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ORIGINAL PAPER

An economical and practical procedure of favipiravir synthesis for the treatment of Covid-19

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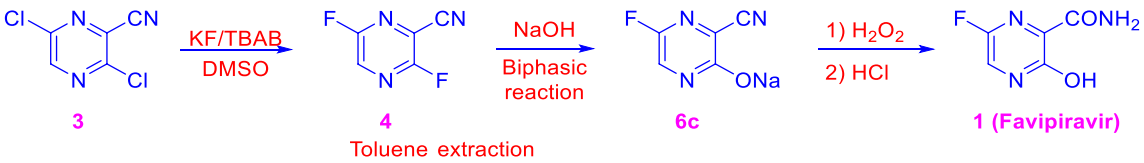
Abstract

Favipiravir is a wide-spectrum antiviral generic drug that has received large attention during the recent COVID-19 pandemic. While there are synthetic strategies for favipiravir synthesis, economical procedures could contribute to industrial scale synthesis and availability. Accordingly, our efforts focused on an economic and scalable procedure for favipiravir synthesis via the 3,6-dichloropyrazine-2-carbonitrile intermediate obtained from 3-aminopyrazine-2-carboxylic acid. The process afforded favipiravir with 43% yield (from 3,6-dichloropyrazine-2-carbonitrile, by fluorination, hydroxylation, and nitrile hydrolysis reactions) and greater than 99% purity without a chromatographic purification step.

Graphical abstract



Keywords Favipiravir synthesis · 3,6-Dichloropyrazine-2-carbonitrile · Covid-19 treatment · Process development · Active Pharmaceutical Ingredient (API) synthesis

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Introduction

Favipiravir (**1**, Fig. 1), also known as T-705, is a wide-spectrum antiviral prodrug initially developed against the influenza virus and later was shown to be effective against other RNA viruses including arenaviruses, bunyaviruses, zika, and ebola viruses (Furuta et al. 2009, 2017; Zhang et al. 2017). Upon cellular uptake, favipiravir is converted to its active form favipiravir-RTP (**2**, Fig. 1) that inhibits viral RNA-dependent RNA polymerase (RdRp) enzyme and consequently the virus replication (Furuta et al. 2009, 2017).

While it was initially developed against influenza, favipiravir has recently been proposed for the coronavirus disease-2019 (COVID-19) treatment caused by Severe Acute Respiratory Syndrome, Coronavirus-2 (SARS-CoV-2) during the pandemic started in 2019. Known safety profile, pharmacokinetic properties, and mechanism of action in addition to the drug becoming generic in 2019 attracted world-wide attention to favipiravir. Accordingly, there have been numerous ongoing clinical trials with favipiravir for the COVID-19 treatment, some of which have already been completed (Agrawal et al. 2020; Elekhnawy et al. 2021; Guner 2021; Joshi et al. 2021).

Various strategies reported for the favipiravir synthesis as summarized in Scheme 1. Accordingly, favipiravir could be synthesized starting from 3-aminopyrazine-2-carboxylic acid (**3**) (Furuta and Egawa 2000; Liu et al. 2017), 3-hydroxy-6-nitropyrazine-2-carboxamide (**4**) (Jordis and Beldar 2009), pyrazine-2-carbonitrile (**5**) (Mengyang 2017; Wang et al. 2017), 2-aminopyrazine (**6**) (Guo et al. 2019), 2-aminomalonamide (**7**) (Hara et al. 2011), diethyl malonate (**8**) (Tiyasakulchai et al. 2021), 3-hydroxypyrazine-2-carboxylic acid

