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The Synthesis of 6-Alkyl-5-Fluorouracil Derivatives

Jin Zong YOU[1], Shao Yuan CHEN[1], Yao Zu CHEN[1,2]*

[1]Department of Chemistry, Zhejiang University, Hangzhou 310027
[2]National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000

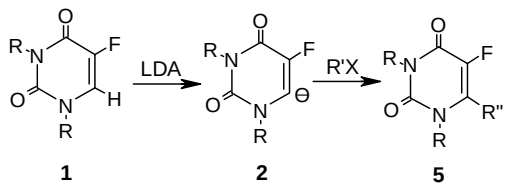
Abstract: 6-alkyl-5-fluorouracil derivatives (**5a~5f**) were synthesized by facile alkylation of lithiation of 5-fluorouracil derivatives with mthyl iodide (MeI) or alkyl trifluoromethanesulfonate (ROTf) in yield of 42~58%. We found that the methylated product was ethyl-substituted derivatives, not methyl-substituted derivatives.

Keywords: Synthesis, alkylation, 6-alkyl-5-fluorouracil derivatives.

As an antitumor drug, because of its low efficacy and high toxicity, several modifications have been made on 5-fluorouracil (5-Fu). Some compounds have been found to be highly efficient and much less toxic for the treatment of various solid tumors[1~4]. Among them, deoxyfluridine (Furtulon) has been used clinically for several years. In our previous work, we have prepared several substituted derivatives of 5-Fu and the primary result shows that some of them have certain antitumor activity[5,6]. Up to now, many N_1, N_3-substituted derivatives of 5-Fu have been synthesized [7~9]. But, 6-substituted products of 5-Fu have been seldom reported.

In recent years, some compounds of 6-substituted 5-Fu such as 6-alkoxy-, aryloxy-, alkythio-5-Fu have been prepared from 6-chloro-5-Fu, which could be synthesized through cyclization of urea and diethyl 2-fluoromalonate[10, 11]. The result showed that some of the 6-subtituted 5-Fu products exhibit excellent antitumor activity. For search of better therapeutic compounds, we investigated the reaction of lithiation of 1,3-dialkyl-5-fluorouracil (DRFu,**1**) with methyl iodide or alkyl trifluoromethanesulfonate (ROTf) (**Scheme 1**).

Scheme 1



1 **2** **5**

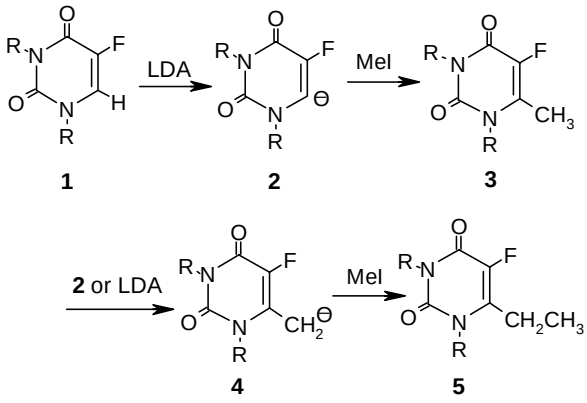
In the course of our study on the reaction, we found that when RX is methyl iodide, the reaction can proceed smoothly. But spectral data (MS, ^{1}H-NMR, IR) showed that the products were 6-ethyl –5-Fu derivatives, not 6-methyl derivatives even if $n_{MeI}/n_{DRFu} \leqslant 1$. We suppose the reaction mechanism was as follows (**Scheme 2**):

Scheme 2

a. R=Me, R'X=MeI, R''=Et; b. R=Et, R'X=MeI, R''=Et

c. R=n-Pr, R'X=MeI, R''=Et; d. R=n-Bu, R'X=MeI, R''=Et

e. R=Me, R'X=n-PrOTf, R''=n-Pr; f. R=Me, R'X=n-BuOTf, R''=n-Bu



1 **2** **3**

4 **5**

a. R=Me, b. R=Et, c. R=n-Pr, d. R=n-Bu

In order to obtain 6-methyl-5-Fu, the above reaction was quenched with water at -78℃ after the reaction began several minutes, but no 6-methyl-5-Fu was obtained, the product was 6-ethyl-5-Fu, too. We think 6-methyl-5-Fu is not stable during the reaction, it is easy to lost an end-proton to form 4e- π bond.

When ethyl iodide was employed, reaction proceeded for several days, 6-ethyl derivative was obtained, but the conversion is very low. If the reagent is propyl, butyl and other saturated halide, alkyl bromide or chloride, the reaction did not occur at all. In order to find a general method for the synthesis of 6-alkyl derivatives, we used n-PrOTf and n-BuOTf as the alkylation reagent, we found the reaction can proceed smoothly. The products were propylation and butylation derivative, without further alkylation.

