

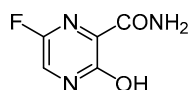
Favipiravir – a modern antiviral drug: synthesis and modifications

Yulia A. Titova^{1*}, Olga V. Fedorova¹

¹ Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 22 S. Kovalevskoi / 20 Akademicheskaya St., Yekaterinburg 620108, Russia; e-mail: titova@ios.uran.ru

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The routes of synthesis are considered, as well as the modifications of the promising modern antiviral drug favipiravir. Literature data from the last 10 years are reported.

Keywords: favipiravir, oseltamivir, pyrazine, ribonucleoside, coronavirus, antiviral activity.

Favipiravir (T-705, 6-fluoro-3-hydroxypyrazine-2-carboxamide) is a novel low molecular weight antiviral compound. It has shown activity against many types of RNA viruses (all strains of influenza A, B, C, arenavirus, bunyavirus, flavivirus, alphavirus, norovirus,¹ as well as the Zika, Usutu,² and Ebola³ viruses). The generally good tolerance of human patients to favipiravir and the high barrier to the development of resistant viral strains indicate that this drug holds great promise for clinical use around the world. It should be noted that a representative of the Zhejiang Hisun Pharmaceutical company from China has announced that this company has received marketing authorization from the Chinese government for favipiravir as a possible medication against the coronavirus causing Covid-19.⁴

Synthesis of favipiravir

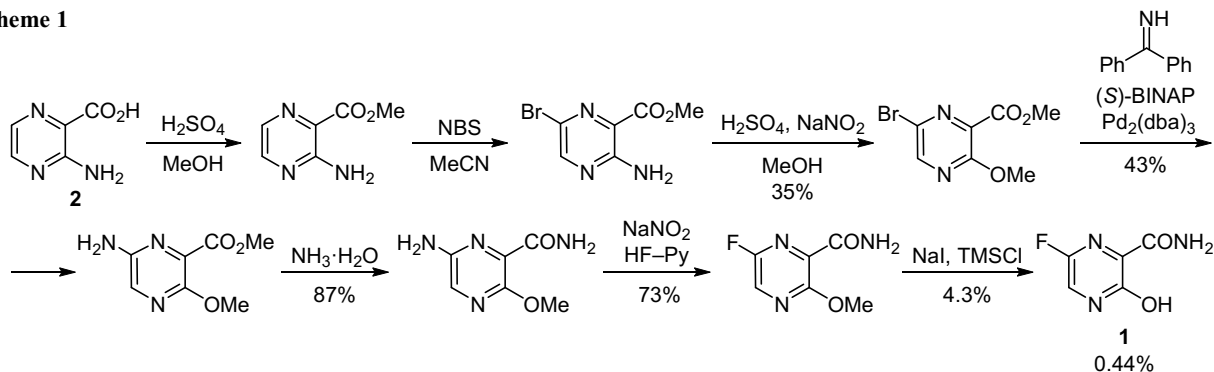
Favipiravir (**1**) was first synthesized in 2000 by a route consisting of seven steps. The starting material was

3-aminopyrazine-2-carboxylic acid (**2**). The amination step was catalyzed by a costly (*S*)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((*S*)-BINAP), fluorination required using the highly corrosive Olah reagent, while the overall reaction yield was approximately 0.44% (Scheme 1).⁵

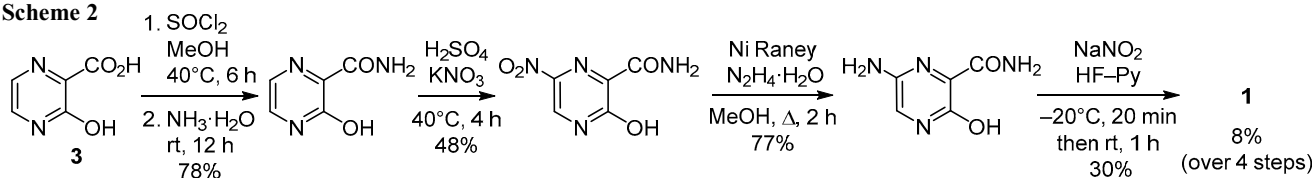
Improved methodologies for the synthesis of favipiravir (**1**) have been reported in recent years. In particular, a four-step method enabled the synthesis of favipiravir (**1**) from commercially available 3-hydroxypyrazine-2-carboxylic acid (**3**), which was subjected to esterification and amidation. The nitration of pyrazine ring was followed by reduction of the nitro group in the presence of Raney nickel, allowing to minimize the amount of byproducts. After the replacement of amino group with a fluorine atom, the overall yield of the target product **1** was 8%⁶ (Scheme 2).

