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ONE-POT SYNTHESIS OF 5-FLUORO-6-ALKOXY-5,6-DIHYDROURACILS[1]

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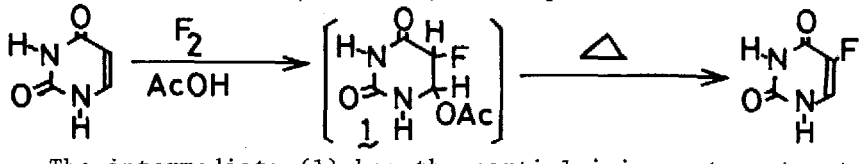
Summary: Fluorine diluted with argon was bubbled into a suspension of uracil in acetic acid at room temperature. Treatment of the reaction mixture with alcohols gave 5-fluoro-6-alkoxy-5,6-dihydrouracils, which lost alcohols on sublimation under vacuum to give 5-fluorouracil quantitatively.

Many kinds of 5-fluorouracil derivatives have been synthesized and some of them are used as anti-tumor agents. These compounds are believed to be converted to 5-fluorouracil and to work as an anti-tumor agent. Therefore, such a derivative as can be taken orally, can work for a long time and has no side-effects is desired. From these points of view, Duschinsky et al. synthesized 5-fluoro-5,6-dihydrouracils and reported some of their biological activities.[2] Their synthesis of 5-fluoro-6-alkoxy-5,6-dihydrouracils consists of two steps: haloalkoxylation of 5-fluorouracil and reductive dehalogenation of 5-fluoro-5-halo-6-alkoxy-5,6-dihydrouracils. Now, we should like to report the one-pot synthesis of the above compounds.

Cech et al. reported the fluorination of uracils in acetic acid and showed that 5-fluoro-6-acetoxy-5,6-dihydro compound was formed as an intermediate.[3]



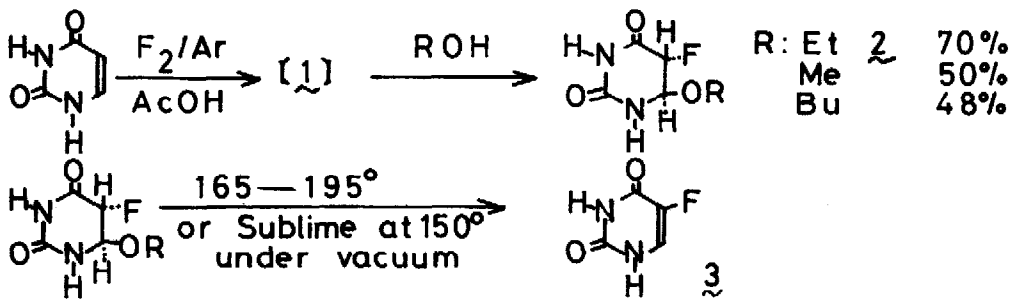
(1)

The intermediate (1) has the partial imino ester structure, and the acetoxy group seemed to be replaced by a proper anion. Thus, fluorine-argon (10%) was bubbled into the suspension of uracil (1 g) in acetic acid (10 ml) at room temperature till uracil dissolved clearly. After bubbling was continued one more hour, ethanol (10 ml) was added and the mixture was concentrated under vacuum. This operation was repeated for three times and the residue was recrystallized from ethanol to give colourless needles (2, 70%). This compound shows peaks at 176 (M^+), 131 ($M-C_2H_5O$), and 88 ($M-C_2H_5O-HCNO$) in its mass spectrum. This suggests 2 is 5-fluoro-6-ethoxy-5,6-dihydrouracil. The assumption is sup-

ported by NMR: ^{1}H-NMR δ(in DMSO-d_6) 5.42 (1H, dd, J_{HF}=46.0 Hz, $J_{5,6}$=4.0 Hz, 5-H), 4.77 (1H, dd, $J_{5,6}$=4.0 Hz, J_{HF}=2.2 Hz), 3.53 (2H, two quartet, J=6.5 Hz, CH_2), and 3.10 (3H, t, J=6.5 Hz, CH_3); ^{19}F-NMR δ[4] 208 (bd, J=46 Hz). As the coupling pattern of 5- and 6-protons is similar to that of 5-fluoro-6-hydroxy-5,6-dihydrouracil,[7] which proposed to be trans form, 2 must be trans form. Compound 2 decomposed from 165° to 195°C to give 5-fluorouracil (3). Sublimation of 2 under vacuum also gave 3 quantitatively.

The same procedure as above, but using methanol or butanol in the place of ethanol, gave 5-fluoro-6-methoxy- or butoxy-5,6-dihydrouracil in the yield of 50% or 48%. The structures of both compounds were determined by mass spectra and ^{1}H and ^{19}F-NMR. Especially, chemical shifts and spin-spin coupling pattern of 5-and 6-protons are quite similar to those of 2. Both products gave 3 quantitatively on sublimation under vacuum.

Previously, Cech[5] treated 5-substituted uracil derivatives in the similar manner as ours and obtained 5-substituted 5-fluoro-6-alkoxy-5,6-dihydrouracils, but they reported that 5-unsubsituted uracils were converted to the corresponding 5-fluorouracils. Only difference between their procedure and ours is that they evaporated the solvent and treated with alcohols, while we added alcohols to the reaction mixture before evaporation of the solvent. This procedure is very useful for synthesis of the thermally unstable title compounds.



References and Notes

1. Part of this work was presented at the 99th annual meeting of the pharmaceutical Society of JAPAN, 1979, Sapporo.
2. R. Duschinsky, T. Gabriel, W. Tantz, A. Nussbaum, M. Hoffer, E. Grunberg, J. H. Burchenal, and J. J. Fox, J. Med. Chem. 10, 47 (1967).
3. D. Cech, and A. Holy, Collect. Czecholov. Chem. Commun., 41, 3335 (1976).
4. $CFCl_3$ as a external standard.
5. D. Cech, L. Hein, R. Wuttke, M. v. Janta-Lipinski, A. Otto, and P. Langen, Nucleic Acids Res., 2, 2177 (1975).

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