Chinese Chemical Letters Vol. 11, No. 10, pp. 865–866, 2000

The Synthesis of 1-Aryl-5-Fluorouracil

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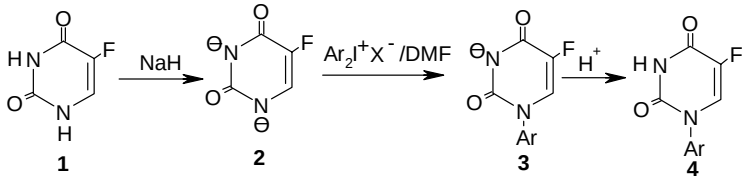
Abstract: A series of new type substituted 5-fluorouracil derivatives, 1-aryl-5-fluorouracil (**4a-4f**), were synthesized *via* diaryliodonium salts and the structure of the title compound was finally confirmed by IR, UV, ^{1}H-NMR, MS and CHN analysis.

Keywords: Synthesis, 1-aryl-5-fluorouracil.

5-Fluorouracil (5-Fu,**1**)[1] is an important antitumor drug. Some derivatives[2,3] have shown better therapeutic efficacy than 5-Fu. In order to find much more better antitumor drugs of its derivatives, several attempts have been made and many different types of its derivatives have been prepared at N_1, N_3 position[4~7]. Moreover, several different ways have been used for alkylation of 5-Fu[7~10]. However, up to now, the arylation of 5-Fu at N_1 or N_3 position hasn't been reported, and the compound of 5-Fu linked directly with aryl ring hasn't been prepared.

In this paper, we report a facile method for the synthesis of arylation products of 5-Fu *via* the diaryliodonium salts ($Ar_2I^+X^-$) reacted with 5-Fu under alkaline condition:



a. Ar=Ph- b. Ar= 4-Me-Ph- c. Ar= 4-Cl-Ph-
d. Ar= 4-MeO-Ph- e. Ar=3-NO_2-Ph- f. Ar= 4-CH_3CONH-Ph-

When **2** reacted with $Ar_2I^+X^-$, only mono-arylated products were obtained. The position of arylation in 5-Fu was determined with analogy from uracil[11], by the bathochromic shift in UV from the neutral pH to alkaline pH of the 3-substituted products. The *in vitro* antitumor activity data will be published elsewhere.

General procedure

To a stirred solution of **1** (1 mmol) in dry DMF (10 mL), NaH (2 mmol) was added and the stirring was continued for 2 hrs. Then $Ar_2I^+X^-$ (1.5 mmol) was added, and the mixture

was heated at 70~80℃ for 36~48 hrs. After the reaction was over, DMF was removed under vacuum and the residue was partioned between CH_2Cl_2 (20 mL) and water (20 mL), the aqueous layer was washed with CH_2Cl_2 (2×20 mL), then adjusted the solution to pH=3~5 with 1mol/L HCl, extracted with CH_2Cl_2 (3×20 mL), and the combined extract was dried over anhydrous magnesium sulfate. After filtration, solvent was removed. The residue was purified on a silica gel eluted with ethyl acetate: hexane=1:2~2:1. The product, a white or a yellow solid was obtained. Further purification can be recrystallized from absolute ethanol.

Reference and notes

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12. **4a**: m.p. 275~277℃, yield 65%; ^{1}HNMR: 7.47(5H, m), 8.22(1H, d, J=6.77Hz), 11.82 (1H, brs); IR: 3063, 1666, 1276, 768; UV: λ max (EtOH) 273 (pH 1, 7, 13); MS *m/z* 206(M^+), Anal. Cacld. For $C_{10}H_7FN_2O_2$, C: 58.25, H: 3.40, N: 13.59, Found: C: 58.11, H: 3.43, N: 13.66.
4b: m.p. 169~171℃, yield 57%; ^{1}HNMR: 2.41 (3H, s), 7.38 (4H, m), 7.42 (1H, d, J=6.82Hz), 9.02 (1H, brs); IR: 3069, 1683, 1271, 819; UV: λ max (EtOH) 273.5 (pH 1, 7, 13); MS *m/z* 220(M^+), Anal. Cacld. For $C_{11}H_9FN_2O_2$, C: 60.00, H: 4.09, N: 12.73, Found: C: 59.88, H: 4.11, N: 12.55.
4c: m.p. 228~230℃, yield 72%; ^{1}HNMR: 7.49 (2H, m), 7.55 (2H, m), 8.19 (1H, d, J=6.65Hz), 11.46 (1H, brs); IR: 3066, 1682, 1271, 825, 612; UV: λ max (EtOH) 274 (pH 1, 7, 13); MS *m/z* 240 (M^+), Anal. Cacld. For $C_{10}H_6ClFN_2O_2$, C: 49.90, H: 2.49, N: 11.64, Found: C: 49.98, H: 2.52, N: 11.78.
4d: m.p. 231~233℃, yield 48%, ^{1}HNMR: 3.86 (3H, s), 6.99 (2H, m), 7.27 (2H, m), 7.41(1H, d, J= 5.40Hz), 8.37 (1H, brs); IR: 3061, 1683, 1256,832; UV: λ max(EtOH) 273.5 (pH 1, 7, 13); MS *m/z* 236 (M^+), Anal.Cacld. For $C_{11}H_9FN_2O_3$, C: 55.93H: 3.81, N: 11.86, Found: C: 56.04, H: 3.88, N: 11.79.
4e: m.p. 168~170℃, yield 55%, ^{1}H-NMR: 7.21 (1H, m), 7.46 (2H, m), 7.55 (1H, d, J=6.23Hz), 7.66(1H, s), 10.39 (1H, brs); IR: 3390, 1624, 1521, 1299, 817; UV: λ max (EtOH) 257 (pH 1, 7, 13); MS *m/z* 251(M^+), Anal. Cacld. For $C_{10}H_6FN_3O_4$, C: 47.81, H: 2.39, N: 16.73, Found: C: 47.92, H: 2.44,N:16.77.
4f: m.p. 171~173℃, yield 32%, ^{1}H-NMR: 2.20(3H,s), 7.12(1H, d, J=7.40Hz), 7.23(1H, s), 7.32 (2H, m), 7.54 (2H, m), 9.76 1H, s); IR: 3300, 1688, 1670,1273, 810; UV: λ max (EtOH) 241 (pH 1, 7, 13); MS *m/z* 263(M^+), Anal. Cacld. For $C_{12}H_{10}FN_3O_3$, C: 45.63, H: 3.80, N: 15.97, Found: C: 45.58, H: 3.85, N: 15.88.

Received 31 March 2000