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A FACILE SYNTHESIS OF 1-(2-TETRAHYDROFURYL)-5-FLUOROURACIL (FTORAFUR)

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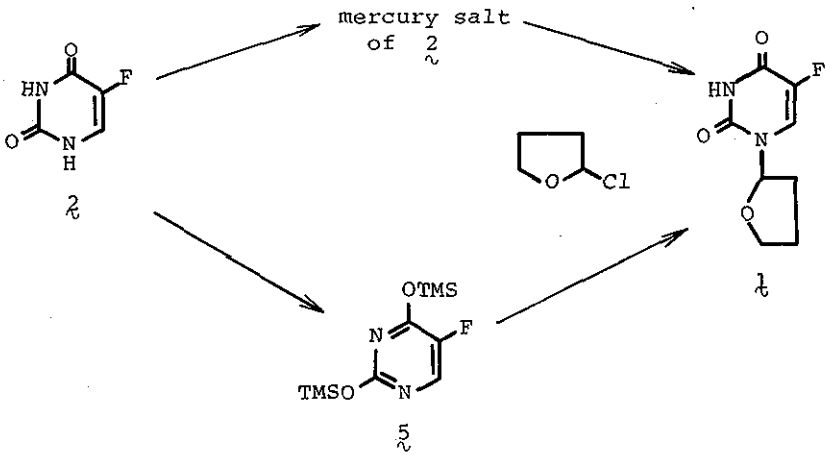
1-(2-Tetrahydrofuryl)-5-fluorouracil (1), a potent anti-tumor agent, was conveniently synthesized by the the condensation of 5-fluorouracil (2) with various 2-alkoxy-2,3,4,5-tetrahydrofurans (3a-j), and the best yield of 1 by this method was obtained in the reaction of 2-t-butoxy analog (3h).

1-(2-Tetrahydrofuryl)-5-fluorouracil (1, Ftorafur) is a clinically effective anti-tumor agent which functions a nucleic acid antagonist. There are many reports on the synthesis of 1,[1,2] and we also examined a simple preparation of this compound. Now we wish to report an alternative synthesis of 1.

The Hilbert-Johnson procedure has been a representative method to prepare pyrimidine nucleosides, and applied by Russian chemist[1] to the first synthesis of 1 by the reaction of 2-chlorotetrahydro-

furan (4) with 2,4-bis(trimethylsilyloxy)-5-fluorouracil (5). The mercury salt of 2 was also used instead of 5. Although several kinds of alternative syntheses[2] of 1 by a reaction of some 2-alkoxy-2,3,4,5-tetrahydrofurans with 5 or 2 in the presence of acidic catalysts, were widely investigated, these methods have some defects in which unstable material was an intermediate and the process needed a severe condition.

Scheme 1

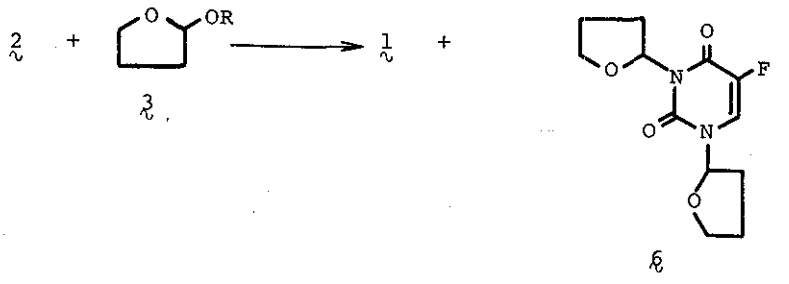


TMS=trimethylsilyl

In order to explore a simplified synthesis of 1, we examined a condensation of 2 with various 2-alkoxy-2,3,4,5-tetrahydrofurans (3a-j)[3] without using any catalysts. Heating 2 (1 g, 7.7 m mol) and 3a-j (11.6 m mol) at 150 - 165° in dimethylformamide for 4 - 5 hr afforded successfully 1 (mp 164 - 165°; lit.,[2] mp 164 -

165°) by simple work-up, namely evaporation of the solvent, followed by recrystallizaiton. Among several 2-alkoxytetrahydrofurans (3a-j), the highest yield of 1 was obtained in case of 2-t-butoxytetrahydrofuran (3h).

Scheme 2



a : R=CH_3, b : R=C_2H_5, c : R=n-C_3H_7
d : R=i-C_3H_7, e : R=n-C_4H_9, f : R=i-C_4H_9
g : R=sec-C_4H_9, h : R=t-C_4H_9, i : R=n-C_5H_{11},
j : R=n-C_6H_{13}

Table 1 The Yield of the Reaction of 2 with 3a-j

Starting furans (3a-j)	a	b	c	d	e	f	g	h	i	j
Yield of 1 (%)	2.5	12.3	13.0	15.0	9.1	7.8	15.6	67.0	8.1	5.2

This reason would be due to the t-butoxy group of 3h which is more susceptible to it's elimination than those of the others. However, the reaction of 2 with 4h in the presence of Lewis acid

($AlCl_3$) gave a less yield of 1 (25 %). Prolongation of the reaction time and addition of more excess of 3 in these reactions improved the yield of 1, but the best yield of 1 was again observed with using 4h. A detailed investigation of these reaction products revealed that a small amount of 2,4-bis(2-tetrahydrofuryl)-5-fluorouracil [6, mp 104 - 106°; mass (m/e) 270 (M^+)] was also obtained. Hydrolysis of 6 by means of acetic acid yielded 1 quantitatively.

Thus, a facile synthesis of 1 is now available. The application of this procedure would provide a new class of preparative method of pyrimidine nucleosides.

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3) These compounds were easily prepared by the addition of the

corresponding alcohol to 2,3-dihydrofuran in the presence of acid catalyst: a) M. H. Normant and M. M. Delépine, Compt. rend., 1949, 228, 102; b) E. L. Eliel, B. E. Nowak, R. A. Daignaut, and V. G. Badding, J. Org. Chem., 1965, 30, 2441.

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