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Studies on Fluorinated Pyrimidines. III.[1] Synthesis of 1-Acyl- and 1,3-Diacyl-5-alkoxycarbonyl-5-fluoro-6-substituted-5,6-dihydrouracils

Osamu Miyashita,* Koichi Matsumura, Hiroshi Shimadzu, and Naoto Hashimoto

Central Research Division, Takeda Chemical Industries, Ltd., Jusohonmachi, Yodogawa-ku, Osaka, 532, Japan

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1-Acyl- and 1,3-diacyl-5-alkoxycarbonyl-5-fluoro-6-substituted-5,6-dihydrouracils were synthesized for study as a class of pro-drugs of 5-fluorouracil (5-FU).

Keywords——1-acyl- and 1,3-diacyl-5-alkoxycarbonyl-5-fluoro-6-substituted-5,6-dihydrouracils; acylation; hexamethyldisilazane; trimethylchlorosilane; isocyanates

In recent years, various acyl derivatives of 5-FU have been prepared for the purpose of improving the efficacy of the antitumor action of 5-FU.[2]

We have prepared a series of 5-alkoxycarbonyl-5-fluoro-6-substituted-5,6-dihydrouracils

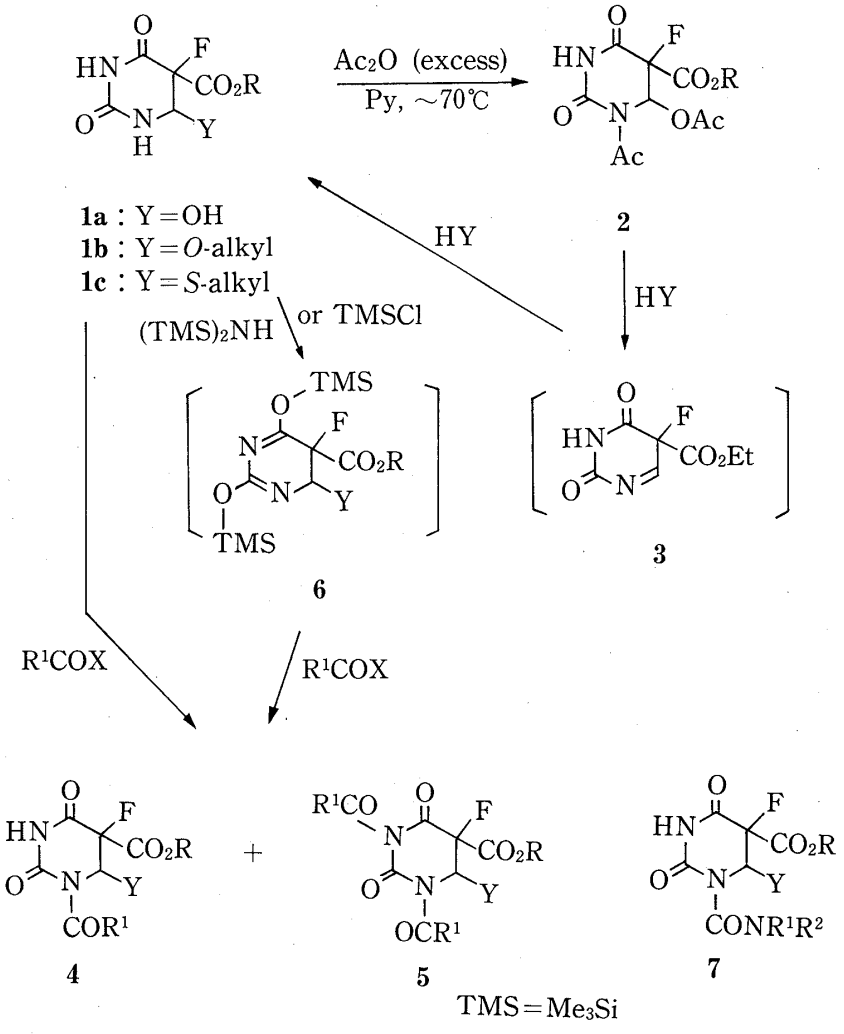


Chart 1

(Y–HFU–COOR, **1**),[3] and have shown that they are prospective pro-drugs of 5-FU. In this note, we wish to describe the synthesis of their acyl derivatives.

