

A practical synthesis of *N*-allyl/propargyl-substituted 5-fluorouracils

Shijie Zhang,^{a,b} Huhui Xia,^c Jian Sun,^d and Wei Zhou^{*c}

^aAcademy of Chinese Medical Sciences, Zhejiang Chinese Medical University, Hangzhou 310053, China.

^bZhejiang Medicine Co., Ltd. Xinchang Pharmaceutical Factory, Shaoxing 312500, China.

^cCollege of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, China

^dQuanjiao NATA Opto Electronic Materials Ltd., Chuzhou 239514, China.

Email: zhouwei@zjut.edu.cn

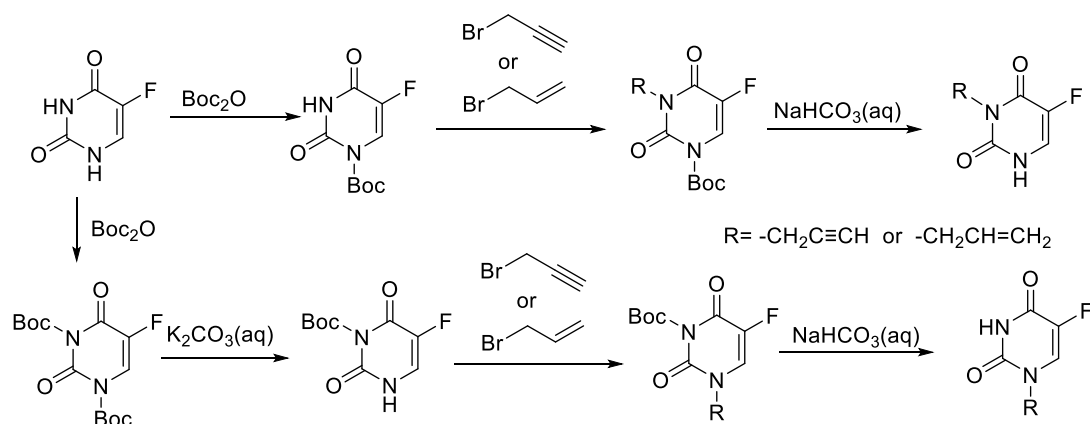
Received 10-13-2022

Accepted Manuscript 12-20-2022

Published on line 01-01-2023

Abstract

Monosubstituted *N*-allyl/propargyl-5-fluorouracils are versatile intermediates for the structural modification of 5-fluorouracil derivatives. However, the regioselective synthesis of these monosubstituted 5-fluorouracils is a challenge. Thus, in the current research work, a practical method for synthesizing *N*₁/*N*₃-allyl/propargyl-5-fluorouracils was developed with di-tertbutyl dicarbonate acting as a protective reagent. The process is easy to operate, gives a good regioselectivity, satisfying yields and a simple post-treatment.



Keywords: 5-Fluorouracil, allyl, propargyl, regioselective synthesis

Introduction

5-Fluorouracil (5-FU, **1**) is an antimetabolite acting as a bioisostere of the natural uracil in living body, and has been widely used in the treatment of colorectal cancer and several solid tumors.¹ 5-FU derivatives incorporating pharmacologically active natural or synthetic molecules, such as 5-FU linked with podophyllotoxin, colchicine, parthenolide, coumarins, thymoquinone, emodin, camptothecin, cisplatin, oxaliplatin, tamibarotene and chalcone, have attracted much attention of many researchers in the field of medicinal chemistry.² Recently, many structural modifications have been focused on merging a particular pharmacologically active molecule at the N_1 or N_3 position of 5-FU using a triazole linkage in order to achieve a higher bioactivity. For example, 5-FU derivatives, incorporating the bioactive molecules parthenolide **3a**, thymoquinone **3b**, or glucose derivative **3c** incorporating the click triazole linker, have shown potential anticancer activities.^{3–5} Moreover, 5-FU with triazole-linked polyheterocyclic compound **3d** has been reported to exhibit a superior antibacterial activity (Figure 1).⁶

