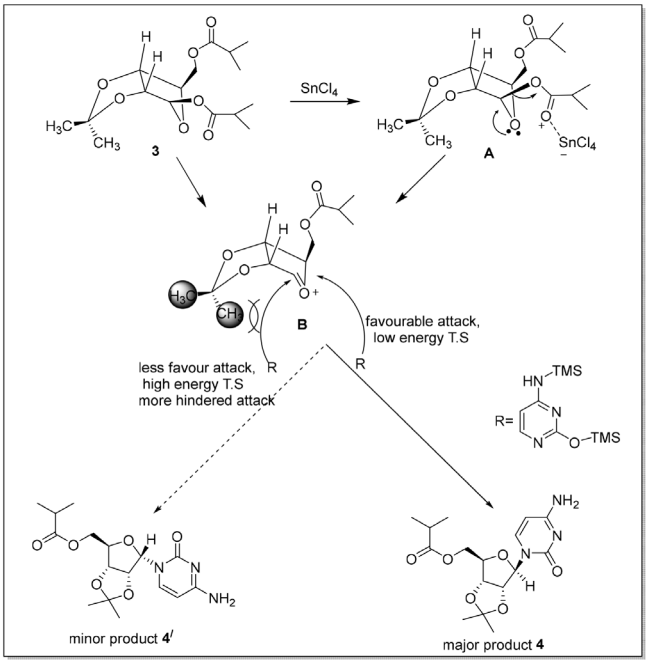
Scheme 2. Present route of synthesis for Molnupiravir.

Table 1
Optimization of reaction conditions.



E	Activator (equiv.)	Solvent	T (°C)	TMS- cytosine (equiv)	Yield (4) (%)[b]
1	I_2 (0.5)	DCM	25	1.2	0
2	$B(C_6F_5)_3$ (0.3)	DCM	25	1.2	0
3	PPh_3.HBr(0.5)	DCM	25	1.2	0
4	TMSOTf(1.2)	DCM	25	1.0	trace
5	TMSOTf(1.2)	DCM	40	2.0	30
6	TMSOTf(2.0)	DCM	40	2.0	20
7	$SnCl_4$ (1.2)	DCM	0	1.0	trace
8	$SnCl_4$ (1.5)	DCM	25	2.0	35
9	**$SnCl_4$ (2.5)**	**DCM**	**25**	**2.0**	**65**
10	$SnCl_4$ (3.5)	DCM	25	2.0	40
11	$SnCl_4$ (2.5)	DCE	25	2.0	64
12	$BF_3.OEt_2$ (1.0)	DCM	25	1.2	0
13	$BF_3.OEt_2$ (3.5)	DCE	70	2.0	0

[a]All the reaction were performed with compound **3** (0.5 g, 1.51 mmol), TMS cytosine in the presence of several activator in 10 mL solvent, [b]Isolated yield (%) after purification.



Scheme 3. A plausible reaction mechanism.

Conclusions

In summary, we have successfully demonstrated the synthesis of molnupiravir starting from D-Ribose. This method is simple and easy to scale up. It is a novel and short approach to produce molnupiravir to meet market demand.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2022.153783.

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Three-step process for the synthesis of favipiravir

Swarnayu Banik [a,b], D.R. Adarsh [a,b], B.V. Subba Reddy [a,b,*]

[a] Fluoro & Agrochemicals, CSIR-IICT, Hyderabad 500 007, India
[b] Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh 201 002, India

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ABSTRACT

A three-step process has been developed for the synthesis of antiviral drug favipiravir (T-705) starting from a readily available ethylenediamine and diethyl 2-oxomalonate. The synthesis involves the formation of ethyl 3-hydroxypyrazine-2-carboxylate by direct condensation of ethylenediamine with diethyl 2-oxomalonate followed by amide formation and electrophilic fluorination. This approach not only consists of three steps but also ensures the usage of inexpensive and easily available starting materials. It is an alternative process that can replace bromination or nitration, $POCl_3$ etc that are used in previous methods.

