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

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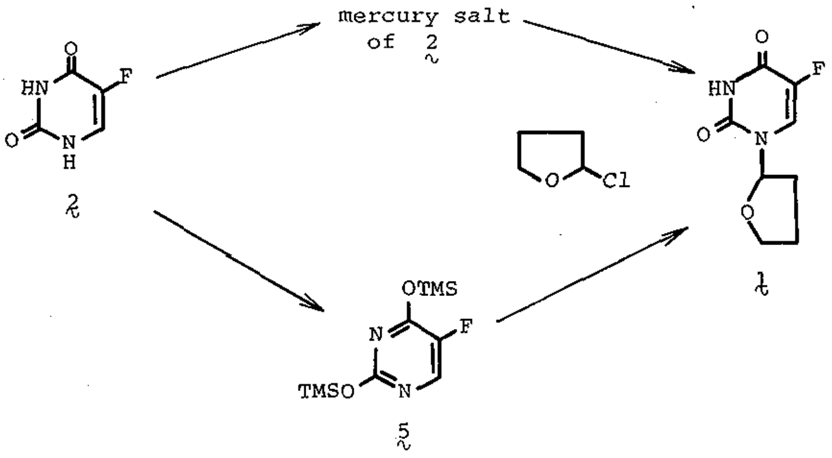
1-(2-Tetrahydrofuryl)-5-fluorouracil (**1**), a potent anti-tumor agent, was conveniently synthesized by the the condensation of 5-fluorouracil (**2**) with various 2-alkoxy-2,3,4,5-tetrahydrofurans (**3**a-j), and the best yield of **1** by this method was obtained in the reaction of 2-*t*-butoxy analog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

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-chlorotetrahydrofuran (**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**

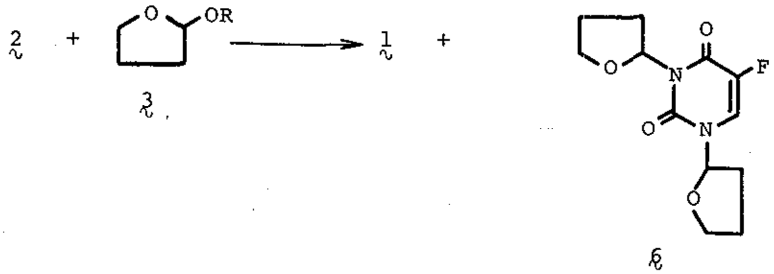


TMS=trimethylsilyl

In order to explore a simplified synthesis of **1**, we examined a condensation of **2** with various 2-alkoxy-2,3,4,5-tetrahydrofurans (**3**a-j)^{3} without using any catalysts. Heating **2** (1 g, 7.7 m mol) and **3**a-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 **4**h. 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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