General procedure

To a freshly prepared solution of LDA (2mmol) in THF (8 mL), a solution of **1** (1mmoL) in THF (5 mL) was added dropwise at -78℃ under nitrogen atmosphere in 0.5 h. After

addition, the stirring continued for 2 hrs with an ice–bath. Then a solution of R'X (MeI, n-PrOTf or n-BuOTf) (1mmol) in dry THF (5 mL) was added dropwise to above mixture at -78℃ in 0.5 h and the mixture was allowed to stand 4 h at –78~40℃, then stirred overnight at room temperature. Then, the mixture was washed with saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2×20mL). Combined the organic layers, dried over anhydrous $MgSO_4$, filtrated and removed solvent. The residue was purified by silica gel chromatography using ethyl acetate: hexane (5:2~1:4) as eluant. A yellow solid or oil was obtained.

References and notes

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12. N-PrOTf and BuOTf were prepared *in situ* by the reaction of Tf_2O and n-PrOH, n-BuOH, without further purification before use.
13. **5a**: m.p 39~41℃; yield:58%; ^{1}H-NMR ($CDCl_3$, 500MHz): 1.27 (3H, t, J=7.48Hz), 2.71 (2H, dq, J_1=7.48Hz, J_{H-F}=3.84Hz), 3.38 (3H, s), 3.44 (3H, s); IR(KBr): 2993, 1714, 1652, 1280; MS: *m/z* 186 (M^+); Anal. Calcd. For $C_8H_{11}FN_2O_2$, C: 51.61, H: 5.91, N: 15.05, Found: C: 51.75, H: 5.96, N: 15.00.
    5b: oil; yield 42%; ^{1}H-NMR ($CDCl_3$, 500MHz): 1.24 (3H,t, J=7.21Hz), 1.27 (3H, t, 7.25Hz), 1.32 (3H, t, J=7.51Hz), 2.67 (dq, J_1=7.51Hz, J_{H-F}=3.87Hz), 3.90 (2H, q, J=7.21Hz), 4.04 (2H,q, J=7.25Hz); IR (film): 2976, 1716, 1672, 1268; MS: *m/z* 214 (M^+), Anal. Calcd. For $C_{10}H_{15}FN_2O_2$, C: 56.07, H: 7.01, N: 13.08, Found: C: 55.89, H: 7.10, N: 13.21.
    5c: oil; yield 56%; ^{1}H-NMR ($CDCl_3$, 500MHz): 0.95 (3H, t, J=7.46Hz), 0.98 (3H, t, J=7.86Hz), 1.28 (3H, t, J=7.44Hz), 1.69 (4H, m), 2.68 (2H, dq, J_1=7.46Hz, J_{H-F}=3.86Hz), 3.78 (2H, t, J=7.86Hz), 3.91 (2H, t, J=7.57Hz), IR (film): 2965, 1720, 1678, 1268; MS: *m/z* 242 (M^+), Anal. Calcd. For $C_{12}H_{19}FN_2O_2$, C: 59.50, H: 7.85, N: 11.57, Found: C: 59.55, H: 7.88, N: 11.66.
    5d: oil; yield 52%; ^{1}H-NMR ($CDCl_3$, 500MHz): 0.94 (3H, t, J=7.38Hz), 0.98 (3H, t, J=7.38 Hz), 1.28 (3H, t, J=7.56Hz), 1.37~1.43 (4H, m), 1.60~1.68 (4H, m), 2.68 (2H,dq, J_1=7.56Hz, J_{H-F}=3.82Hz), 3.82 (2H, t, J=7.91Hz), 3.95 (2H, t, J=7.58Hz); IR (film): 2960, 1710, 1670,1270; MS: *m/z* 270 (M^+), Anal. Calcd. For $C_{14}H_{23}FN_2O_2$, C: 62.22, H: 8.52, N: 10.37, Found: C: 62.16, H: 8.48, N: 10.36.
    5e: oil; yield 48%; ^{1}H-NMR ($CDCl_3$, 500MHz): 0.99 (3H, t, J=7.40Hz), 1.71 (2H, m), 2.70 (2H,dq, J_1=7.45Hz, J_{H-F}=3.83Hz), 3.30 (3H, s), 3.37 (3H, s); IR (film): 2968, 1718, 1678, 1278; MS *m/z* 200 (M^+) Anal. Calcd. For $C_9H_{13}FN_2O_2$, C: 54.00, H: 6.50, N: 14.00, Found: C: 54.06,

H: 6.55, N: 14.11.

5f: oil; yield 51%; ^{1}H-NMR ($CDCl_3$, 500MHz): 0.98 (3H, t, J=7.43Hz), 1.39 (2H, m), 1.65 (2H, m), 2.71 (2H, dq, J_1=7.43Hz, J_{H-F}=3.48Hz), 3.30 (3H, s), 3.36 (3H, s); IR (film): 2970, 1710, 1672,1272; MS: *m/z* 214 (M^+), Anal. Calcd. For $C_{10}H_{15}FN_2O_2$, C: 56.07, H: 7.01, N: 13.08, Found: C: 56.16, H: 7.06, N: 13.01.

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