A convenient synthesis of gimeracil

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A practical three-step synthetic approach to gimeracil in a 68% overall yield is described, using 2,4-dimethoxypyridine as the starting material with 3,5-dichloro-2,4-dimethoxypyridine and 3,5-dichloro-2,4-dihydroxypyridine as intermediates. The advantages of this procedure include short reaction steps, simple operation and good yield.

Keywords: gimeracil, synthesis of gimeracil, S-1, protodechlorination, S_NAr

The anti-cancer drug S-1 (trade name Teysuno in Japan) contains three ingredients: tegafur (**1**), gimeracil (**2**) and oteracil (**3**). It is commonly used for the treatment of advanced gastric cancer (Fig. 1).[1] Recently, it has also been used in combination with cisplatin to treat other kinds of cancers, such as head and neck cancer, colorectal cancer and non-small-cell lung cancers in several countries.[2–4] Within the drug, the molar ratio of tegafur, gimeracil and oteracil is 1:1:0.4.[5] Among these ingredients, tegafur (**1**) is the actual chemotherapeutic agent. It is a prodrug of 5-fluorouridine (5-FU). Gimeracil (**2**) can reversibly block dihydropyrimidine dehydrogenase (DPD), resulting in higher 5-FU levels and a prolonged half-life.

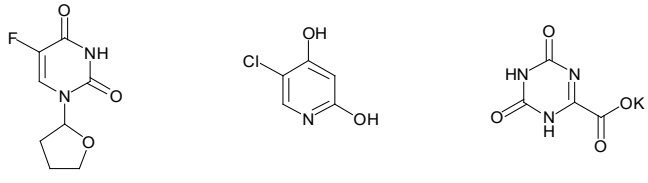
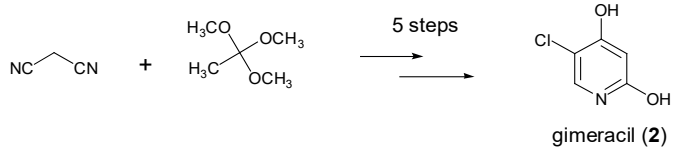


Fig. 1 Structures of tegafur (**1**), gimeracil (**2**) and oteracil (**3**).

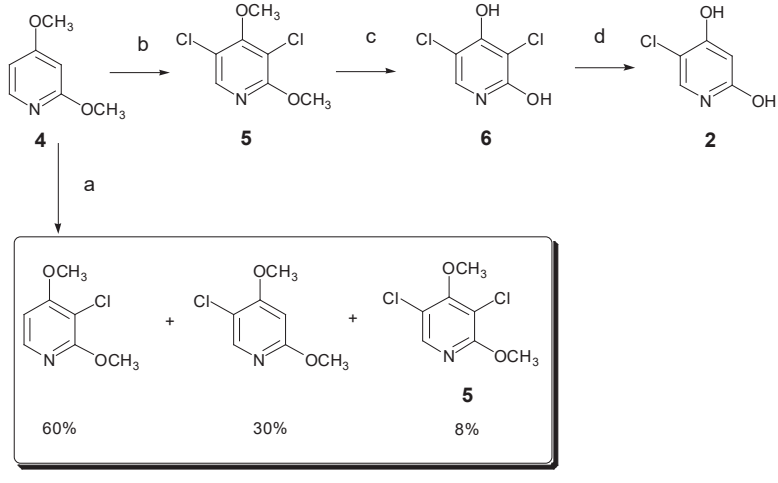
Gimeracil (**2**), 5-chloro-2,4-dihydroxypyridine, has been known for over 60 years with several synthetic methods reported.[6–9] However, most of these methods have several drawbacks such as long synthetic steps, necessity of the use of special equipment (*e.g.* a sealed tube) and time-consuming procedures. To the best of our knowledge, the conventional manufacturing procedure is based on the synthetic route reported by Ogawa and co-workers in 1993.[9] This synthetic route involves five steps from commercially available malononitrile and trimethyl orthoacetate (Scheme 1). As a part of our investigation of the medication S-1, we have developed an efficient three-step preparation of gimeracil from easily available 2,4-dimethoxypyridine (**4**), which can be purchased from chemical reagent companies such as Alfa Aesar. This procedure for gimeracil has been patented by us and reported in Chinese.[10] Here we report the details of our investigations.