First, 1-Ac–AcO–HFU–COOR compounds (**2a**; R=Me, **2b**; R=Et) were prepared by further acetylation of AcO–HFU–COOR (R=Me and Et) as probable common starting materials for a series of 1-Ac–Y–HFU–COOR (**4**).

However, it was found that the reaction of **2b** with ethanol or phenylmercaptan did not give the expected 1-Ac–EtO–HFU–COOEt (**4c**) or 1-Ac–PhS–HFU–COOEt (**4j**), but gave only EtO–HFU–COOEt (**1b**) or PhS–HFU–COOEt (**1c**). These results indicated that the substitution reaction at C-6 does not take place simply through an S_N 2 mechanism, but proceeds through addition of the nucleophile to the C–N double bond between C-6 and N-1 of an imino intermediate (**3**) formed after the removal of both the acetyl group on N-1 and the acetoxy group on C-6 (Chart 1).

The desired 1-Acyl–Y–HFU–COOR (**4**) and 1,3-diacyl-Y-HFU–COOR (**5**) were then prepared either by acylating **1b** and **1c** with acid anhydride in the presence of a tertiary amine (method I) or by acylating the silylated intermediate (**6**) with acyl halide in the presence of anhydrous aluminum chloride (method II). Using method II with 2 equivalents of reagents, 1,3-diacyl derivatives (**5**) were produced. However, partial deacylation of the N^3-acyl group occurred during the following chromatographic purification. The results are summarized in Tables I and II.

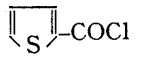
When a mixture of **1b** and an isocyanate was heated either under reflux in dioxane in the presence of an amine or in a sealed tube at 120°C (method III), a 1-(*N*-substi-

Table I. 1-Acyl Derivatives (**4**)

Ent.	Starting material: 1, R, Y	Method, Solv.	Reaction conditions[a]: Acyl. agent, Additive	Temp. (°C), Time (h)	Product: No.	R^1	Yield (%)
1	Me	I	Ac_2O	60—70	**4a**	Me	93
	OMe	A	py	0.5			
2	Et	I	Ac_2O	re	**4b**	Me	81
	OMe	DME	py	3			
3	Et	I	Ac_2O	rt	**4c**	Me	77
	OEt	A	py	ON			
4	Et	II	$ClCH_2COCl$	rt	**4d**	CH_2Cl	73
	OMe	DME	$AlCl_3$	3			
5	Et	I	$(C_5H_{11}CO)_2O$	re	**4e**	C_5H_{11}	44
	OEt	py	—	3			
6	Et	I	$(PhOCH_2CO)_2O$	re	**4f**	$PhOCH_2$	68
	OEt	D	py	6			
7	Et	I	$(C_9H_{19}CO)_2O$	re	**4g**	C_9H_{19}	26
	OEt	py	—	3			
8	Et	I	$(Me_2CHCO)_2O$	re	**4h**	Me_2CH	94[b]
	OC_8H_{17}	D	py	5			
9	Bu	I	$(C_5H_{11}CO)_2O$	re	**4i**	C_5H_{11}	94[b]
	OBu	D	py	4			
10	Et	I	Ac_2O	60—70	**4j**	Me	95
	SPh	A	py	2			
11	Et	I	$(PhOCH_2CO)_2O$	re	**4k**	$PhOCH_2$	40
	S-c-Hexyl[c]	D	py	7			
12	Et	I	PhCOCl	rt	**4l**	Ph	9
	OMe	DME	Et_3N	2			
13	Et	II	Me_3CCOCl	rt	**4m**	Me_3C	23
	OMe	DME	$AlCl_3$	3			

a) re=heated under reflux, rt=room temperature, ON=overnight.
b) A half of the starting material was recovered.
c) c-Hexyl=cyclohexyl.