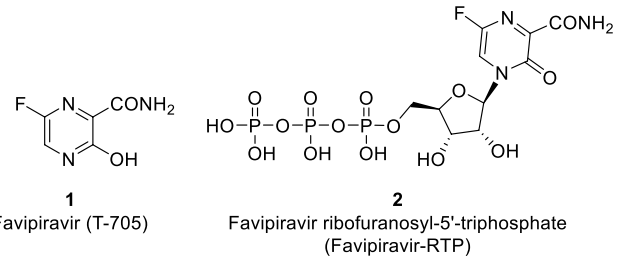
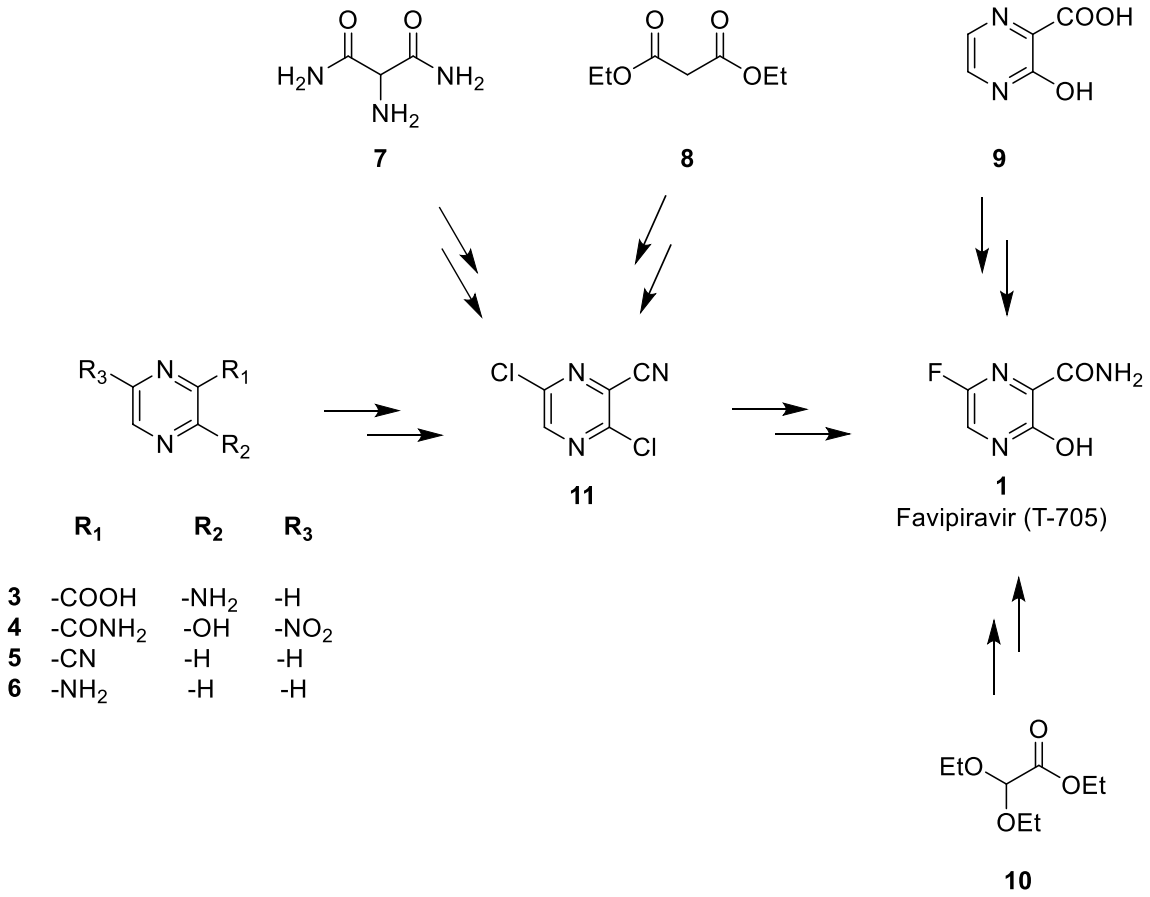