Results and discussion

Our synthetic method is outlined in Scheme 2. The starting material 2,4-dimethoxypyridine (**4**) could be prepared from 2,4-dichloropyridine by nucleophilic substitution of the chlorine atoms with freshly prepared sodium methoxide in *N*-methyl-2-pyrrolidone under a nitrogen atmosphere.[11] Thus,



Scheme 1 The most widely used synthetic route to gimeracil (**2**) in industry.



Scheme 2 Reagents and conditions: (a) NCS (1.1 equiv.), acetonitrile, 50 °C; (b) NCS (2.2 equiv.), acetonitrile, 50 °C, 88%; (c) 3 M HCl, 70 °C, 90%; (d) NaI, AcOH, 60 °C, 86%.

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2,4-dimethoxypyridine (**4**) was first chlorinated at both C-3 and C-5 positions to afford 3,5-dichloro-2,4-dimethoxypyridine (**5**) in 88% yield, with *N*-chlorosuccinimide (NCS) as the chlorination reagent. Selective monochlorination at the C-5 position using NCS was attempted, but the regioselectivity was poor. The main product was 3-chloro-2,4-dimethoxypyridine instead of 5-chloro-2,4-dimethoxypyridine (Scheme 2, path a). Sulfuryl chloride, another widely used chlorination reagent, gave low yields (8–10%). Compound **5** was hydrolysed in hydrochloric acid to afford 3,5-dichloro-2,4-dihydroxypyridine (**6**) in 90% yield.

Previous reports revealed that the halogen atoms at the C-3 and C-5 positions behaved rather differently.[6] When treated with concentrated hydrobromic acid, only the halogen atoms at the C-3 position could be removed.[6] Thus, den Hertog and co-workers reported that 5-chloro-2,4-dihydroxypyridine (**2**) could be prepared by heating compound **6** with a solution of hydrobromic acid and sodium bisulfite.[6] However, this synthetic procedure needed some severe conditions, such as high temperature (200 °C) and special equipment (sealed tube), making this protocol unsuitable for large scale preparation. It was assumed that the reaction might proceed by protonation of the enol and then abstraction of the chloride by bromide ions to reform the pyridine. Since iodide ions exhibit much stronger nucleophilicity than bromide ions, we thought to improve the synthetic procedure by using iodide ions as the nucleophiles. It was found that the C-3 chlorine atom was removed by heating compound **6** in a mixture of sodium iodide and acetic acid at 60 °C in excellent yield.

In conclusion, we have developed a convenient three-step synthetic approach to 5-chloro-2,4-dihydroxypyridine (**2**) in 68% overall yield from commercially available 2,4-dimethoxypyridine (**4**). This procedure has potential for industrial production with the advantages of short steps, simple operations and good yield.

Experimental

Commercial reagents were used without further purification. Melting points were measured on a SGW X-4 (INESA) melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) instrument. ^{13}C NMR spectra were obtained on a JNM-EX400 (100 MHz) instrument. Mass spectra (MS) were determined on a Bruker MicroTof II mass spectrometer or a Waters High Resolution UPLC-TOFMS spectrometer. IR spectra were obtained using KBr disks on a FTIR Bruker Tensor 27 spectrometer and are given in the ESI for compounds **5**, **6** and **2**.

Synthesis of 2,4-dimethoxypyridine (**4**)[11]

Freshly prepared sodium methoxide (24 g, 0.44 mol) was added to a solution of 2,4-dichloropyridine (15 g, 0.10 mol) in anhydrous *N*-methyl-2-pyrrolidone (80 mL). The resulting mixture was stirred at 120° C for 6 h. The mixture was then cooled to room temperature, diluted with ethyl acetate (800 mL) and washed with water. The organic layer was dried over Na_2SO_4 and concentrated to give 2,4-dimethoxypyridine (**4**) as a colourless oil, which was pure enough to use in the next step: Yield 11.2 g (80%); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.80 (s, 3H), 3.84 (s, 3H), 6.33 (d, J = 2.0 Hz, 1H), 6.60 (dd, J = 2.0 Hz, J = 5.6 Hz, 1H), 7.97 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.5, 165.4, 147.4, 106.1, 93.8, 55.3, 53.1; HRMS (ESI) *m/z* calcd for $C_7H_{10}NO_2$: $[M + H]^+$: 140.0706; found: 140.0707.