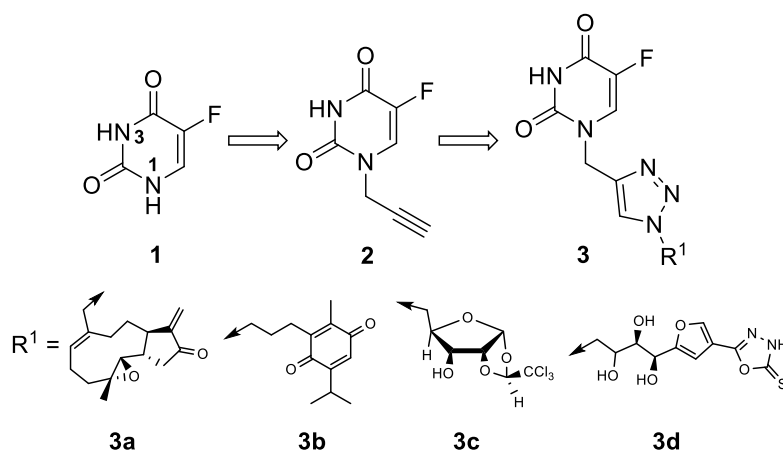
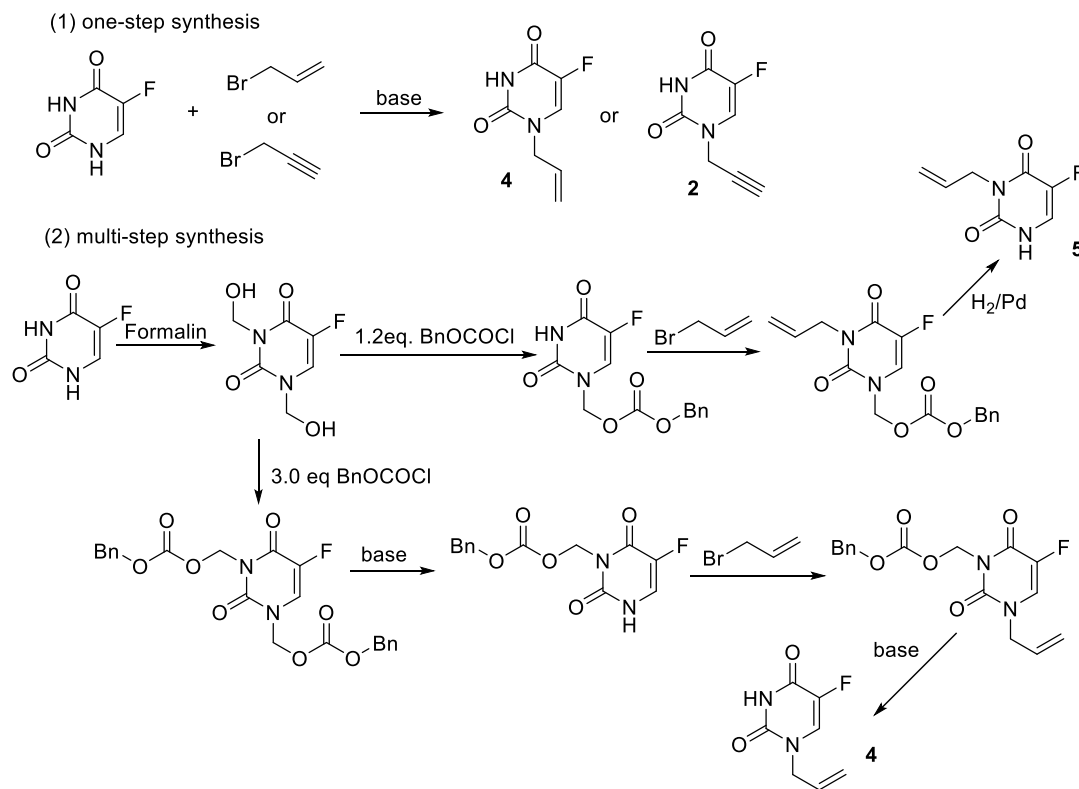


Figure 1. Chemical structures of 5-FU, 1-propargyl-3H-5-FU, and its triazole derivatives.

Since triazole moieties have been developed as versatile pharmacophoric linkers, connecting two biological units into one molecule called hybrids,^{7–8} alkyne or alkene-decorated 5-FUs, especially 1-propargyl-5-FU **2**, have been used as a key intermediate to furnish various isoxazole or triazole-functionalized 5-FU derivatives **3** via 1,3-dipolar cycloaddition reactions with nitrile oxides or azide dipoles.

Given the proved applications of allyl or propargyl-containing 5-FUs in the development of the bioactive 5-FU derivatives, extensive research has been focused on the synthesis of 1-propargyl-5-FU **2** and 1-allyl-5-FU **4**. A common method for the preparation of N_1 -substituted 5-FUs (**2** and **4**) was through nucleophilic substitution of 5-FU with bromopropyne or bromopropylene in the presence of a base such as K₂CO₃, NaH or DBU (Scheme 1, eq 1).^{3, 9–12} Although this method provides a simple and direct route to propargyl or allyl-monosubstituted 5-FUs, the poor regioselectivity and low reaction yields are still challenging problems. In a modified method, the combination of Pd(PPh₃)₄/1,1'-Bis(diphenylphosphino)ferrocene(DPPF) and allyl acetate was used instead of bromopropylene, giving N_1 -allyl-5-FU **4** in a moderate yield.¹³ Alternatively, a multiple-step pathway could be used to synthesize the monosubstituted 5-FUs, where 5-FU was first transformed into the key intermediates featuring N_1 -CH₂OCOOBn or N_3 -CH₂OCOOBn by multiple steps, followed by allylation and deprotection to give allyl-substituted 5-FUs **4** and **5** (Scheme 1, eq 2).¹⁴ Although multiple methods have been utilized for the synthesis of propargyl/allyl-substituted 5-FUs, there are some disadvantages such as low reaction