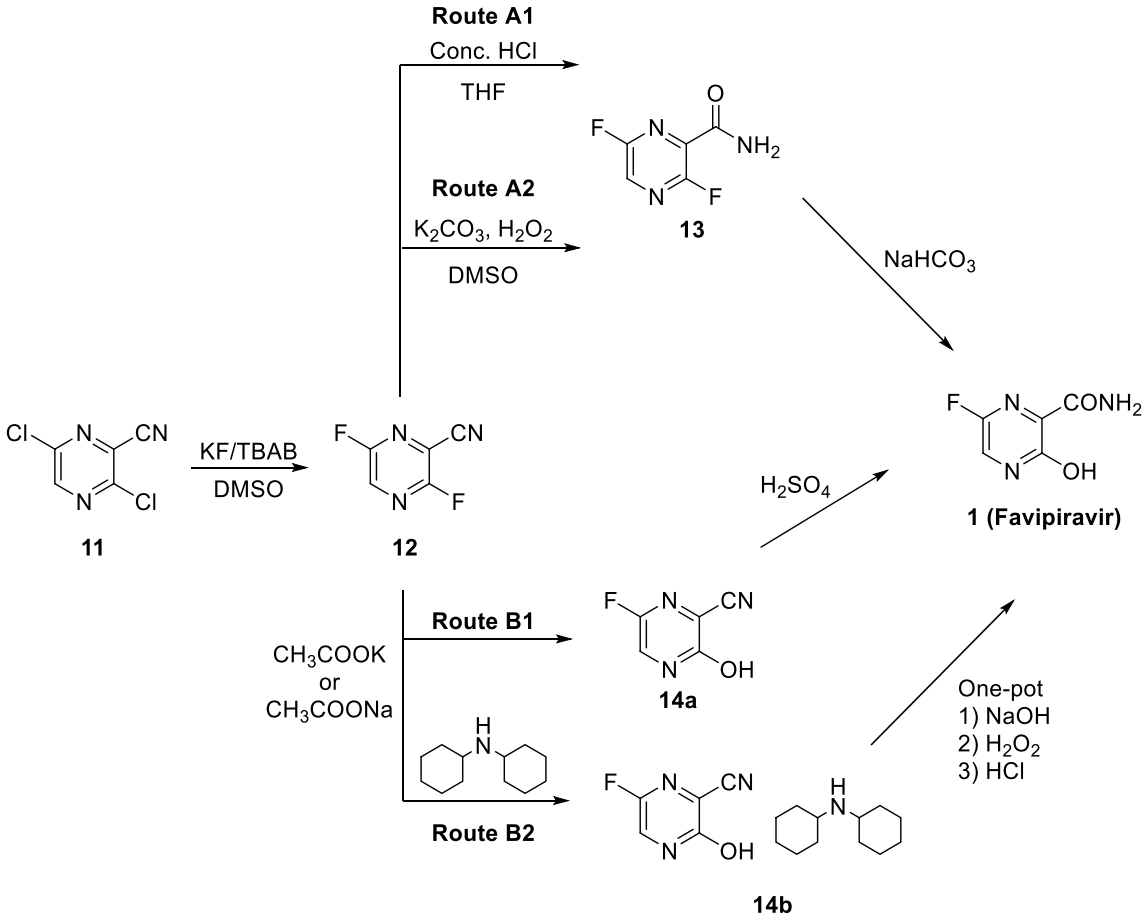