Introduction

During this pandemic, several repurposed drugs such as chloroquine, hydroxychloroquine, favipiravir, remdesivir have been tested to combat COVID-19 [1]. Subsequently, molnupiravir and paxlovid (nirmatrelvir plus ritonavir) have been developed to treat different variants of SARS-CoV-2 (Fig. 1) [2].

In particular, favipiravir was originally developed by Fujifilm to treat influenza in Japan [3]. It is a pyrazine derivative and acts as a prodrug that inhibits viral RNA polymerase [4]. It is also found to be effective against West Nile virus, Yellow Fever virus, Ebola and flaviviruses [5]. In spite of the development of novel vaccines against COVID-19 [6], favipiravir is a widely used prophylaxis to treat the patients suffering from Corona virus because of its affordability. Consequently, several approaches have been developed for the synthesis of favipiravir [7]. However, some of these methods involve the use of toxic reagents like $POCl_3$, NaCN, expensive transition metal catalysts and highly corrosive HF for the Balz-Schiemann reaction [7] Furthermore, most of them proceed through the formation a highly toxic intermediate, i.e. 3,6-dichloropyrazine-2-carbonitrile [8]. Therefore, the development of a short and eco-friendly approach using non-toxic reagents and solvents is highly desirable.

Results and discussion

Following our interest on the development of novel approaches for the synthesis of biologically active molecules [9], we herein report a short three-step process to favipiravir starting from ethylenediamine and 2-oxomalonate. Accordingly, we attempted the coupling of ethylenediamine (**1**) with diethyl 2-oxomalonate (**2**) under various conditions. Initially, the reaction was performed in EtOH at room temperature but no desired product was formed. Therefore the mixture was heated under reflux for 24 h. Interestingly, the expected product, i.e ethyl 3-hydroxypyrazine-2-carboxylate (**3**) was obtained in 37% yield. Next we tried the reaction in presence of DDQ but to our surprise desired product **(3)** did not form. Then we tried the same reaction in presence of acetonitrile but unfortunately trace amount of ethyl 3-hydroxypyrazine-2-carboxylate (**3**) was obtained. To improve the yield, the reaction was further carried out in EtOH in presence of catalytic amount of AcOH at 60 °C temperature under oxygen [10]. After 13 h, the desired product (**3**) was obtained in 63% yield. Subsequently, the ester functionality was converted into amide by treating with 25% aqueous ammonia at room temperature over 5 h to give the amide (**4**) in 82% yield (Scheme 1).

Finally, we attempted the electrophilic fluorination of hydroxypyrazinamide (**4**) using different N-F reagents like Selectfluor and NFSI under diverse reaction conditions. To optimize reaction conditions, several experiments were conducted using various bases and solvents (Table 1).

As shown in the above Table 1, the fluorination of compound **4** was initially carried out in the absence of base using selectfluor in DMAc at 80 °C. But no fluorination was observed (entry 1, Table 1). Therefore, the above reaction was repeated in the presence of K_2CO_3. Interestingly,

* Corresponding author at: Fluoro & Agrochemicals, CSIR-IICT, Hyderabad 500 007, India.
E-mail address: basireddy@iict.res.in (B.V.S. Reddy).

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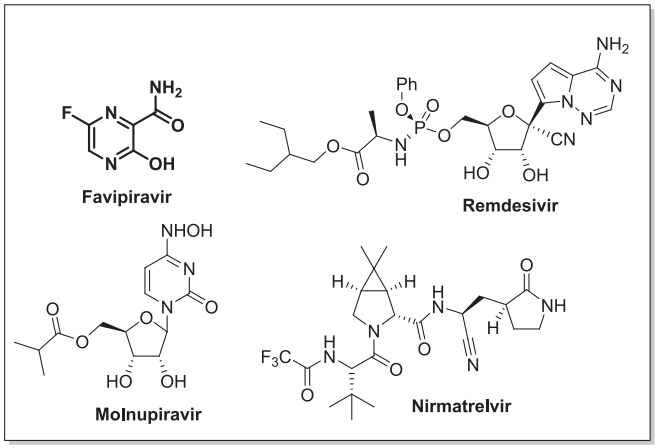
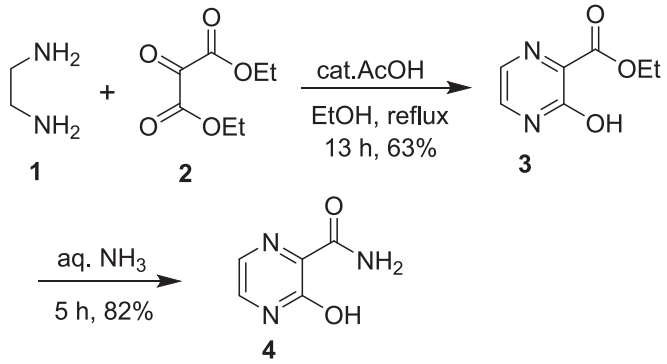
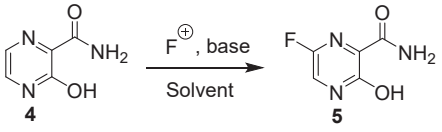