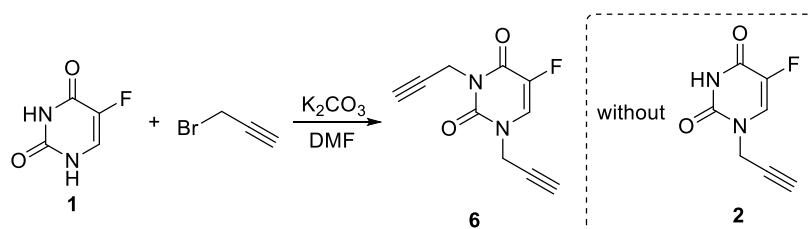
yields,¹⁰⁻¹² using an expensive catalyst¹³ and complex synthetic procedures.¹⁴ Furthermore, few of these methods were involved in the preparation of *N*₃-substituted 5-FUs (**7** and **5**). Therefore, it is still of interest to develop a general and efficient method for the synthesis of allyl/propargyl-monosubstituted 5-FUs.



Scheme 1. 1) One-step synthesis of 5-FUs **2** and **4**, and 2) multi-step synthesis of 5-FUs **4** and **5**.

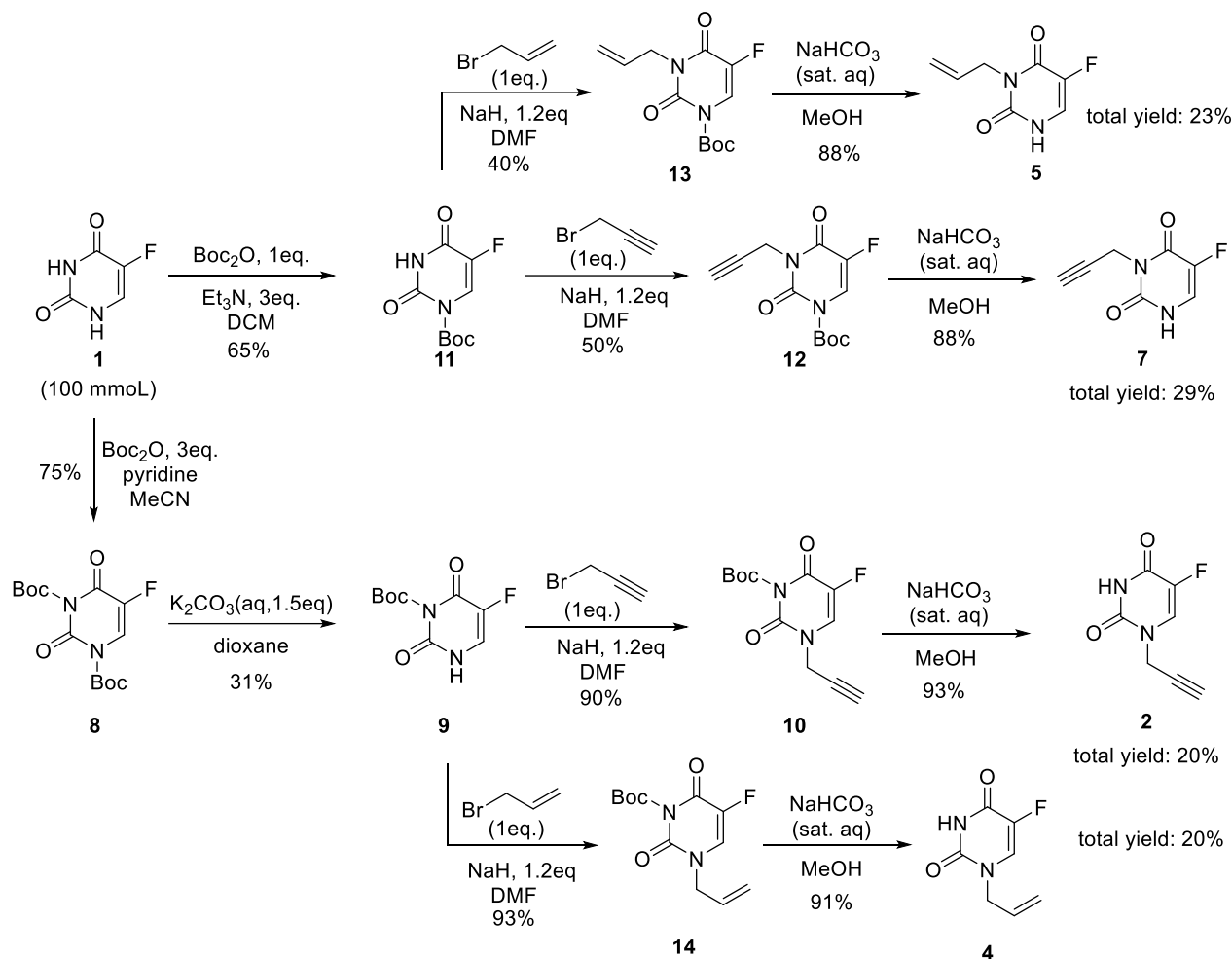
Results and Discussion

The methods reported to synthesize 1-propargyl-5-FU **2** from the reaction of 5-FU and bromopropyne using K_2CO_3 as a base in DMF have problems of a low regioselectivity and a poor yield.^{3,9} To improve the regioselectivity and yield, the reaction conditions of 5-FU and bromopropyne with K_2CO_3 (1 equiv to 5-FU) in DMF were optimized (Table S1, see supporting information); however, a single product *N*₁, *N*₃-dipropargyl-5-FU **6** was obtained instead of *N*₁-propargyl-5-FU **2**. Interestingly, no trace of compound **2** was detected by ¹H-NMR analysis of the isolated product (Scheme 2).



Scheme 2. The reaction of 5-FU and bromopropyne with K_2CO_3 as a base.

Usually, the proton N_1 -H of 5-FU is much more reactive than that of the N_3 position. A plausible reaction mechanism was assumed, where the proton at the N_1 position of 5-FU was firstly replaced by propargyl, and the resulting intermediate significantly improved the reaction activity of the proton at the N_3 position. Therefore, there was no single substitution product **2**, but always the double substitution product **6**. While this reaction was carried out with 5-FU and bromopropylene, it was observed that N_1 , N_3 -diallyl-5-FU and N_1 -allyl-5-FU were both generated. In this reaction mechanism, N_1 -allyl-5-FU is formed in the first step, and then a double substituted product is generated.



Scheme 3. Synthetic route of N -monosubstituted allyl/propargyl-5-FU.

