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Selective N_1-Tetrahydrofurylation of 5-Substituted Uracils

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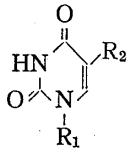
Selective N_1-tetrahydrofurylation of uracils has been performed in satisfactory yield by direct addition of uracils to 2,3-dihydrofuran in the presence of PCl_5 in hexamethylphosphoramide (HMPA).

Keywords——N_1-tetrahydrofurylation; 5-substituted uracils; 2,3-dihydrofuran; phosphorus pentachloride; hexamethylphosphoramide

The 5-fluorouracil derivative possessing a 2-tetrahydrofuryl group at the N_1-position is known as an effective antitumor agent. It has been reported that selective N_1-tetrahydrofurylation of 5-fluorouracil (5-FU) (**1**) can be attained by the well-established methods, involving condensation of mercury salt[2] of 5-FU or 2,4-bistrimethylsilyl-5-FU[3] with 2-halo, 2-alkoxy, 2-acyloxy-tetrahydrofurans. In a few cases, the direct introduction of tetrahydrofuryl group at the N_1-position of 5-FU has been studied,[4] but, satisfactory yields of N_1-substituted products have not been obtained owing to accompanied formation of some by-products.



1: R_1=H, R_2=F
2: R_1=2-tetrahydrofuryl, R_2=F
3: R_1=2-tetrahydrofuryl, R_2=H
4: R_1=2-tetrahydrofuryl, R_2=CH_3
5: R_1=2-tetrahydrofuryl, R_2=Br
6: R_1=2-tetrahydrofuryl, R_2=I

Chart 1

We now report direct and selective N_1-tetrahydrofurylation of uracils using commercially available 2,3-dihydrofuran in the presence of PCl_5 in hexamethylphosphoramide (HMPA). In contrast to conventional procedures, these reactions proceed under the mild conditions

TABLE I. 1-(2-Tetrahydrofuryl)-5-Substituted Uracils

Compound No.	Reaction time (hr)	mp (°C)	Yield (%)
2	0.5	169—171$^{a)}$	88
3	5.5	104—105$^{b)}$	92
4	1.0	188—188.5$^{c)}$	58
5	1.5	208—210 (dec.)$^{d)}$	54
6	1.5	174—175 (dec.)$^{e)}$	59

a) lit.[3a] mp 168—169°,
b) lit.[3a] mp 99—101°,
c) lit.[3b] mp 182—184°,
d) lit.[3b] mp 208—210° (dec.),
e) lit.[3c] mp 174—176° (dec.).

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[1] Location: *Kanate, Ohimachi, Ashigarakamigun, Kanagawa, 258, Japan.*

[2] S.A. Hiller, R.A. Zhuk, and M.Yu. Lidak, *Dokl. Akad. Nauk. SSSR*, **176**, 332 (1967) [*Chem. Abstr.*, **68**, 29664*j* (1968)].

[3] *a*) R.A. Earl and L.B. Townsend, *J. Heterocycl. Chem.*, **9**, 1141 (1972); *b*) S.A. Giller, Japan Kokai Patent 19757 (1975); *c*) Taiho Yakuhin, Japan Kokai Patent 105673 (1975).

[4] T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, O. Kusama, H. Sugi, and K. Kawasaki, *Heterocycles*, **5**, 529 (1977); Mitsui Toatsu Chemical Co., Ltd., Japan Kokai Patent 89678 (1977).

in high yields ranging from 54 to 92%. In a typical procedure, to a mixture of 5-FU (15.4 mmol) (**1**), PCl_5 (7.7 mmol) and HMPA was added 2,3-dihydrofuran (20.0 mmol) in the period of 30 min under stirring at room temperature. After addition, the mixture was poured into ice water, neutralized with alkali, and extracted with $CHCl_3$. Evaporation of the solvent gave a crystalline product, which was recrystallized from EtOH to provide (**2**), mp 169—171°. Other uracil derivatives were prepared under the similar conditions, and the results are summarized in the Table.