Fig. 1 Structures of favipiravir (**1**) and its active analog favipiravir-RTP (**2**)



Scheme 1 General routes with different starting materials (**3–10**) reported for the favipiravir synthesis



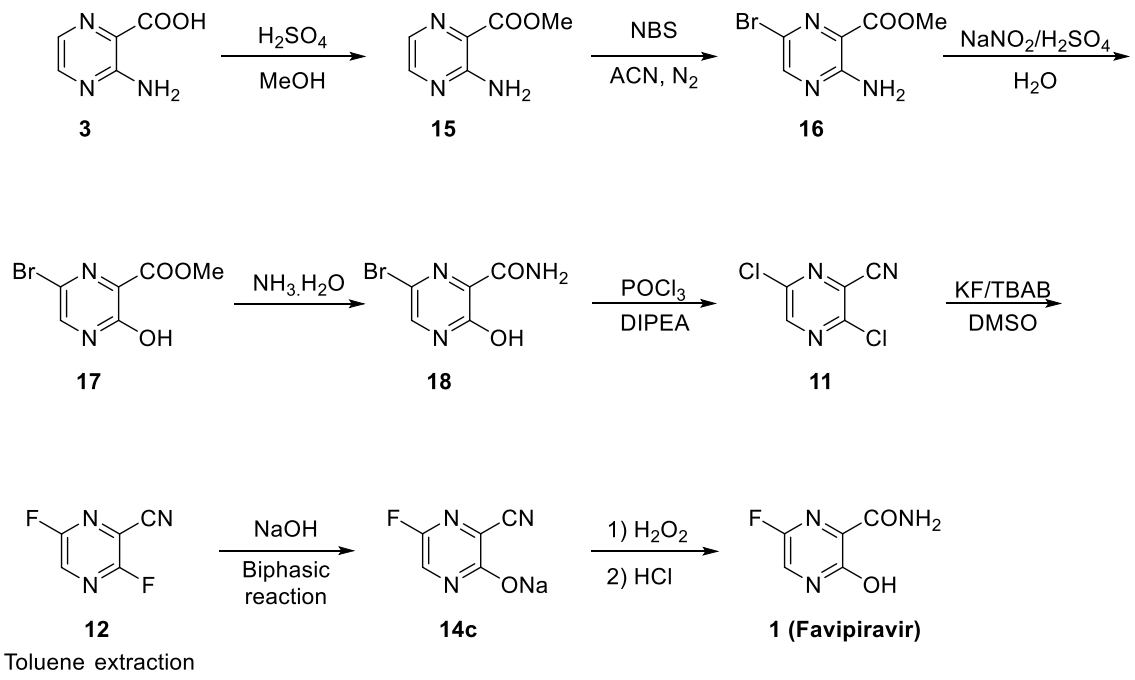
Scheme 2 General routes for the favipiravir synthesis starting from 3,6-dichloropyrazine-2-carbonitrile (**11**)

(**9**) (Shi et al. 2014), and ethyl diethoxyacetate (**10**) (Nakamura et al. 2015), as reviewed earlier (Titova and Fedorova 2020; Gouda and Qurban 2021; Tiyasakulchai et al. 2021; Arora et al. 2021).

Among the reported strategies, an economical synthesis of favipiravir could be achieved via 3,6-dichloropyrazine-2-carbonitrile (**11**) with a three-step reaction (Scheme 2). In the initial step, the 3,6-dichloro intermediate (**11**) is fluorinated with KF yielding **12**. The 3,6-difluoro intermediate (**12**) is then subjected to various two-step reactions to achieve favipiravir (Scheme 2, Routes A1–A2 and B1–B2). Upon isolation, the nitrile group in **12** is hydrolyzed with concentrated HCl to give **13** followed by hydroxylation with aqueous $NaHCO_3$ in Route A1 (Guo et al. 2019; Jordis and Beldar 2009). A recent approach (Route A2) has combined fluorination (**12**), nitrile hydrolysis (**13**), and hydroxylation in a one-pot procedure (Liu et al. 2017). In this method, intermediate **12** is not isolated. Route B1-B2 proceeds through hydroxylation of the 3-fluoro group (**14a** and **14b**) followed by nitrile hydrolysis (Takamatsu and Yonezawa 2010; Zhang et al. 2013). In route B1, the column purified **12** was treated with sodium acetate for hydroxylation (**14a**). Intermediate **14a** is then treated with H_2SO_4 to yield favipiravir (Zhang et al. 2013). In route B2, a DMF solution of intermediate **12** is treated with potassium acetate followed by dicyclohexylamine addition to afford the dicyclohexylamine salt of 6-fluoro-3-hydroxypyrazine-2-carbonitrile (**14b**). This salt (**14b**) is then partitioned between dilute aqueous NaOH solution and toluene to remove the dicyclohexylamine, followed by nitrile hydrolysis in the aqueous phase with H_2O_2 to give the sodium salt of favipiravir. Therefore, HCl treatment at the last step is used for neuralization (Takamatsu and Yonezawa 2010).

In this work we describe an optimized procedure for the favipiravir synthesis starting from 3-aminopyrazine-2-carboxylic acid (**3**) and via 3,6-dichloropyrazine-2-carbonitrile (**11**) (Scheme 3), with a specific focus given to the steps from **11** to favipiravir (**1**).