Then, the synthesis of the monosubstituted 5-FUs by a multi-step method was evaluated with a strategy of protection/alkylation/deprotection. Since the N -protecting groups were commonly used to prepare pyrimidine derivatives, such as benzoyl, trichloroethoxyformyl, benzyloxyformyl, benzyl and diphenylmethyl moieties, different N -protecting methods were tested and ultimately di-*tert*-butyl dicarbonate (Boc_2O) was selected as the N -protecting reagent of the starting material 5-FU **1**. After several optimizations of the reaction conditions, N_1 - Boc -substituted intermediate **11** was directly obtained in 65% yield, by the regioselective reaction of 5-FU **1** and 1.0 equiv of Boc_2O , with Et_3N as a base. In contrast, N_3 -monosubstituted 5-FU **9** needed a reaction sequence of N_1 , N_3 -di- Boc protection and regioselective deprotection of N_1 - Boc group. In detail, N_1 , N_3 -di- Boc -5-FU **8** was provided by reacting 5-FU **1** and 3.0 equiv of Boc_2O with pyridine as a base, followed by the regioselective

deprotection of N_1 -Boc group to give the desired N_3 -Boc-5-FU **9**. Then the subsequent propargylation of intermediates **11** and **9** were performed with bromopropyne, and finally, the desired N_3 -propargyl-5-FU and N_1 -propargyl-5-FU (**7** and **2**) were prepared after deprotection of the Boc group, with total yields of 29% and 20%, respectively (Scheme 3). Using the same procedure, when bromopropylene was used instead of bromopropyne, the corresponding allyl-substituted 5-FUs, **4** and **5**, were obtained with total yields of 20% and 23%, respectively (Scheme 3).

Conclusions

In summary, the developed method uses 5-FU as starting material and Boc anhydride as a protective reagent to regioselectively produce N_1/N_3 -Boc-5-FU, and provides a practical synthesis of allyl/propargyl-monosubstituted 5-FUs. This method is easy to operate, leads to a good regioselectivity, satisfying yield and simple post-treatment. The produced allyl/propargyl-functionalized 5-FUs can have wide applications in the subsequent preparation of diverse 5-FU derivatives with specific pharmacological activities.

