SHORT PAPER

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Synthesis of 1-arylated derivatives of 5-fluorouracil as potential antitumor drugs†

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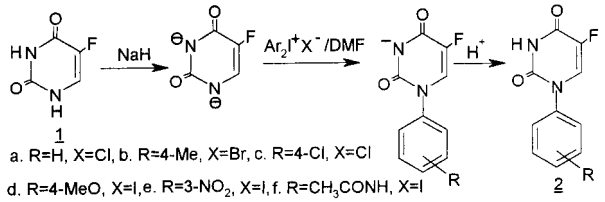
1-Aryl-5-fluorouracil derivates are synthesized by the reaction of 5-fluorouracil with diaryliodonium salts.

5-Fluorouracil (**1**)[1] is an important antitumor drug, which since its discovery has been the subject of study for the preparation of derivatives which might have improved therapeutic efficacy. Some derivatives such as 1-(tetrahydro-2-furanyl)- 5-fluorouracil (FT-207 or Ftorafur),[2] 1,3-bis(tetrahydro-2-furanyl)-5-fluorouracil (FD),[3] 1-hexylcarbamoyl-5-fluorouracil (HCFC),[4] have shown better therapeutic efficacy than **1**. In order to find improved antitumor drugs which are derivatives of **1**, many different types of its derivatives have been prepared which are substituted at the N^1 and/or N^3 positions.[5–11] However, the arylation of **1** at the N^1 or N^3 positions has not been reported. Since diaryliodonium salts are efficient electrophilic arylating agents which have been effective at C, N, S, *etc*.,[12] we investigated the reaction between **1** and diaryliodonium salts. In this paper, we report a facile method for the synthesis of arylated products of **1** from the reaction of diaryliodonium salts with **1** under basic conditions.



When **1** was reacted with sodium hydride and then $Ar_2I^+X^-$, mono-arylated products which were characterized by ^{1}H NMR, IR and typical mass fragmention patterns were obtained (see Table). The position of arylation in **1** was determined by the Shugar-Fox method[13], in which the bathochromic shift in UV from neutral to alkaline pH of the 3-substituted products of uracil (20~30 nm shift) is compared with the lack of such shift of the 1-substituted products of uracil. When the molar ratio of $Ar_2I^+X^-$ to **1** was increased, no diaryl derivatives were obtained. The *in vitro* antitumor activity data will be published elsewhere.

Table 1 Reaction of 5-fluorouracil with $Ar_2I^+X^-$,

Entry	R	X	Product	Isolated yield(%)	m.p. (°C)
a	H	Cl	**2a**	65	275~277
b	4-Me	Br	**2b**	57	169~171
c	4-Cl	Cl	**2c**	72	228~230
d	4-MeO	I	**2d**	48	231~233
e	3-NO_2	I	**2e**	55	168~170
f	4-MeCONH	I	**2f**	32	171~173

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Experimental

Melting points were taken on a Yanaco Micro Melting Point apparatus and are uncorrected. UV spectra were recorded on a Beckman DU-50 spectrophotometer. Infrared spectra were recorded on a Nexus 470 FT-IR spectrometer ^{1}H-NMR spectra were recorded on a Nexus 470 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on an Advance DMX 500 spectrometer at 500MHz (in d_6^- DMSO solution with TMS as internal standard). Mass spectra were recorded on a MAP GC-MS spectrometer.

The diaryliodonium salts were prepared by standard procedures.[14]

General procedure for the synthesis of **2a–2f**: To a well stirred solution of 1 (1mmol) in dry DMF (10 ml), NaH (2 mmol) was added and the stirring was continued for 2h. $Ar_2I^+X^-$ (1.5 mmol) was then added, and the mixture was heated at 70–80ºC for 36–48 h. After the reaction was over (monitored by TLC), the DMF was removed under vacuum and the residue was portioned between CH_2Cl_2 (20 ml) and water (20 ml). The aqueous layer was washed with CH_2Cl_2 (2x20 ml) and then adjusted to pH = 3~5 with 1N HCl, extracted with CH_2Cl_2 (3×20 ml), and the combined organic extracts were dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by column chromography over silica gel eluted with ethyl acetate: hexane = 1:2~2:1. The products were obtained as white or yellow solids and were recrystalized from absolute ethanol. Yields and melting points are listed in Table 1.

2a: ^{1}H-MR: 7.47 (5H, m), 8.22 (1H, d, *J*=6.77Hz), 11.82 (1H, brs); IR: 3063, 1666, 1276, 768; UV: μ_{max} (EtOH) 273 (pH 1, 7, 13); MS: *m/z*=206 (M^+); Anal. Calc. 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.

2b: ^{1}H NMR: 2.4 (3H, s), 7.38 (4H, m), 7.42 (1H, d, *J*=6.82Hz), 9.02 (1H, brs); IR: 3069, 1683, 1271, 819; UV: ν_{max} (EtOH) 273.5 (pH 1, 7, 13); MS: *m/z*=220 (M^+); Anal. Calc. 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.

2c: ^{1}H-NMR: 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: ν_{max} (EtOH) 274 (pH 1, 7, 13); MS: *m/z*=240 (M^+); Anal. Calc. 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.

2d: ^{1}H-NMR: 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: ν_{max} (EtOH) 273.5 (pH 1, 7, 13); MS: *m/z*=236 (M^+); Anal. Calc. for $C_{11}H_9FN_2O_3$, C: 55.93, H: 3.81, N: 11.86, Found: C: 56.04, H: 3.88, N: 11.79.

2e: ^{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: ν_{max} (EtOH) 257 (pH 1, 7, 13); MS: *m/z*=251 (M^+); Anal. Calc. 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.

2f: ^{1}H-NMR: 2.20 (3H, s), 7.12 (1H, d, *J*=7.4Hz), 7.23 (1H, s), 7.32 (2H, m), 7.54 (2H, m), 9.76 (1H, s); IR: 3300, 1688, 1670, 1273, 810; UV: ν_{max} (EtOH) 241 (pH 1, 7, 13); MS: *m/z*=263(M^+); Anal. Calc. 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.

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