A research group from China proposed a route for the synthesis of favipiravir (**1**) through a key intermediate – methyl 3-amino-6-bromopyrazine-2-carboxylate (**4**). According to them, the purity of this compound was

Scheme 1

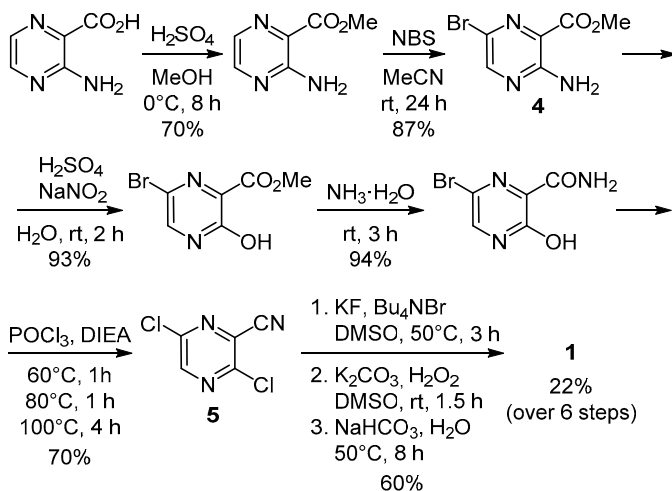


Scheme 2



important for successful preparation of 3,6-dichloropyrazine-2-carbonitrile (**5**). In addition, a one-pot procedure involving substitution of chlorine atom with fluorine, hydrolysis, and aminolysis of nitrile group was demonstrated⁷ (Scheme 3).

Scheme 3



The preparation of favipiravir (**1**) from pyrazin-2-amine (**6**) has been accomplished *via* regioselective chlorination of pyrazine ring, bromination, palladium-catalyzed

cyanation, diazotation, and Sandmeyer chlorination. The subsequent nucleophilic fluorination, nitrile hydrolysis, and replacement of fluorine atom with a hydroxy group provided the target product **1** in 12–18% yield, depending on the reaction conditions for the first step of the synthesis⁸ (Scheme 4).

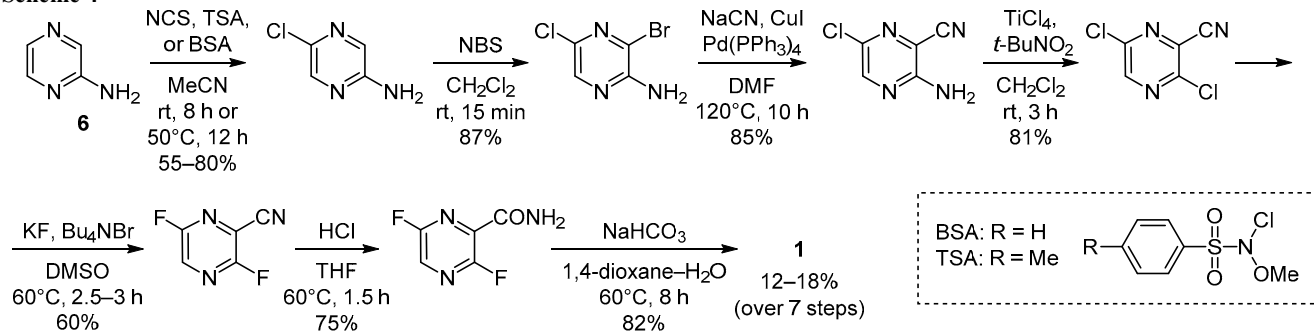
A nontrivial method for the preparation of favipiravir (**1**) has been proposed, starting from ethyl diethoxyacetate (**7**) through the fluorinated isoxazolo[4,5-*b*]pyrazine derivative **8**, followed by isoxazole ring cleavage⁹ (Scheme 5).

