Fluoride-Assisted Nucleophilic Substitution of 6-Alkyl-5-bromouracils with Nitrogen-Containing Heterocycles[1]

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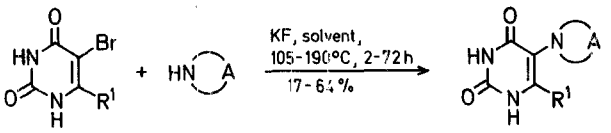
In the course of our efforts to prepare novel pyrimidine inhibitors of dihydrofolate reductase as chemotherapeutic agents, we required a series of 6-alkyl-5-(1-azaheterocyclic)-uracils **3** as synthetic intermediates. A reasonable approach to these compounds was presumed to be nucleophilic attack of the requisite amines on the corresponding 5-bromouracils. Although such substitution has been effected in good yield on 6-unsubstituted 5-bromouracils with primary and secondary amines[2], no report has appeared utilizing 6-alkyl-5-bromouracils. Moreover, our efforts toward the reaction of 5-bromo-6-ethyluracil with piperidine resulted only in the recovery of starting material. Gerns et al.[3] report, in addition, decreased reactivity of aromatic amines with 5-bromo-6-methyluracil compared with 5-bromouracil. Such effects may be due to a combination of the electron donating properties of the alkyl group and the increased steric bulk provided.

Clark et al. have demonstrated the assistance of potassium fluoride in a number of displacements on haloalkanes with alcohols, primary amines, and thiols[4,5]. The assistance was presumed to result from increased nucleophilicity of the nucleophile through the intermediacy of a hydrogen bond between the fluoride anion and the nucleophile. Application of such potassium fluoride assistance allowed the displacement of 6-alkyl-5-bromouracils **1** with a variety of azaheterocycles **2** (Table).



1 **2** **3a-g**

3	R^1	A
a	CH_3	$-(CH_2)_{12}-$
b	C_2H_5	$-(CH_2)_5-$
c	C_2H_5	$-(CH_2)_2-C(O)(O)-(CH_2)_2-$
d	C_2H_5	
e	C_2H_5	$-(CH_2)_2-N(C_6H_5)-(CH_2)_2-$
f	C_2H_5	
g	n-C_3H_7	$-(CH_2)_2-N(CH_2-C_6H_5)-(CH_2)_2-$

Moderate yields of the products **3** were obtained. Although yields were not optimized, in most cases reaction in the absence of a solvent resulted in improved yields. Perhaps the primary amine hydrogen bond with fluoride ion is favored in the absence of solvents. Preparation of the azabicyclo analog **3d** indicates that such assistance by potassium fluoride is also able to overcome substantial steric bulk of the incoming nucleophile. This methodology should be useful in the preparation of a wide variety of difficulty accessible azaheterocyclic systems.

