A FACILE SYNTHESIS OF 1,3-DIALKYL-5-FLUOROURACILS BY MEANS OF PHASE TRANSFER CATALYSIS

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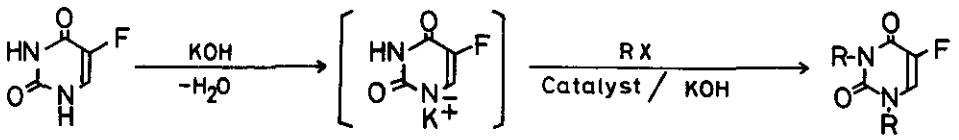
Abstract —— The reaction of 5-fluorouracil with an alkyl halide in the presence of a phase transfer catalyst and potassium hydroxide gives 1,3-dialkyl-5-fluorouracil in good yield.

A variety of 5-fluorouracil (5-FU) derivatives have been synthesized in order to study their antitumor activity.[1] From the synthetic viewpoint, however, much more effort to introduce efficiently a substituent on the 5-FU ring should be devoted since even simple acylation[2] and alkylation are known to proceed in low yield.[3] Thus, synthetic problems in the chemistry of 5-FU result mainly from the weak nucleophilicity and low solubility of 5-FU. Employment of aprotic polar solvents such as DMF and pyridine for solubilization of 5-FU is inconvenient during the work-up procedure and large scale operation. Recently, Ogilvie et al. reported alkylation of uracils using a large excess of tetrabutylammonium fluoride and alkylating agents.[4] As a part of our continued interest in the preparation and properties of 5-FU derivatives,[5] we report here a facile synthesis of 1,3-dialkyl-5-FU using solid-liquid phase transfer catalysis.[6]

In order to examine the solubility and nucleophilicity of a quaternary ammonium salt of 5-FU, the tetrabutylammonium salt was prepared by treatment with an equimolar amount of tetrabutylammonium hydroxide. The salt dissolved easily in relatively non-polar solvents such as dichloromethane and chlorobenzene, in which 5-FU itself is essentially insoluble. The quaternary salt of 5-FU similarly prepared by treatment with two molar equivalent of tetrabutylammonium hydroxide reacted smoothly in dichloromethane with alkyl halides to give 1,3-dialkyl-5-FU derivatives in excellent yields (r.t., overnight, n-C_3H_7Br 94%; n-C_4H_9Br 89%; $PhCH_2Cl$ 86%). These results prompted us to utilize phase transfer methods which permit catalytic use of quaternary ammonium salt and *in situ* formation of the corresponding salt of 5-FU. Typically, the monopotassium salt was prepared prior to the reaction as follows. Treatment of 5-FU with potassium hydroxide (2.5 equiv)

Table. Synthesis of 1,3-Dialkyl-5-FU Derivatives by Phase Transfer Method



RX	Solv.	Cat.[a]	Yield[b] (%)	Mp (°C) or bp (°C/mmHg)
$n\text{-}C_3H_7Br$	PhCl	A	83	44-45
	PhMe	A	76	
$n\text{-}C_4H_9Br$	PhCl	A	80	47-49
	PhCl	B	71	
	PhCl	C	69	
	PhMe	A	79	
$n\text{-}C_5H_{11}Br$	PhCl	A	80	36-37
	PhMe	A	70	
$n\text{-}C_{16}H_{33}Br$	PhCl	A	80	67-69
CH_3COCH_2Cl	PhCl	A	58[c]	128-130
MeO_2CCH_2Br	PhCl	A	75	200-250/0.4[d]

a) A: Tetrabutylammonium chloride, B: Tetrabutylammonium bromide, C: Tributylhexadecylphosphonium bromide.

b) All new compounds gave satisfactory spectral data (IR and NMR) and combustion analysis.

c) The same product was obtained in 15% yield by treatment of 5-FU with chloroacetone in the presence of K_2CO_3 in DMSO.[3c]

d) Oven temperature.

in methanol resulted in precipitation of the salt.[7] Removal of methanol and water thus formed provided a residue to which was added chlorobenzene, tetrabutylammonium chloride (10 mol%) and butyl bromide (3 equiv), and the resulting mixture was heated at 100°C for 50h. In a similar manner, various alkyl halides were treated with 5-FU. The results are summarized in the table. Chlorobenzene and toluene are the best reaction solvents. Tetrabutylammonium chloride is effective as a phase transfer catalyst, but its absence gives a dialkylation product in very low yield.

Recently, Hedayatulah reported a liquid-liquid phase transfer method for the synthesis of 1,3-dimethyl-5-fluorouracil.[8] According to his procedure, 5-FU was treated with other alkyl halides such as benzyl chloride and butyl bromide.

However, with our system only methyl bromide gave a good yield of the 1,3-dimethyl derivative as reported.

In summary, our phase transfer method provides a practical synthesis of dialkyl-5-FU. The main advantages are the use of a catalytic amount of a quaternary ammonium salt and the absence of polar solvent.

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