Fluorination of **11** is a critical step for the synthesis of favipiravir. During isolation we encountered a significant loss of intermediate **12** due to sublimation under vacuum. Although it was not discussed in the literature, such a reason could be a driving force for the recent one-pot procedure (Route A2), where **12** is not isolated from the reaction



Scheme 3 Synthesis of favipiravir (**1**) in this work starting from *3-aminopyrazine-2-carboxylic acid* (**3**) and via 3,6-dichloropyrazine-2-carbonitrile (**11**)

mixture (Liu et al. 2017). However, this procedure yielded a very dark, dirty mixture, where favipiravir could not be isolated. Therefore, we seek a novel procedure to extract intermediate **12** from the reaction mixture and use it for the following reaction without further processes. Accordingly, we have developed a new procedure shown in Scheme 3. Upon fluorination of **11** with KF, the intermediate **12** is extracted with toluene. Then in toluene, **12** is subjected to hydroxylation with dilute aqueous NaOH in a biphasic reaction yielding **14c** as the sodium salt of **14a**, followed by nitrile hydrolysis and neutralization in the same pot. Our novel method eliminated the need to isolate intermediate **12** as solid. Moreover, this new procedure uses NaOH, a much cheaper alternative of CH_3COONa/K, and therefore could be an advantage for industrial synthesis of favipiravir. Overall, we have developed a new economical procedure of the favipiravir synthesis.

Results and discussion

Recent COVID-19 pandemic has attracted interest of simple and economical procedures for the synthesis of favipiravir, which became a generic drug in 2019 (Titova and Fedorova 2020). Therefore, we focused on a novel method that can be applicable for industrial synthesis of favipiravir using the critical intermediate 3,6-dichloropyrazine-2-carbonitrile (**11**) which can be synthesized starting from 3-aminopyrazine-2-carboxylic acid (**3**).

We have followed a previously established route for the synthesis of **11** with modification at the chlorination-dehydration step (Scheme 3) (Zhang et al. 2013; Liu et al. 2017). The procedure started with Fischer esterification of commercially available 3-aminopyrazine-2-carboxylic acid (**3**) to give **15** followed by bromination at the position-6 with NBS (**16**). Diazotization hydrolysis of the diazonium salt yielded the 3-hydroxy intermediate (**17**) followed by aminolysis (**18**). Chlorination and dehydration of **18** with $POCl_3$ with a modified procedure finally afforded **11** with better yields compared to those reported earlier (Liu et al. 2017; Zhang et al. 2013). According to the previous methods, **18** was heated with $POCl_3$ and DIPEA initially at 55–60 °C for 1 h, then at 80 °C for another hour, followed by heating at 100–110 °C for 4 h. In the current procedure, we have found that a gradual increase in temperature is not necessary and refluxing the mixture at a fixed 80 °C for 3 h is sufficient for all three transformations during the reaction. Furthermore, crystallization of the crude product with n-heptane afforded **11** with 92% yield and 96% purity, eliminating the need (Zhang et al. 2013) for column chromatography. Similar to previously reported (Guo et al. 2019), we observed allergenic properties of intermediate **11** that required special handling described in detail in the experimental section.

For the synthesis of **1**, we optimized a new procedure which starts with fluorination of the dichloro groups in **11**

(Scheme 3). Commonly used conditions with KF/TBAB in DMSO were preferred since these conditions have been widely applied and afford acceptable yields (60–65%) (Guo et al. 2019; Jordis and Beldar 2009). To improve the yield of **12,** we run a series of test reactions. Based on the trial reactions we conducted, the optimum conditions were found to be DMSO as the solvent and KF and TBAB as the reagents. Among those trials, 18-Crown-6 (crown ether) was also found to be as high yielding. However, due to its cost-effectiveness, TBAB was preferred as the optimum reagent to yield the intermediate **12**.