Synthesis of 3,5-dichloro-2,4-dimethoxypyridine (**5**)

NCS (25.0 g, 187 mmol) was added to a solution of 2,4-dimethoxypyridine (**4**) (10.0 g, 71.9 mmol) in acetonitrile (70 mL). The mixture was stirred for 3 h at 50 °C before it was evaporated to dryness. Water (50 mL) was poured into the residue. The precipitate was collected, washed with water and dried to afford a crude product. This was crystallised from anhydrous ethanol to give product **5** as a colourless solid: Yield 13.1 g (88%); m.p. 49–50 °C (lit.[12] 57 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.94 (s, 3H), 3.95 (s, 3H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.2, 159.9, 144.5, 118.9, 111.8, 61.5, 55.2; LRMS (ESI) *m/z* (%): 208 (100) [M ($^{35}Cl_2$) + 1]$^+$, 210 (62) [M (^{35}Cl, ^{37}Cl) + 1]$^+$, 212 (15) [M ($^{37}Cl_2$) + 1]$^+$; HRMS (ESI) *m/z* calcd for $C_7H_8{}^{35}Cl_2NO_2$: $[M + H]^+$: 207.9927; found: 207.9942; calcd for $C_7H_8{}^{35}Cl^{37}ClNO_2$: $[M + H]^+$: 209.9898; found: 209.9916; calcd for $C_7H_8{}^{37}Cl_2NO_2$: $[M + H]^+$: 211.9871; found: 211.9887.

Synthesis of 3,5-dichloro-2,4-dihydroxypyridine (**6**): Compound **5** (10.0 g, 48.0 mmol) and 3 M hydrochloric acid (50 mL) were added to a reaction flask. The reaction mixture was heated for 6 h at 70 °C and then cooled to room temperature to precipitate compound **6**. The precipitate was collected, washed with water (70 mL) and oven-dried to afford **6** as a colourless solid: Yield 7.8 g (90%); m.p. 298–301 °C (lit.[13] 298–303 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61 (s, 1H), 11.89 (br, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.6, 158.4, 131.9, 106.2, 105.0; LRMS (ESI) *m/z* (%): 180 (100) [M ($^{35}Cl_2$) + 1]$^+$, 182 (65) [M (^{35}Cl, ^{37}Cl) + 1]$^+$, 184 (12) [M ($^{37}Cl_2$) + 1]$^+$; HRMS (ESI) *m/z* calcd for $C_5H_4{}^{35}Cl_2NO_2$: $[M + H]^+$: 179.9614; found: 179.9612; calcd for $C_5H_4{}^{35}Cl^{37}ClNO_2$: $[M + H]^+$: 181.9585; found 181.9582; calcd for $C_5H_5{}^{37}Cl_2NO_2$: $[M + H]^+$: 183.9557; found: 183.9559.

Synthesis of 5-chloro-2,4-dihydroxypyridine (**2**): A mixture of compound **6** (8.0 g, 44 mmol), acetonitrile (100 mL), acetic acid (3 mL) and sodium iodide (13.2 g, 88 mmol) was heated for 8 h at 60 °C. Then the mixture was cooled to room temperature and poured into 10% sodium thiosulfate solution (200 mL) to precipitate a colourless solid, which was recrystallised from water to give pure compound **2**: Yield 5.6 g (86%)**;** m.p. 272–273 °C (lit.[7] 273–274 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.70 (s, 1H), 7.51 (s, 1H), 11.29 (br, 2H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5, 163.2, 134.6, 105.6, 98.7; LRMS (ESI) *m/z* (%): 146 (100) [M (^{35}Cl + 1]$^+$, 148 (30) [M (^{37}Cl) + 1]$^+$; HRMS (ESI) *m/z* calcd for $C_5H_5{}^{35}ClNO_2$: $[M + H]^+$: 146.0003; found: 146.0012; calcd for $C_5H_5{}^{37}ClNO_2$: $[M + H]^+$: 147.9975; found: 147.9975.

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Electronic Supplementary Information

The ESI (^{1}H NMR, ^{13}C NMR and IR spectra of compounds **2**, **5** and **6** and the ^{1}H NMR and ^{13}C NMR spectra of **4**) is available through http://ingentaconnect.com/content/stl/jcr/2018/00000042/00000001/ art00008

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