Experimental Section

General. Melting points were recorded using the XRC-1 apparatus and are uncorrected. IR spectra were obtained on a Thermo Nicolet Avatar 370 FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III spectrometer at 600 MHz using TMS as internal standard. HRMS spectra were recorded on a Waters GCT Premier instrument with EI mode. All the chemicals and solvents were analytical reagents and commercially available and used as received.

Synthesis of 1-Boc-5-FU (11).¹⁵ A mixture of 5-FU (13.0 g, 100 mmol), Boc anhydride (22.0 g, 100 mmol), and triethylamine (43.4 mL) in DCM (200 mL) was stirred at 20 °C until 5-FU disappeared by TLC monitoring. The solvent was concentrated under vacuum, and the crude product was purified by column chromatography to obtain **11**, white solid, 15.0 g, yield 65%, mp 148-150 °C [lit¹⁵ 149-150 °C]. ^1H NMR (600 MHz, DMSO- d_6) δ 11.95(br, 1H, NH), 8.19(d, J 7.2 Hz, 1H, ArH), 1.52(s, 9H, C(CH₃)₃); ^{13}C NMR (151 MHz, DMSO- d_6) δ 157.5(d, J 27.0 Hz), 147.9, 146.6, 140.3(d, J 234.3 Hz), 125.0(d, J 37.1 Hz), 86.5, 27.8.

Synthesis of 1-Boc-3-propargyl-5-FU (12).¹⁰ 1-Boc-5-FU (4.6 g, 20 mmol) was mixed with 60% NaH (0.96 g, 24 mmol) in DMF (50 mL) and stirred for 45 min at 0–5 °C. Bromopropyne (2.4 g, 20 mmol) was added dropwise and then stirred at rt until no reactant was detected by TLC. The mixture was poured into ice-water, extracted with ethyl acetate, and washed with water. The organic layer was dried with anhydrous magnesium sulfate, concentrated under vacuum, and purified by column chromatography to obtain **12**, white solid, 2.7 g, yield 50%, mp 125-127 °C; IR (KBr) cm^{-1} : 215, 2984, 1712, 1683, 1356, 1211, 863, 670; ^1H NMR (600 MHz, DMSO- d_6) δ 8.34(d, J 6.6 Hz, 1H, ArH), 4.53(s, 2H, N-CH₂-C), 3.22(s, 1H, C \equiv CH), 1.55(s, 9H, C(CH₃)₃); ^{13}C NMR (151 MHz, DMSO- d_6) δ 156.2(d, J 27.2 Hz), 147.8, 146.2, 139.7(d, J 232.7 Hz), 124.5(d, J 37.0 Hz), 87.2, 78.6, 74.2, 31.2, 27.7; HRMS calcd for C₁₂H₁₃FN₂O₄: 268.0859, found 268.0857.

Synthesis of 3-propargyl-5-FU (7).¹⁶ A mixture of 1-Boc-3-propargyl-5-FU (1.5 g, 5.6 mmol), saturated NaHCO₃ (10 mL) in methanol (20 mL) was stirred at 45 °C for 45 min. The solvent was concentrated under vacuum to remove methanol and extracted with DCM (25 mL \times 3). The organic layer was dried with anhydrous magnesium sulfate, concentrated under vacuum, and purified by column chromatography to obtain **7**, as white solid, 0.83

g, yield 88%; mp 172–173 °C [lit¹⁶ 187–188 °C]; IR (KBr) cm^{-1} : 3320, 3226, 2346, 1718, 1448, 1209, 933, 772; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.29(br, 1H, NH), 7.92(t, *J* 5.8 Hz, 1H, ArH), 4.50(d, *J* 2.2 Hz, 2H, N-CH₂-C), 3.16(t, *J* 2.4 Hz, 1H, C \equiv CH). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 157.0(d, *J* 26.0 Hz), 149.6, 139.7(d, *J* 226.7 Hz), 126.0(d, *J* 31.6 Hz), 79.1, 73.6, 30.2; HRMS calcd for C₇H₅FN₂O₂: 168.0335, found 168.0331.

Synthesis of 1-Boc-3-allyl-5-FU (13). Similar procedure with the synthesis of **12** using bromopropylene (2.4 g, 20 mmol) instead of bromopropyne to obtain 1-Boc-3-allyl-5-FU **13**, white solid, 2.2 g, yield 40%, mp 70–72 °C, IR (KBr) cm^{-1} : 3230, 2976, 1715, 1658, 1467, 1223, 805, 770; ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.31(d, *J* = 6.9 Hz, 1H, ArH), 5.83–5.78(m, 1H, C=CH), 5.18–5.12(m, 2H, CH₂=C), 4.39(d, *J* 5.2 Hz, 2H, N-CH₂-C), 1.54(s, 9H, C(CH₃)₃); ¹³C NMR (151 MHz, DMSO-*d*₆) δ 156.6(d, *J* 26.7 Hz), 148.0, 146.5, 139.8(d, *J* 232.2 Hz), 132.1, 124.0(d, *J* 37.1 Hz), 117.6, 86.9, 43.7, 27.7; HRMS calcd for C₁₂H₁₅FN₂O₄: 270.1016, found 270.1018.