Fig. 1. Examples of Covid-19 drugs.



Scheme 1. Synthesis of 3-hydroxypyrazine-2-carboxamide (4).

Table 1
Optimization of electrophilic fluorination of 4.[a]



Entry	F^+ source	Base	Solvent	Yield (%)[b]
1.	Selectfluor	–	DMAc	–
2.	Selectfluor	K_2CO_3	DMAc	41
3.	Selectfluor	K_2CO_3	CH_3CN	59
4.	Selectfluor	–	AcOH	–
5.	Selectfluor	K_2CO_3	CH_3CN/ MeOH	47[c]
6.	NFSI	K_2CO_3	CH_3CN	51
7.	Selectfluor	Ag_2CO_3	CH_3CN	–
8.	Selectfluor	Pyridine	CH_3CN	–
9.	**Selectfluor**	**K_2CO_3**	**CH_3CN**	**70**[d]
10.	Selectfluor	K_2CO_3	CH_3CN	70[e]

[a] All reactions of **4** (0.72 mmol) were performed using fluorinating agent (0.72 mmol), base (0.79 mmol) in 1 mL solvent under reflux over 12 h.
[b] Isolated yield.
[c] CH_3CN:MeOH (1:1) as solvent.
[d] 1.6 equiv of Selectfluor was used.
[e] 1.8 equiv of Selectfluor was used.

the desired fluorinated product was obtained in 41% yield (entry 2, Table 1). To know the effect of solvent, the reaction was further carried out in polar aprotic solvent acetonitrile. The yield was considerably improved to 59% (entry 3, Table 1). To our surprise, the reaction did not proceed in AcOH (entry 4, Table 1). The next reaction was performed in a 1:1 mixture of acetonitrile and methanol. The yield was slightly decreased compared to acetonitrile alone (entry 5, Table 1). To improve the conversion, the reaction was further carried out using NFSI in the presence of K_2CO_3 in acetonitrile.

The product was obtained only in 51%, which is comparatively lower yield than selectfluor (entry 6, Table 1). Therefore, further experiments were conducted using selectfluor. To know the effect of base, the reaction was carried out using weak bases like pyridine and silver carbonate. Indeed, the reaction did not proceed under the above conditions (entries 7 and 8, Table 1). It is obvious that the reaction did not proceed without a base (entries 1 & 4, Table 1). To our delight, the best yield (70%) was obtained when the quantity of selectfluor was increased to 1.6 equiv (entry 9, Table1). No further improvement in yield was observed even by increasing the amount of selectfluor to 1.8 equiv (entry 10, Table 1). Under optimized conditions, the reaction requires 1.1 equiv of K_2CO_3, 1.6 equiv of selectfluor in acetonitrile under reflux conditions (entry 9, Table 1).

Conclusions

In summary, we have successfully developed a three-step process for the synthesis of favipiravir. It is a novel approach to produce favipiravir without the generation of highly toxic 3,6-dichloropyrazine-2-carbonitrile, which is a common intermediate in most of the reported processes.

CRediT authorship contribution statement

Swarnayu Banik: Methodology. **D.R. Adarsh:** Writing – original draft. **B.V. Subba Reddy:** Investigation, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2023.100895.

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