The main directions of modification applied to favipiravir

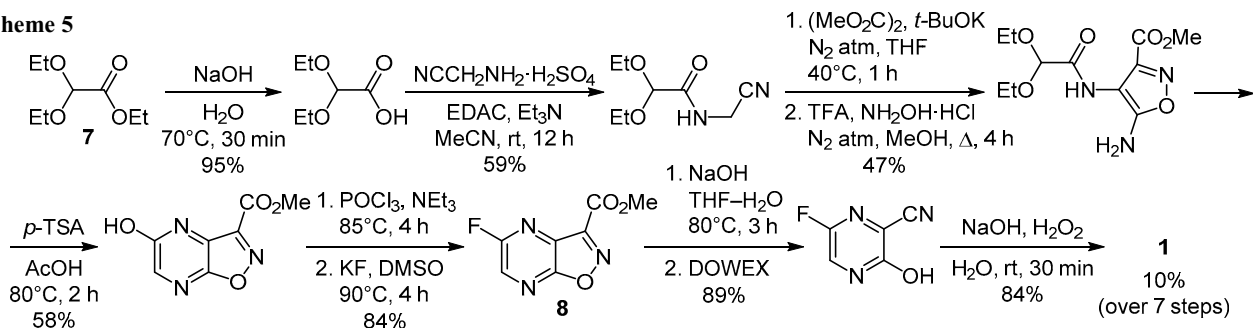
As shown in 2013, the key limiting step in the antiviral action mechanism of favipiravir (**1**) is its transformation into the active metabolite – favipiravir ribonucleoside triphosphate.¹⁰ This discovery motivated studies aimed at the preparation of favipiravir derivatives on the basis of various monosaccharides, such as the synthesis of favipiravir ribosides, as well as favipiravir ribonucleoside-5-monophosphate (**9**) (Scheme 6). The low stability of the obtained ribonucleosides was noted even under mild conditions: the nucleosidic bond was prone to cleavage, as well as the heterocyclic fragment underwent decomposition.¹¹

The alkylation of phosphate moiety in favipiravir ribosides has been also described (Scheme 7). The obtained compounds exhibited antiviral activity, comparable to favipiravir.¹²