The identification of each product was made by mixed melting point test and the comparison of the nuclear magnetic resonance (NMR), mass (MS) spectral data with the corresponding authentic samples prepared from 2-chlorotetrahydrofuran and 2,4-bistrimethylsilyluracils. When this reaction was carried out in N,N-dimethylformamide (DMF) or N,N-dimethylacetamide (DMAc), the yields were poor in each case, furthermore, using PCl_3 instead of PCl_5, the regioselectivity in this reaction decreased. The action of PCl_5 in these reactions is of interest, so that further investigations are now undertaken.

Experimental[5]

1-(2-Tetrahydrofuryl)-5-fluorouracil (2)——To a suspension of 2.0 g of 5-fluorouracil and 1.6 g of PCl_5 in 4 ml of HMPA was added dropwise 1.4 g of 2,3-dihydrofuran with stirring at room temperature for 30 min. After addition, the reaction mixture was poured into water, neutralized with 20% NaOH, and extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crystalline product, which was recrystallized from EtOH to provide **2** (2.7 g, 88%), as colorless needles, mp 169—171°. MS *m/e*: 200 (M^+). NMR (in $CDCl_3$) δ: 7.43 (1H, d, $J=6$ Hz, C_6-H).

1-(2-Tetrahydrofuryl)-uracil (3)——To a stirred suspension of 0.5 g of uracil and 0.11 g of PCl_5 in 7 ml of HMPA was added dropwise 0.5 g of 2,3-dihydrofuran at room temperature for 40 min, and the stirring was continued for further 4.5 hr. The reaction mixture was poured into ice water, neutralized with 20% NaOH, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over anhydrous $MgSO_4$ and evaporated. The residue was chromatographed on silica gel using benzene–EtOH (20: 1) as eluent to give **3** (0.75 g, 92%), as colorless crystals, mp 104—105°. MS *m/e*: 182 (M^+). NMR (in $CDCl_3$) δ: 5.82 (1H, d, $J=8$ Hz, C_5-H). 7.47 (1H, d, $J=8$ Hz, C_6-H).

1-(2-Tetrahydrofuryl)-5-methyluracil (4)——To a suspension of 1 g of 5-methyluracil and 0.81 g of PCl_5 in 5 ml of HMPA was added dropwise 0.83 g of 2,3-dihydrofuran in the period of 1 hr with stirring at room temperature. After addition, the reaction mixture was poured into ice water to give a crystalline product, which was collected by filtration and recrystallized from $CHCl_3$–*n*-hexane to afford **4** (0.9 g, 58%), as colorless crystals, mp 188—188.5°. MS *m/e*: 196 (M^+). NMR (in $CDCl_3$) δ: 1.96 (3H, $C\underline{H}_3$), 7.23 (1H, C_6-H).

1-(2-Tetrahydrofuryl)-5-bromouracil (5)——To a suspension of 0.3 g of 5-bromouracil and 0.33 g of PCl_5 in 1 ml of HMPA was added dropwise 0.17 g of 2,3-dihydrofuran with stirring at room temperature. After 1.5 hr, the reaction mixture was treated in a similar procedure of compound (**2**), recrystallized from EtOH to give **5** (0.22 g, 54%), as colorless crystals, mp 208—210° (dec.). MS *m/e*: 260 (M^+), 262 (M^++2). NMR (in $CDCl_3$) δ: 7.67 (1H, s, C_6-H).

1-(2-Tetrahydrofuryl)-5-iodouracil (6)——To a suspension of 0.3 g of 5-iodouracil and 0.26 g of PCl_5 in 1 ml of HMPA was added dropwise 0.13 g of 2,3-dihydrofuran with stirring at room temperature for 15 min, and the stirring was continued for further 1.5 hr. The reaction mixture was worked up in a similar procedure as above. The resulting product was recrystallized from EtOH to afford **6** (0.23 g, 59%), as pale yellow crystals, mp 174—175° (dec.). MS *m/e*: 308 (M^+). NMR (in $CDCl_3$) δ: 7.71 (1H, s, C_6-H).

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[5] All melting points were measured on a micro-melting point apparatus (Yanagimoto) and are uncorrected. NMR spectra were taken with a JNM-PNM60 spectrometer (Japan Electron Optics Co.) in $CDCl_3$ using tetramethylsilane as an internal standard. Mass spectra were measured with RMU-7L spectrometer (Hitachi).