In the earlier methods, the difluoro intermediate (**12**) is extracted with an organic solvent as diethyl ether (Guo et al. 2019) or ethyl acetate (Jordis and Beldar 2009) followed by column chromatography. However, we observed sublimation of **12** under vacuum which reduced the yield dramatically (< 40%). Therefore, we sought to extract **12** with a solvent and use it directly for the next reaction. Among the tested solvents (i.e., n-hexane, toluene, and ethyl acetate), toluene was preferred since **12** could be extracted with toluene with acceptable purity (68%), while ethyl acetate extraction yielded a black and greasy solution. Although n-hexane extraction also yielded a clean solution of **12** with 99% purity, toluene would bear the advantage of safety for large-scale applications (Joshi and Adhikari 2019). Therefore, we used a toluene solution of **12** in a biphasic reaction with aqueous NaOH for the hydroxylation at the position-3 (Scheme 3). Vigorous mixing of **12** with 2 N NaOH at room temperature yielded the sodium salt **14c** in the aqueous phase. Removal of the organic phase was followed by H_2O_2 treatment of the aqueous phase for nitrile hydrolysis which afforded favipiravir as sodium salt. Next, HCl neutralization yielded favipiravir with > 99% purity. The new protocol described here afforded favipiravir with 43% yield over three steps.

Experimental

Favipiravir was characterized with ^{1}H-NMR (400 MHz, Bruker), ^{13}C-NMR (100 MHz, Bruker), ^{19}F-NMR (564 MHz, Varian), and the intermediates were characterized with ^{1}H-NMR (400 MHz, Bruker) and ^{13}C-NMR (100 MHz, Bruker). Chemical shifts for protons and carbons were reported in ppm relative to TMS. DMSO-d_6 (2.50 ppm) and DMSO-d_6 (39.52 ppm) were used as the internal standards for ^{1}H-NMR spectra and ^{13}C-NMR spectra, respectively. ^{19}F chemical shifts were reported in ppm referenced to $CFCl_3$ (δ 0 ppm) as the external standard. Starting material **3** was obtained from commercial sources and used without further purification.

6-Fluoro-3-hydroxypyrazine-2-carboxamide (1, Favipiravir)

Toluene (200 mL) was added to a suspension of KF (50 g, 860 mmol, 7.48 equiv.) and tetrabutylammonium bromide (TBAB) (17.4 g, 54 mmol, 0.47 equiv.) in DMSO (100 mL), and the mixture was distilled at 50 °C under vacuum to a DMSO suspension in order to remove any water. Another 200 mL of toluene was added to the remaining suspension, and the mixture was distilled once more under the same conditions. To the remaining suspension, 3,6-dichloropyrazine-2-carbonitrile (**11**, 20 g, 115 mmol) was added and the reaction mixture was stirred at 75 °C for 3 h. The product formation and reaction completion were monitored in parallel with HPLC and TLC. HPLC conditions = isocratic 1:1, H_2O (0.1% TFA): acetonitrile (0.1% TFA), 1 mL/min, room temperature (Shimadzu, LC-2030C 3D) equipped with C18 column, GL Science Inertsil Sustain, 250 × 4.6 mm, 5 µm); TLC (10:1, *n*-hexane: EtOAc). Upon reaction completion, the mixture was cooled to room temperature, water was added (100 mL), and the mixture stirred for another 15 min before toluene addition (100 mL). Then, the mixture was taken in a separating funnel to remove the water phase. The brown-colored organic phase was washed with water (100 mL) and saline solution (3 × 100 mL), respectively. Charcoal (6 g) was added, stirred for an hour at room temperature, and filtered affording a light brown solution of **12** in toluene. To this, 2 N NaOH solution (200 mL) was added and stirred vigorously at room temperature for 2 h. The mixture was taken in a separating funnel to obtain **14c** as the sodium salt of **14a** in aqueous phase. To this aqueous solution, charcoal (6 g) was added, stirred at room temperature for an hour, and filtered. To the filtrate, H_2O_2 (15 g) was added dropwise on an ice bath and the mixture was stirred at room temperature for an hour before heating to 45 °C. Then, 24 mL of concentrated HCl was added dropwise to adjust the pH to 1.6 that led to precipitation of favipiravir. The mixture was cooled down and filtered. The solid was washed with 20 mL cold water and 20 mL cold ethanol, respectively, and dried under vacuum at 50 °C yielding 6.9 g (49.6 mmol) favipiravir with > 99% purity (43% yield over three steps). The product was further crystalized in ethanol to yield a light-yellow solid. mp: 188–191 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.41 (s, 1H), 8.75 (s, 1H), 8.50 (d, J = 7.5 Hz, 2H). ^{13}C-NMR (101 MHz, DMSO-d_6): δ 168.83, 159.80, 152.48 (d, J = 244 Hz), 136.21, 122.02. ^{19}F-NMR (564 MHz, DMSO-d_6): δ −92.80. NMR spectra are consistent with the literature (Achanta et al., 2021; Guo et al., 2019; Liu et al., 2017; Zhang et al., 2013). ESI–MS calculated for $C_5H_4FN_3O_2$—H $[M\text{-}H]^-$ (156.02); found, 155.70.