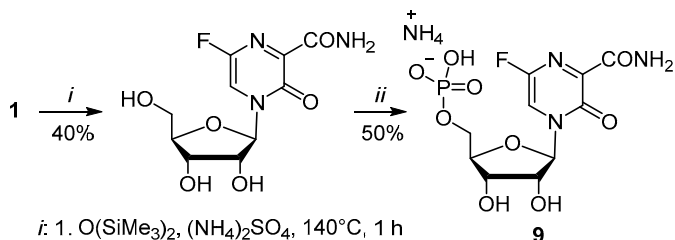
Scheme 4



Scheme 5

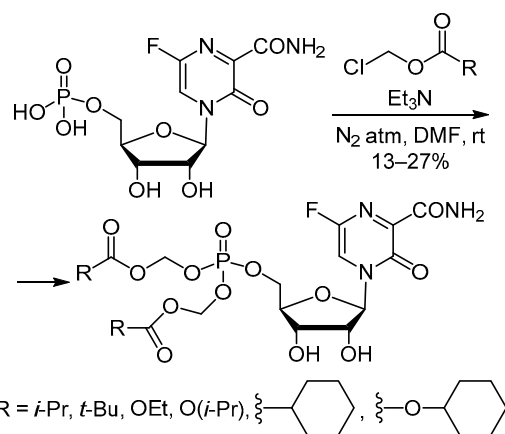


Scheme 6



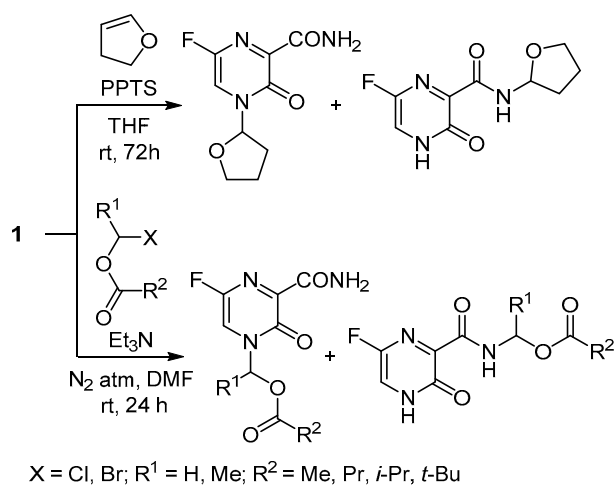
- i*: 1. $O(\text{SiMe}_3)_2$, $(\text{NH}_4)_2\text{SO}_4$, 140°C , 1 h
 2. 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose
 SnCl_4 , MeCN, rt, 7 h
 3. Bu_2SnO , MeOH, 80°C , 24 h
ii: 1. POCl_3 , Py, H_2O -MeCN, 0°C , 20 min
 2. NH_4HCO_3 , H_2O , 0°C , 30 min

Scheme 7



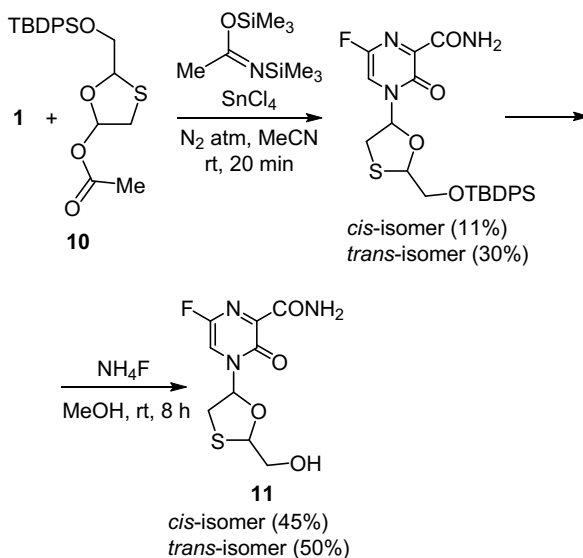
An attempt was made to modify favipiravir (**1**) at the pyrazine ring nitrogen atom by treatment with esters, similarly to the formation of glycosidic bond in the riboside triphosphate derivative of favipiravir. Byproducts due to the substitution of amide group were also obtained (Scheme 8). The synthesized compounds showed strong antiviral activity against the H1N1 influenza virus, as well as had superior pharmacokinetic characteristics compared to favipiravir.¹³

Scheme 8



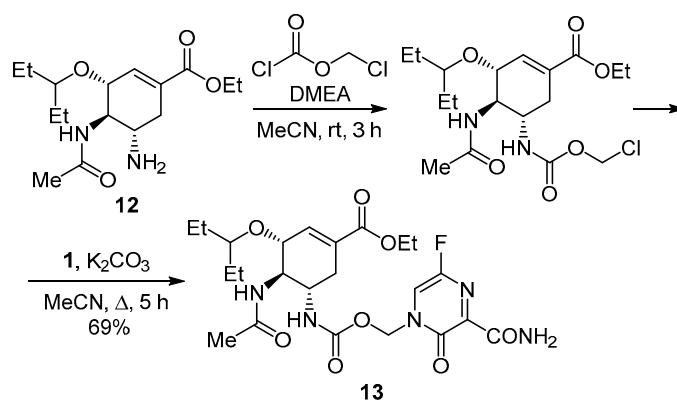
A similar modification of 6-fluoro-3-hydroxypyrazine-2-carboxamide (**1**) has been described, involving oxathiolane derivative **10**. The *cis*-isomer of the obtained 2-(hydroxymethyl)oxathiolane-containing favipiravir derivative **11** (Scheme 9) showed activity against the H1N1 influenza virus, while the *trans*-isomer had activity against HIV.¹⁴