Synthesis of 3-allyl-1-5-FU (5).¹⁷ Similar procedure with the synthesis of **7** using 1-Boc-3-allyl-5-FU **13** (2.2 g, 8.0 mmol) instead of 1-Boc-3-propargyl-5-FU **12** to obtain **5**, white solid, 1.2 g, yield 88%; mp 67–68 °C [lit¹⁷ 78.5–80 °C]; IR (KBr) cm^{-1} : 3423, 3216, 1700, 1660, 1580, 1432, 1168, 743; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.14(br, 1H, NH), 7.88(d, *J* 5.6 Hz, 1H, ArH), 5.85–5.79(m, 1H, C=CH), 5.12–5.07(m, 2H, CH₂=C), 4.37(d, *J* 5.1 Hz, 2H, N-CH₂-C); ¹³C NMR (151 MHz, DMSO-*d*₆) δ 157.5(d, *J* 25.5 Hz), 150.0, 139.8(d, *J* 226.1 Hz), 132.5, 125.6(d, *J* 31.6 Hz), 117.1, 42.7; HRMS calcd for C₇H₇FN₂O₂: 170.0492, found 170.0499.

Synthesis of 1,3-diBoc-5-FU (8).¹⁸ A mixture of 5-FU (13.0 g, 100 mmol), acetonitrile (100 mL), Boc anhydride (66.0 g, 300 mmol), and pyridine (8 mL) was stirred at 55 °C until no 5-FU was detected by TLC. After concentration under vacuum, the residue was poured into water (50 mL) and extracted with DCM (20 mL \times 3), dried over anhydrous magnesium sulfate. The filtrate was concentrated and purified by column chromatography to obtain **8**, white solid, 25.0 g, yield 75%, mp 111–113 °C; IR (KBr) cm^{-1} : 3181, 3020, 2957, 1758, 1723, 1610, 1376, 642; ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.36(d, *J* 7.3 Hz, 1H, ArH), 1.54(s, 9H, C(CH₃)₃), 1.53(s, 9H, C(CH₃)₃); ¹³C NMR (151 MHz, DMSO-*d*₆) δ 154.9(d, *J* 29.0 Hz), 147.2, 146.8, 144.6, 139.5(d, *J* 234.8 Hz), 125.9(d, *J* 37.3 Hz), 87.7, 87.5, 27.7, 27.5; HRMS calcd for C₁₄H₁₉FN₂O₆: 330.1227, found 330.1235.

Synthesis of 3-Boc-5-FU (9).¹⁸ 1,3-diBoc-5-FU **8** (10.0 g, 30 mmol) was dissolved in dioxane (50 mL), and the mixture was added with 10 mL aqueous K₂CO₃ (6.2 g, 45 mmol) dropwise. After stirring for 8 h at rt, the mixture was concentrated under vacuum to remove dioxane. Then, water (50 mL) was added and extracted with DCM (20 mL \times 3). The organic layer was dried, concentrated and purified by column chromatography to obtain **9**, white solid, 2.4 g, yield 31%, mp 128–130 °C; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.52(br, 1H, NH), 7.98(d, *J* 6.1 Hz, 1H, ArH), 1.52(s, 9H, C(CH₃)₃); ¹³C NMR (151 MHz, DMSO-*d*₆) δ 155.6(d, *J* 27.8 Hz), 147.9, 147.5, 139.5(d, *J* 228.7 Hz), 127.7(d, *J* 31.9 Hz), 87.0, 27.5; IR (KBr) cm^{-1} : 3197, 3099, 2832, 1732, 1621, 1153, 842, 612; HRMS calcd for C₉H₁₁FN₂O₄: 230.0703, found 230.0694.

Synthesis of 3-Boc-1-propargyl-5-FU (10). A similar procedure as the synthesis of **12** using 3-Boc-5-FU **9** (0.5 g, 2.0 mmol) to obtain **10**, white solid, 0.48 g, yield 90%, mp 113–114 °C; IR (KBr) cm^{-1} : 3287, 2964, 1710, 1685, 1452, 1356, 856, 786; ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.34(d, *J* 6.6 Hz, 1H, ArH), 4.53(d, *J* 2.2 Hz, 2H, N-CH₂-C), 3.54(t, *J* 2.2 Hz, 1H, C \equiv CH), 1.53(s, 9H, C(CH₃)₃); ¹³C NMR (151 MHz, DMSO-*d*₆) δ 155.0(d, *J* 27.9 Hz), 147.2, 147.1, 139.5(d, *J* 231.7 Hz), 130.4(d, *J* 34.3 Hz), 87.7, 77.9, 77.3, 38.4, 27.5; HRMS calcd for C₁₂H₁₃FN₂O₄: 268.0859, found 268.0855.

