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A NOVEL SYNTHESIS OF 5-FLUOROURACIL DERIVATIVES HAVING OXACYCLOALKANE MOIETIES

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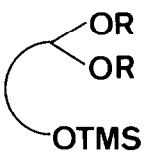
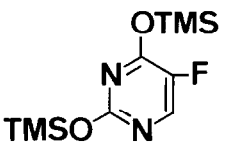
ABSTRACT: 5-Fluorouracil derivatives having oxacycloalkane moieties were synthesized in good yields by the reaction of trimethylsilyloxyalkanal dialkyl acetals with 2,4-bis(trimethylsilyl)-5-fluorouracil in the presence of $SnCl_4$.

Several 5-fluorouracil (5-FU) derivatives having tetrahydrofuran moieties at the N^1-position are known to show significant antitumor activities in experimental tumors and in clinical trials.[1] For almost all of the syntheses of these compounds so far reported have been employed the conventional approaches in that 5-FU or its derivatives are condensed with 2-functionalized tetrahydrofurans.[2] In conjunction with our efforts[3] to search for an efficacious antitumor agent, we required a new synthetic method of 5-FU derivatives having oxacycloalkane moieties, conditionally on the starting materials being readily available. Reported herein is a new approach to a synthesis of the 5-FU derivatives **3**, which is based on the Lewis acid-catalyzed condensation of trimethylsilyloxyalkanal dialkyl acetals (TMS-acetal, **1**) and 2,4-bis(trimethylsilyl)-5-fluorouracil (TMS-5-FU, **2**).



1



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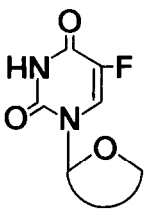

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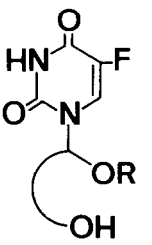

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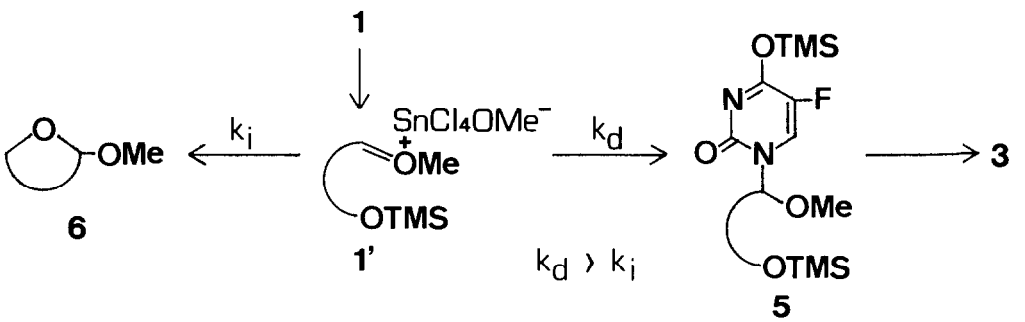
The following preparation of 1-(tetrahydrofuran-2-yl)-5-fluorouracil (**3a**) is representative. Readily available TMS-acetal **1a**[4] (2.27g, 0.011 mol) and **2** (2.74g, 0.01 mol) were dissolved in 30 ml of CH_3CN. To this was added dropwise a solution of $SnCl_4$ (0.58 ml, 0.005 mol) dissolved in 2 ml of $ClCH_2CH_2Cl$ at 0°C under vigorous stirring. After stirring for an additional 1 hr at 23-25°C, the reaction mixture was worked up in the usual way to afford **3a** in 84% yield. The spectral data were identical in all respects with those of an authentic sample.[5] In Table are listed the yields of the typical 5-FU derivatives **3**.

5-FU derivatives bearing six and seven membered rings containing another heteroatom were also synthesized in a manner similar to that described above; in the reaction leading to the seven membered ring derivative **3d**, the yield (28%) dropped sharply, and the non-cyclized product **4d** was formed in 45% yield as the by-product. Introduction of the substituents onto the acetal **1a** provided the 5-FU derivatives (**3e-3h**) having the corresponding substituted tetrahydrofurans in excellent yields. The stereochemistry of the reaction product was substantiated either by comparison with the independently prepared samples[6] or by leading the products to the stereochemically defined compounds.[8)9)] A most striking feature is the remarkable control of stereochemistry in the reaction of TMS-acetal **1h** with **2** in which the thermodynamically unfavorable *cis* isomer was formed exclusively.[10)]

Although several Friedel-Crafts catalysts other than $SnCl_4$ have been examined in some aprotic solvents, the combination of $SnCl_4$ or CF_3SO_3TMS and CH_3CN as a solvent gave the best yields of the products in these reactions.[11)] The optimum reaction temperature is dependent upon the amount of the Lewis acid employed; in the use of 1.5 molar equivalent of the Lewis acid, for example, the reaction temperature should be kept at least below -30°C.