Scheme 9



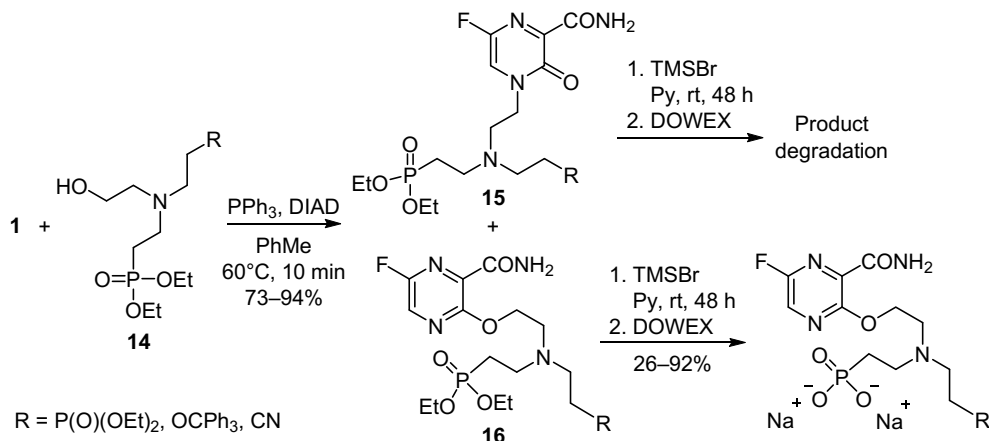
The combination of favipiravir (**1**) and the antiviral drug oseltamivir (**12**) in one molecule (Scheme 10) produced an advantageous synergic effect. The obtained compound **13** showed improved antiviral activity against the H5N2 influenza virus.¹⁵

Scheme 10



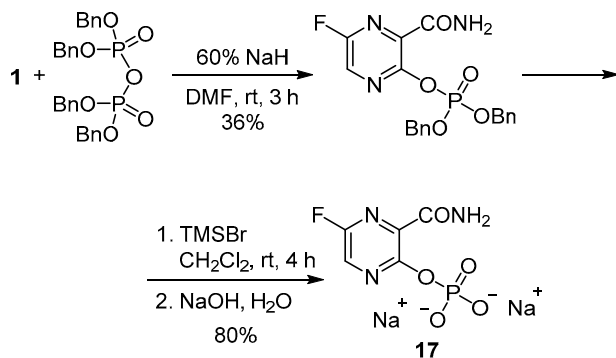
The attempts to perform alkylation of favipiravir (**1**) with nitrogen-containing acyclic phosphonates **14** by using the Mitsunobu reaction led to the preparation of *N*- and *O*-regioisomers **15** and **16**. However, *N*-isomer **15** was found to be unstable under the conditions used for the removal of protecting groups (Scheme 11). Some of the obtained *O*-regioisomers **16** selectively inhibited the human enzymes HGPRT and PfHGXPT. Also, the oxygen-containing acyclic phosphonates employed as alkylating agents led only to the *O*-alkylation products of favipiravir (**1**).¹⁶

Scheme 11



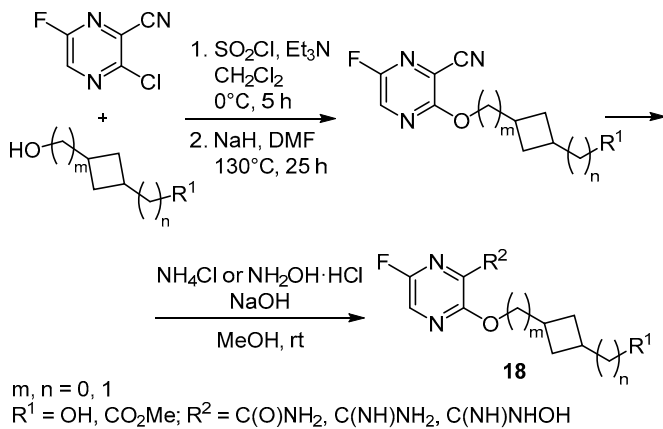
The preparation of favipiravir phosphate **17** has been described (Scheme 12), and this derivative was characterized by improved solubility and pharmacokinetic properties.¹⁷

Scheme 12



Cyclobutane-containing favipiravir derivatives **18** (Scheme 13) were active against a series of influenza virus strains.¹⁸

Scheme 13



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