Table II. 1,3-Diacyl Derivatives (5)

Ent.	Starting material 1, R Y	Method Solv.	Reaction conditions Acyl. agent Additive	Temp. (°C) Time (h)	Product No.	R^1	Yield (%)
1	Et	II	AcCl	rt	**5a**	Me	38(26)[a]
	OMe	DME	$AlCl_3$	3			
2	Et	II	Me_3CCOCl	rt	**5b**	Me_3C	9(23)[a]
	OMe	DME	$AlCl_3$	3			
3	Et	II	c-Hexyl-COCl	rt	**5c**	c-Hexyl	60(39)[a]
	OBu-*sec*	DME	$AlCl_3$	3			
4	Et	II	PhCOCl	rt	**5d**	Ph	73
	OMe	DME–DC	$AlCl_3$	3			
5	Et	I	PhCOCl	rt	**5d**	Ph	35(9)[a]
	OMe	DME	Et_3N	2			
6	Et	II		rt	**5e**		64
	OMe	DME	$AlCl_3$	3			

a) The indicated amount of the corresponding 1-acyl derivative (**4**) was also isolated.

Table III. 1-Carbamoyl Derivatives (7)

Ent.	Starting material 1, R Y	Method Solv.	Reaction conditions Acyl. agent Additive	Temp. (°C) Time (h)	Product No.	R^1 R^2	Yield (%)
1	Et	III	MeNCO	120	**7a**	H	80
	OEt	D	Et_3N	3		Me	
2	Et	IV	$ClCONEt_2$	70	**7b**	Et	13
	OMe	DME	$AlCl_3$	0.5		Et	
3	Et	III	BuNCO	re	**7c**	H	30
	OMe	D	Et_3N	5		Bu	
4	Et	III	MeNCO	120[a]	**7d**	H	62
	OBu-*sec*	D	Et_3N	3		Me	
5	Et	III	PhNCO	130—150	**7e**	H	37
	OMe	(neat)	—	0.5		Ph	
6	Et	III	c-Hexyl–NCO	re	**7f**	H	34
	OMe	D	Et_3N	4		c-Hexyl	
7	Et	IV	c-Hexyl–NCO	re	**7f**	H	16
	OMe	DME	$AlCl_3$	1		c-Hexyl	
8	Et	III	PhNCO	150	**7g**	H	48
	OEt	(neat)	—	0.5		Ph	
9	Et	III	BuNCO	re	**7h**	H	17
	OBu-*sec*	D	Et_3N	3		Bu	
10	Et	IV	$ClCONPh_2$	re	**7i**	Ph	40
	OBu-*sec*	D	$AlCl_3$–Et_3N	2		Ph	

a) Heated in a sealed tube.

tuted)carbamoyl compound (**7**) was obtained. Acid-catalyzed condensation of the silylated **1b** with an isocyanate or with an (*N*,*N*-disubstituted)carbamoyl chloride (method IV) was also tried, but the reaction gave only a poor yield of **7** (method IV, Table III).

The position(s) of acylation was estimated from the following observations. The proton magnetic resonance (PMR) signals of N^1–H and N^3–H protons of **1** appeared between 8.5—9.5 and 10.5—11.0 (in DMSO-d_6) or 7.0—8.0 and 8.5—9.5 (in $CDCl_3$), respectively. One or both of the signals disappeared when 1- or 1,3-diacylation occurred. Also a downfield shift of the H-6 signal from 4.5—5.0 to 5.5—6.5 was observed when N-1 was acylated.

Experimental

Melting points are uncorrected. PMR spectra were recorded on a Varian T-60 spectrometer. Tetramethylsilane was used as an internal standard for all spectra, and deuterated dimethylsulfoxide was used as the solvent, unless otherwise specified. Chemical shifts are expressed in δ (ppm) values. In some cases, only the data for H-6 are cited. Thin-layer chromatography was performed on pre-coated Kieselgel 60F 254 sheets. Column chromatography was carried out using Kieselgel 60. Solutions were concentrated by evaporation *in vacuo*. The solvents used for reaction and recrystallization are abbreviated as follows; A=acetone, B=benzene, C=chloroform, DC=dichloromothane, D=dioxane, DME=1,2-dimethoxyethane, EA=ethyl acetate, H=hexane, and py=pyridine.