When TMS-acetal **1a** was treated with **2** in CH_3CN at -5°C for 3 hr by using 0.25 molar equivalent of $SnCl_4$, the non-cyclized compound **4a** was isolated in 81% yield.[12)] On the other hand, on treating the reaction mixture at -5°C for 3 hr and thereafter at 5°C for 3 hr, exclusive formation of the cyclization product **3a** was observed.[12)] Thus, the reaction pathway may be rationalized as shown below. Electrophilic attack of $SnCl_4$ on the oxygen atom of the acetal **1** would

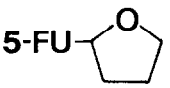
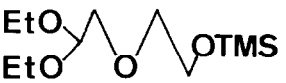
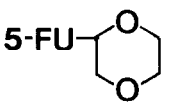
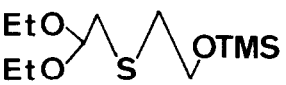
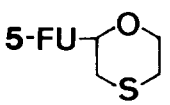
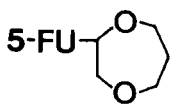
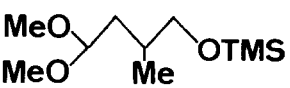
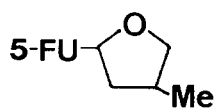
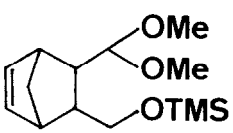
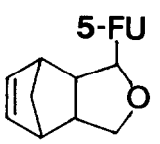
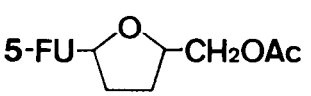
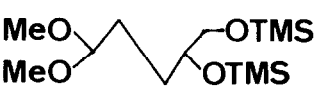
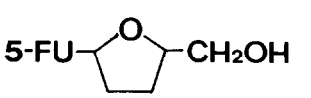


generate the oxonium ion **1'**. Subsequent nucleophilic displacement by **2** probably leads to the formation of the intermediate **5** which undergoes intramolecular ring closure rather slowly to afford the product **3**. It should be noted that the rate constant for the nucleophilic displacement (k_d) leading to **5** is larger than that for intramolecular ring closure (k_i) of **1'** to form 2-methoxy oxacycloalkane **6**.

We are continuing to explore other aspects of this new type of reaction including the use in the preparation of naturally occurring nucleosides.

Acknowledgment: We thank Dr. M. Miyoshi, vice-director and Dr. I. Chibata, director of our research laboratory, for their encouragement.

Table Yields of 5-FU Derivatives **3**

Compd. No	TMS-acetal **1**	Product **3**[i]	Yield %[ii], cis/trans[iii]
a			84
b			75
c			79
d			28
e			72	1/3
f			61	—[iv]
g			67	5/1
h			62	cis[v]

i) All products were identified by ^{1}H NMR spectra and gave satisfactory elemental analyses. ii) Isolated yield. iii) Isolated ratio. iv) The stereochemistry is not determined. v) *cis*-Isomer was formed exclusively.

References and Footnotes

1) See, for example, a) A. F. Cook and M. J. Holman, J. Med.Chem., 22, 1330 (1979); b) *idem*, J. Org. Chem., 43, 4200 (1978); c) A. J. Lin, R. S. Benjamin, P. N. Rao, and T. L. Leo, J. Med. Chem., 22, 1096 (1979), and references cited therein.

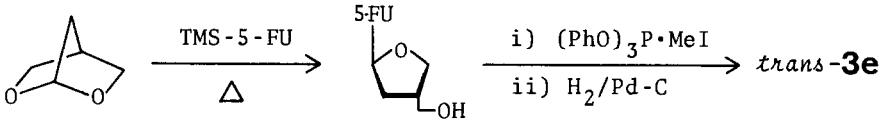
2) H. Nomura, Y. Yoshioka, and I. Minami, Chem. Pharm. Bull., 27, 899 (1979) and references cited therein.

3) a) T. Nishitani, T. Iwasaki, Y. Mushika, and M. Miyoshi, J. Org. Chem., 44, 2019 (1979); b) T. Nishitani, T. Iwasaki, Y. Mushika, I. Inoue, and M. Miyoshi, Chem. Pharm. Bull., 28,1137 (1980).

4) TMS-acetals **1a** and **1e** were prepared from furan-2-carboxylic acid and 3-methylfuran-2-carboxylic acid, respectively, using electrode reaction as a key step. A similar procedure was applied to the synthesis of TMS-acetals **1f-1h** from 2-substituted furans. TMS-acetals **1b, d**, and **1c** were prepared by the reaction of bromoacetaldehyde diethyl acetal with the corresponding diols and mercaptoethanol, respectively, followed by silylation with trimethylchlorosilane. Some of the results have already been presented in a preliminary form at the 1st Symposium on Electroorganic Chemistry, Kyoto, 1980.

5) M. Yasumoto, I. Yamawaki, T. Marunaka, and S. Hashimoto, J. Med. Chem., 21, 738 (1978).

6) The *trans* isomer of compound **3e** was prepared independently from 2,6-dioxabicyclo[2,2,1]heptane[7] as depicted in the following scheme.



7) H. K. Hall, Jr. and F. DeBlauwe, J. Am. Chem. Soc., 98, 655 (1975).

8) We thank Prof. C. Heidelberger who kindly sent us a copy of the NMR spectrum of compound **3h**.

9) The stereochemistry of compound **3g** was determined by transformation of compound **3h** into **3g** by the usual procedure.

10) The reasons for the exclusive formation of the *cis* isomer are not obvious. The 4-hydroxymethyl group of the sugar moiety sometimes plays an important role in the stereoselectivities of some Friedel-Crafts-catalyzed nucleoside synthesis. See, for example, H. I. Skulnick, "Chemistry and Biology of Nucleosides and Nucleotides", ed. by R. E. Harmon, R. K. Robins and L. B. Townsend, Academic Press, New York, 1978, pp 211-227.

11) The same results were reported in the Friedel-Crafts-catalyzed silyl Hilbert-Johnson reaction. See, U. Niedballa and H. Vorbrüggen, J. Org. Chem., 39, 3654 (1974).

12) The yield was determined by HPLC.

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