6-Dichloropyrazine-2-carbonitrile (11)

Intermediate **11** should be handled with special caution since it is allergenic to the skin (Guo et al., 2019). Wearing double layers of gloves and a respirator is highly recommended. $POCl_3$ (153.3 g, 1 mol, 4 equiv.) was added to 6-bromo-3-hydroxypyrazine-2-carboxamide (**18**) (55 g, 0.25 mol) at room temperature. Then, the mixture was heated to 80 °C in 15 min to give a homogeneous mixture. To this solution, DIPEA (96.9 g, 0.75 mol, 3 equiv.) was added and the reaction mixture was stirred at 80 °C for 3 h. The mixture was cooled down to room temperature, and ice cubes (1000 g) were added slowly while stirring. The solution was extracted with ethyl acetate (3 × 500 mL), and the organic fractions were combined, stirred with charcoal (5 g) at room temperature, filtered, and concentrated. The crude was taken in 1000 mL n-heptane, heated to 90–92 °C, then allowed to cool to room temperature, filtered, and the crystals were dried for 30 min at 40 °C under vacuum yielding **11** as yellow crystals (40 g, 0.23 mol, 92% yield). mp: 92–94 °C (Lit: 93–94, 87–88; 89.7–89.8 °C).(Jordis and Beldar 2009; Liu et al. 2017; Guo et al. 2019) ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.03. ^{13}C-NMR (101 MHz, DMSO-d_6): δ 149.20, 148.25, 146.52, 128.36, 113.67.

Methyl 3-aminopyrazine-2-carboxylate (15)

To a cooled suspension of 3-aminopyrazine-2-carboxylic acid (**3**, 243 g, 1.75 mol) in 2430 mL methanol (1803 g, 56.3 mol, 32 equiv.), concentrated H_2SO_4 (243 mL, 4.53 mol, 2.6 equiv.) was added dropwise over two hours. The reaction mixture was then stirred at room temperature for 2 days followed by evaporation at 50 °C to remove the methanol. The remaining mixture was treated with 1600 mL solution of 320 g Na_2CO_3 in water to adjust the pH to 7.5. The suspension was suction filtered, and the solid was dried under vacuum at 50 °C for 24 h, yielding 380 g dark brown solid crude product. The crude product **15** was used directly for the next reaction (Compound **16**, Method-1). Alternatively, the crude product was extracted three times with ethyl acetate water (500 × 500 mL) to remove the salt by-product (Na_2SO_4). Then the organic phases were concentrated and dried and the crude product **15** was used for the next step (Compound **16**, Method-2) without further purification. mp:169–170.8 °C (Lit: 172.1–172.8 °C).(Zhang et al. 2013) ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.26 (d, J = 2.2 Hz, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.35 (s, 2H), 3.84 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-d_6): δ 166.50, 155.92, 147.89, 132.52, 123.17, 52.16.