Synthesis of 1-propargyl-5-FU (2).⁶ A similar procedure as the synthesis of **7** using 3-Boc-1-propargyl-5-FU **10** (0.48 g, 1.8 mmol) to obtain **2**, colorless crystal, 0.28 g, yield 93%; mp 168–170 °C [lit⁶ 169–171 °C]; IR (KBr) cm^{-1} : 3359, 3012, 1670, 1605, 1280, 1136, 923, 806; ¹H-NMR (600MHz, DMSO-*d*₆) δ : 11.94(br, 1H, NH), 8.13(d, *J* 6.6 Hz, 1H, ArH), 4.47(d, *J* 2.2 Hz, 2H, N-CH₂-C), 3.44(t, *J* 2.2 Hz, 1H, C \equiv CH); ¹³C NMR (151 MHz, DMSO-*d*₆) δ 157.3(d, *J* 25.9 Hz), 149.0, 139.8(d, *J* 230.6 Hz), 128.8(d, *J* 34.0 Hz), 78.0, 76.1, 36.9; HRMS Calcd for C₇H₅FN₂O₂: 168.0335, found 168.0333.

Synthesis of 3-Boc-1-allyl-5-FU (14). Similar procedure with the synthesis of **10** using 3-Boc-5-FU **9** (0.5 g, 2.0 mmol) and bromopropylene (2.4 g, 20 mmol), to obtain 3-Boc-1-allyl-5-FU **14**, white solid, 0.5 g, yield 93%, mp 123–124 °C; IR (KBr) cm^{-1} : 3053, 2932, 2154, 1689, 1396, 1257, 862, 724; ^1H NMR (600 MHz, DMSO- d_6) δ 8.22(d, J 6.8 Hz, 1H, ArH), 5.94–5.87(m, 1H, CH=C), 5.26–5.24(m, 2H, C=CH₂), 4.30(d, J 5.5 Hz, 2H, N-CH₂-C), 1.52(s, 9H, C(CH₃)₃); ^{13}C NMR (151 MHz, DMSO- d_6) δ 155.1(d, J 27.8 Hz), 147.5, 147.3, 139.4(d, J 230.7 Hz), 132.4, 131.1(d, J 33.6 Hz), 119.1, 87.4, 50.7, 27.5; HRMS calcd for C₁₂H₁₅FN₂O₄: 270.1016, found 270.1019.

Synthesis of 1-allyl-5-FU (4).¹³ Similar procedure with the synthesis of **2** using 3-Boc-1-allyl-5-FU **14** (0.5 g, 2.0 mmol) instead of 1-Boc-3-propargyl-5-FU **10** to obtain **4**, colorless needle crystal, 0.31 g, yield 91%; mp 125–126 °C [lit¹³ 101 °C]; IR (KBr) cm^{-1} : 3382, 3200, 1705, 1663, 1573, 1328, 1149, 756; ^1H NMR (600 MHz, DMSO- d_6) δ 11.82(br, 1H, NH), 8.02(d, J 6.7 Hz, 1H, ArH), 5.91–5.85(m, 1H, C=CH), 5.21–5.16(m, 2H, CH₂=C), 4.25(d, J 5.1 Hz, 2H, N-CH₂-C); ^{13}C NMR (151 MHz, DMSO- d_6) δ 157.9(d, J 25.8 Hz), 149.8, 140.2(d, J 229.4 Hz), 133.1, 130.2(d, J 33.2 Hz), 118.2, 49.8; HRMS calcd for C₇H₇FN₂O₂: 170.0492, found 170.0500.

Acknowledgements

We thank Linyan Wang from the Academy of Chinese Medical Sciences, Zhejiang Chinese Medical University for the technical support. This work was supported by Zhejiang Provincial Natural Science Foundation of China (Grant No. LTGC23C070001).

Supplementary Material

The online version of this article contains supplementary materials.