Table. 6-Alkyl-5-(1-azaheterocyclic)-uracils **3a–g** prepared

Product	Reaction Conditions solvent/temperature/time	Yield [%]	m.p. [°C]	Molecular Formula[a]	I.R. (KBr) ν[cm^{-1}]	^{1}H-N.M.R. (DMSO) δ[ppm]
3a	ethylene glycol/190°C/2 h	17	272° (dec.)	$C_{17}H_{29}N_3O_2$ (307.4)	–	0.9–1.8 (br. s, 20H); 2.13 (s, 3H, CH_3); 2.65–3.0 (br. s, 4H, $-CH_2-N-CH_2-$); 10.6 (s, 1H, NH); 10.9 (br. s, 1H, NH)
3b	neat/105°C/72 h	77	254–257°	$C_{11}H_{17}N_3O_2$ (223.2)	3190, 2945, 1735, 1720, 1650	1.05 (t, 3H, J = 6 Hz, CH_3); 1.5 (br. s, 6H); 2.3–3.4 (m, 6H, CH_2CH_3 + $-CH_2-N-CH_2-$)
3c	neat/105°C/72 h	57	329–330°	$C_{13}H_{19}N_3O_4$ (249.3)	3450, 3180, 2980, 1730, 1665	1.1 (t, 3H, J = 7 Hz, CH_3); 1.6 (t, 4H, J = 6 Hz); 2.5–3.7 (m, 6H, CH_2 + $-CH_2-N-CH_2-$); 3.8 (s, 4H); 10.6 (br. s, 2H, NH)
3d	DMSO/115°C/4 h	64	285–286°	$C_{14}H_{21}N_3O_2 \cdot 0.1H_2O$ (265.1)	3169, 3162, 2969, 1712, 1653, 1462, 525	1.1 (t, 3H, J = 7 Hz, CH_3); 1.3–2.0 (m, 10H); 2.4–2.9 (m, 4H, CH_2CH_3 + N—CH_2); 3.4 (m, 2H, N—CH_2); 10.45 (s, 1H, NH); 10.7 (s, 1H, NH)
3e	neat/105°C/72 h neat/140°C/4 h	46 63	270–272°	$C_{16}H_{20}N_4O_2$ (300.4)	3420 (br.), 3200 (br.), 1730, 1655, 1240	1.1 (t, 3H, J = 6 Hz, CH_3); 2.5 (m, 2H, CH_2); 2.7–3.4 (m, 8H$_{piperazine}$ + 1NH); 6.6–7.3 (m, 5H$_{arom}$); 10.7 (s, 1H, NH)
3f	DMSO/115°C/4 h	31	246–250°	$C_{15}H_{17}N_3O_2$ (271.3)	–	0.9–1.2 (t, 3H, J = 6 Hz, CH_3); 2.2–3.4 (m, 8H); 6.8–7.1 (m, 4H); 10.5 (br. s, 1H, NH); 10.7 (br. s, 1H, NH)
3g	neat/140°C/4 h	59	233–235°	$C_{18}H_{24}N_4O_2$ (328.4)	3460, 1700, 1645, 1455, 1325, 1220	0.92 (t, 3H, J = 6 Hz, CH_3); 1.51 (m, 2H, CH_2); 1.75–2.9 (m, CH_2)[b]; 3.45 (s, 2H, $C_6H_5CH_2$); 7.15 (m, 5H$_{arom}$); 10.6 (s, 1H, NH); 10.9 (s, 1H, NH)

[a] Satisfactory microanalyses obtained: C ±0.32, H ±0.20, N ±0.25, H_2O (**3d**) −0.13; exception: **3a**, N −1.08.
[b] Superimposed with DMSO.

Melting points were determined with a Thomas-Hoover apparatus. ^{1}H-N.M.R. spectra were recorded with a Varian ZM-390 spectrometer. I.R. spectra were recorded on a Digilab FTS14 or Nicolet MX1 spectrophotometer. 5-Bromo-6-ethyluracil (**1**; $R^1 = C_2H_5$) and 5-bromo-6-propyluracil (**1**; $R^1 = n$-C_3H_7) were prepared as described[6]; 5-bromo-6-ethyluracil: m.p. 233–234°C (Lit.[6], 230–231°C), 5-bromo-6-propyluracil: m.p. 235–236°C. Anhydrous potassium fluoride was dried at 280°C before use.

5-[4-(Benzyl)-1-piperazinyl]-6-propyl-2,4(1*H*,3*H*)-pyrimidinedione (3g); Typical Procedure:

A mixture of 5-bromo-6-propyluracil (**1**; $R^1 = n$—C_3H_7; 53.3 g, 0.299 mol) and anhydrous potassium fluoride (23.7 g, 0.252 mol) in 1-benzylpiperazine (176 ml, 1.0 mol) is heated under reflux at 140°C for 4 h. The mixture is cooled to 80°C and ethanol (100 ml) is added to reduce the viscosity. The mixture is then poured into ice/water (1000 ml). The solid is collected and washed with water (1000 ml). Recrystallization from ethanol and drying in vacuo at 59°C for 16 h gives product **3g** as an off-white solid; yield: 44.1 g (59%); m.p. 233–235°C.

$C_{18}H_{24}N_4O_2$ (328.4)	calc.	C 65.83	H 7.37	N 17.06
	found	66.07	7.35	16.81

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