Methyl 3-amino-6-bromopyrazine-2-carboxylate (16)

Method 1

TO a suspension of **15** (93.5 g) in 467 mL acetonitrile, *N*-bromosuccinimide (NBS, 57 g, 0.32 mol) was added in portions under nitrogen atmosphere and stirred at room temperature for 24 h. Then, 200 mL solution of 40 g Na_2CO_3 in water was added to adjust the pH to 7–8, the mixture was filtered, and the solid was dried under vacuum. The crude product was dissolved in 1.2 L CH_2Cl_2 refluxing for 30 min, and the warm suspension was filtered off to remove any insoluble impurities. The filtrate was concentrated; the crude was taken in 1 L 95% ethanol, refluxed to dissolve, then gradually cooled off for crystallization, filtered, and dried under vacuum at 50 °C yielding 33 g **16** (0.142 mmol, 33% yield over two steps) with 96% purity.

Method 2

TO the extraction isolated **15** (33 g, 0.215 mmol) in 328 mL acetonitrile, portions of NBS (40.2 g, 0.226 mmol, 1.05 equiv.) were added under nitrogen atmosphere and the reaction was stirred for 24 h at room temperature. Then, 200 ml solution of 40 g Na_2CO_3 in water was added to adjust the pH to 7–8, and without filtering, the mixture was concentrated to remove acetonitrile. The remaining precipitate was dried under vacuum and then dissolved in 0.5 L CH_2Cl_2 refluxing for 30 min. The warm suspension was filtered off to remove insoluble impurities. The filtrate was concentrated, and the crude was taken in 1 L 95% ethanol, refluxed to dissolve, then gradually cooled off for crystallization, filtered, and dried under vacuum at 50 °C yielding 44 g **16** (0.19 mmol, 88% yield). mp: 174.4–175.2 °C (Lit: 174–176 °C) (Liu et al. 2017). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.43 (s, 1H), 7.57 (s, 2H), 3.85 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-d_6): δ 165.41, 155.00, 150.20, 122.69, 122.42, 52.39.

Methyl 6-bromo-3-hydroxypyrazine-2-carboxylate (17)

A method similar to those reported earlier (Zhang et al. 2013; Liu et al. 2017) was used with modification. Portions of $NaNO_2$ (2.2 g, 31.4 mmol, 1.5 equiv.) were added to concentrated H_2SO_4 (15 mL, 280 mmol) while stirring on a water bath (50 °C) until a clear solution is obtained. This mixture was added dropwise to a solution of **16** (5 g, 21.5 mmol) in concentrated H_2SO_4 (15 mL, 280 mmol) over 20 min on an ice bath. Then, the ice bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The mixture was added to 200 mL ice-water dropwise over 30 min and stirred for another 30 min. After the pH was

adjusted to pH 5 with 10 mL solution of 2 g NaOH in water, the product was extracted with ethyl acetate (3 × 100 mL). The organic phases were combined, washed with H_2O, concentrated, and dried under vacuum at 50 °C, yielding yellow-cream-colored solid (4.45 g, 19.1 mmol, 89% yield). mp: 117.6–119 °C (Lit: 120–122 °C).(Liu et al. 2017) TLC: EtOAc:PE (1:1). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.90 (s, 1H), 8.40 (s, 1H), 3.84 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-d_6): δ 163.19, 52.63.

6-Bromo-3-hydroxypyrazine-2-carboxamide (18)

A solution of **17** (3 g, 12.9 mmol) in aqueous ammonia (30 mL, 32%) was stirred at room temperature for 3 h. Then the pH was adjusted to pH 4 with 50 mL 6 N HCl; the precipitate was filtered, washed with water, and dried under vacuum at 50 °C overnight yielding 2.5 g cream colored solid (11.47 mmol, 89% yield). mp: dark color appearance at 189–194 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.56 (s, 1H), 8.84 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H). ^{13}C-NMR (101 MHz, DMSO-d_6): δ 166.53, 166.30, 147.21, 132.74, 116.98.

Conclusion

In summary, we have developed a novel procedure for the synthesis of favipiravir via 3,6-dichloropyrazine-2-carbonitrile (**11**). Since we eliminated the need to purify intermediate **12**, the current method would contribute to the economical, scalable, and facile synthesis of favipiravir, which is a generic antiviral drug used in clinic worldwide. Moreover, this alternative synthesis of favipiravir could provide advantages in novel antiviral drug development from favipiravir analogs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11696-022-02595-1.

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