Acylation Procedures

Method I. As typical procedures, the preparations of **4a** and **5d** are described.

1) **1-Acetyl-5-fluoro-6-methoxy-5-methoxycarbonyl-5,6-dihydrouracil (4a)**——A solution of **1b** (R=Me, Y=OMe) (3.30 g, 17.4 mmol), Ac_2O (3 ml), and pyridine (3 ml) in 5 ml of acetone was heated at 60—70°C for 0.5 h. The low boiling substances were removed, and the resulting syrup was chromatographed on silica gel, giving 2.0 g of **1b** and 1.45 g (93% based on the reacted **1b**) of **4a** as a white solid. The latter was recrystallized from chloroform–hexane as colorless flakes of **4a**.

2) **1,3-Dibenzoyl-5-ethoxycarbonyl-5-fluoro-6-methoxy-5,6-dihydrouracil (5d)**——PhCOCl (12.4 g, 80 mmol) was added dropwise to a solution of **1b** (R=Et, Y=OMe) (9.36 g, 40 mmol) and Et_3N (8.90 g, 88 mmol) in 100 ml of DME in an ice bath, then the mixture was allowed to stand at room temperature overnight. The crystals of **5d** that separated from the above mixture were collected by filtration and the mother liquor was chromatographed on silica gel, giving 0.7 g of **5d** and 1.21 g (9%) of the 1-benzoyl derivative (**4l**). The total yield of **5d** was 6.20 g (35%).

Method II. As typical procedures, the preparations of **4d** and **5d** are described.

1) **1-Chloroacetyl-5-ethoxycarbonyl-5-fluoro-6-methoxy-5,6-dihydrouracil (4d)**——A solution of Me_3SiCl in 50 ml of benzene was added to a mixture of **1b** (R=Et, Y=OMe) (9.36 g, 40 mmol) and Et_3N (8.10 g, 80 mmol) in 200 ml of benzene at 35°C, then the mixture was heated under reflux for 1 h. After removal of white precipitates by filtration, the filtrate was concentrated to give a colorless oil that was dissolved in 50 ml of DME. The resulting solution was added to a mixture of $ClCH_2COCl$ (9.04 g, 80 mmol) and a catalytic amount of anhydrous $AlCl_3$ in 100 ml of DME. The reaction mixture was kept at room temperature for 3 h. Removal of the solvent gave a yellow oil that was chromatographed on silica gel, giving 9.0 g (73%) of **4d** as a colorless oil.

The following compounds were prepared in a similar manner. **4a**: mp 124—126°C (C–H). *Anal.* Calcd for $C_9H_{11}FN_2O_6$: C, 41.23; H, 4.23; N, 10.68. Found: C, 41.13; H, 4.18; N, 10.70. PMR: 5.98 (d, J_{HF}=2 Hz). **4b**: mp 98—100°C (crude). PMR: 6.02 (d, J_{HF}=3 Hz). **4c**: mp 85—86°C (C–H). *Anal.* Calcd for $C_{11}H_{15}FN_2O_6$: C, 45.52; H, 5.21; N, 9.65. Found: C, 45.49; H, 5.23; N, 9.55. PMR: 6.06 (d, J_{HF}=2 Hz). **4d**: oil. PMR: 6.10 (d, J_{HF}=2.5 Hz). **4e**: oil. *Anal.* Calcd for $C_{15}H_{23}FN_2O_6$: C, 52.02; H, 6.69; N, 8.09. Found: C, 52.01; H, 6.58; N, 8.01. PMR ($CDCl_3$): 5.98 (d, J_{HF}=2 Hz). **4f**: oil. PMR: 6.18 (d, J_{HF}=3 Hz). **4g**: oil. *Anal.* Calcd for $C_{19}H_{31}FN_2O_6$: C, 56.70; H, 7.76; N, 6.96. Found: C, 57.48; H, 8.05; N, 6.72. PMR ($CDCl_3$): 6.20 (d, J_{HF}=2 Hz). **4h**: oil. PMR: 6.02 (d, J_{HF}=3 Hz). **4i**: oil. PMR ($CDCl_3$): 6.20 (d, J_{HF}=3 Hz). **4j**: mp 107—108°C (crude). PMR: 6.38 (br). **4k**: oil. PMR 6.22 (d, J_{HF}=2 Hz). **4l**: oil. PMR 5.90 (d, J_{HF}=2 Hz). **4m**: oil. PMR: 5.53 (d, J_{HF}=3 Hz).