References

1. Longley, D. B.; Harkin, D. P.; Johnston, P. G. *Nat. Rev. Cancer* **2003**, 3, 330–338.
<https://doi.org/10.1038/nrc1074>
2. Cardona-G. W.; Herrera-R. A.; Castrillon-L. W.; Ramirez-M. H. *Curr. Med. Chem.* **2021**, 28, 5551–5601.
<https://doi.org/10.2174/0929867328666210211164314>
3. Ding, Y. H.; Li, S. Z.; Ge, W. Z.; Liu, Z. Q.; Zhang, X.H.; Wang, M.M.; Chen, T. Y.; Chen, Y.; Zhang Q. *Eur. J. Med. Chem.* **2019**, 183, 111706–11719.
<https://doi.org/10.1016/j.ejmech.2019.111706>
4. Ndreshkjana, B.; Capci A.; Klein V.; Chanvorachote P.; Muenzner, J. K.; Huebner, K.; Steinmann, S.; Erlenbach-Wuenssch, K.; Geppert, C. I.; Agaimy, A.; Bailout, F.; El-Baba, C.; Gali-Muhtasib, H.; Roehe, A. V.; Hartmann, A.; Tsogoeva, S. B.; Schneider-Stock, R. *Cell Death Dis.* **2019**, 10, 379–394.
<https://doi.org/10.1038/s41419-019-1611-4>
5. Halay, E.; Ay, E.; Salva, E.; Ay, K.; Karayildirim, T. *Chem. Heterocycl. Comp.* **2018**, 54, 158–166.
<https://doi.org/10.1007/s10593-018-2248-4>
6. El-Sayed, W. A.; Abdel-Rahman, A. A. H. *Z. Naturforsch.* **2010**, 65b, 57–66.
<https://doi.org/10.1515/znb-2010-0110>

7. Dheer, D.; Singh, V.; Shankar, R. *Bioorg. Chem.* **2017**, 71, 30-54.
<http://dx.doi.org/10.1016/j.bioorg.2017.01.010>
8. Xu, Z.; Zhao, S. J.; Liu, Y. *Eur. J. Med. Chem.* **2019**, 183, 111700-111736.
<https://doi.org/10.1016/j.ejmech.2019.111700>
9. Sanduja, M.; Gupta, J.; Singh, H.; Pagare, P. P.; Rana, A. *J. Saudi Chem. Soc.* **2020**, 24, 251-266.
<https://doi.org/10.1016/j.jscs.2019.12.001>
10. Weiss, J. T.; Fraser, C.; Rubio-Ruiz, B.; Myers, S. H.; Crispin, R.; Dawson, J. C.; Brunton, V. G.; Patton, E. E.; Carragher, N. O.; Unciti-Broceta, A. *Front. Chem.* **2014**, 2, 1-9.
<https://doi.org/10.3389/fchem.2014.00056>
11. Stenton, B.; Oliveira, B.; Conde, J.; Negrao, M.; Godinho Ferreira, M.; Fior, R.; Bernardes, G. *ChemRxiv*, **2018**, 1-21. This content is a preprint and has not been peer-reviewed.
<https://doi.org/10.26434/chemrxiv.7327904.v1>
12. Weiss, J. T.; Dawson, J. C.; MacLeod, K. G.; Rybski, W.; Fraser, C.; Torres-Sanchez, C.; Patton, E. E.; Bradley, M.; Carragher, N. O.; Unciti-Broceta, A. *Nat. Comm.* **2014**, 5, 4277-4285.
<https://doi.org/10.1038/ncomms4277>
13. Amblard, F.; Nolan, S. P.; Schinazi, R. F.; Agrofoglio, L.A. *Tetrahedron* **2005**, 61, 537-544.
<https://doi.org/10.1016/j.tet.2004.11.019>
14. Nagase, T.; Seike, K.; Shiraishi, K.; Yamada, Y.; Ozaki, S. *Chem. Lett.* **1988**, 1381-1384.
<https://doi.org/10.1246/cl.1988.1381>
15. Niu, H. Y.; Zhang, X. T.; Zhao, G. Y.; Li, N.; Kong, S. N.; Xiao, C.; Qu, G. R.; Guo, H. M. *CHIN. J. Org. Chem.* **2011**, 31, 695-700.
[Synthesis of N-3 Alkylation of Pyrimidine and Its Derivatives \(sioc-journal.cn\)](http://www.sioc-journal.cn)
16. Kasprzak A. ; M. Koszytkowska-Stawińska; Nowicka A. M. ; Buchowicz, W. ; Poplawska, M. , *J. Org. Chem.* **2019**, 84, 15900–15914
<https://doi.org/10.1021/acs.joc.9b02353>
17. Brooke, G. M.; Ferguson, J. A. K. J., *J. Chem. Soc., Perkin. Trans. 1*, **1986**, 515-520.
<https://doi.org/10.1039/P19860000515>
18. Buslov, I.; Hu, X. *Adv. Syn.&Cat.*, **2014**, 356, 3325-3330.
<http://dx.doi.org/10.1002/adsc.201400646>

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>)