2) **1,3-Dibenzoyl-5-ethoxycarbonyl-5-fluoro-6-methoxy-5,6-dihydrouracil (5d)**——A mixture of **1b** (R=Et, Y=OMe) (9.36 g, 40 mmol) and hexamethyldisilazane (16.1 g, 100 mmol) was heated at 150—160°C for 2 h. Removal of excess hexamethyldisilazane gave the bissilyloxy intermediate (**6**) as a yellow oil (15.4 g). PMR ($CDCl_3$): 0.32 (18H, s), 1.26 (3H, t, J=7 Hz), 3.40 (3H, s), 4.27 (2H, q, J=7 Hz), 4.78 (1H, d, J_{HF}=3 Hz).

Reaction of **6** with PhCOCl: A solution of **6** in 30 ml of DME was added to a mixture of PhCOCl (11.24 g, 80 mmol) and anhydrous $AlCl_3$ (0.5 g) in 20 ml of dichloromethane at room temperature. The mixture was kept at that temperature for 3 h. The crystals that separated were collected by filtration, giving 7.2 g of **5d**. Removal of the solvent from the filtrate gave another crop of **5d**. The total yield of **5d** was 12.85 g (73%). The physicochemical data of **5d** thus obtained are consistent with those of **5d** obtained by method I.

The following compounds were prepared in a similar manner. **5a**: oil. PMR: 6.10 (d, J_{HF}=3 Hz). **5b**: oil. PMR: 5.65 (d, J_{HF}=3 Hz). **5c**: oil. PMR: 6.10 (d, J_{HF}=3 Hz). **5d**: mp 155—156°C (A–C–H). *Anal.* Calcd for $C_{22}H_{19}FN_2O_7$: C, 59.73; H, 4.33; N, 6.33. Found: C, 59.54; H, 4.29; N, 6.24. PMR: 6.18 (d, J_{HF}=3 Hz). **5e**; mp 130—132°C (A–C–H). PMR: (d, J_{HF}=3 Hz).

Method III. 5-Ethoxycarbonyl-5-fluoro-6-methoxy-1-phenylcarbamoyl-5,6-dihydrouracil (7g)——A mixture of **1b** (R=Et, Y=OMe) (6.3 g, 27 mmol) and 17.5 ml of PhNCO was heated at 130—140°C for 1 h. The reaction mixture was evaporated to dryness to give a solid. It was chromatographed on silica gel, giving **7g** as a crude solid that was recrystallized from benzene–hexane to give 3.49 g (48%) of **7g** as colorless flakes.

Method IV. 5-Ethoxycarbonyl-1-(*N*,*N*-diethyl)carbamoyl-5-fluoro-6-methoxy-5,6-dihydrouracil (7b)——A solution of **1b** (R=Et, Y=OMe) (2.32 g, 10 mmol) and Et_3N (1.21 g, 12 mmol) in 20 ml of DME was treated

with a solution of Me_3SiCl (1.30 g, 12 mmol) in 10 ml of DME at room temperature for 1 h, then at 70°C for 0.5 h. Precipitates were filtered off, and the filtrate was heated under reflux for 1 h after addition of *N*,*N*-diethylcarbamoyl chloride (1.49 g, 11 mmol) and 0.3 g of anhydrous $AlCl_3$. The reaction mixture was brought to dryness, giving a solid that was chromatographed on silica gel to give 0.42 g (13%) of **7b** as colorless flakes.

The following compounds were prepared in a similar manner. **7a**: mp 158—159°C (EA–B). *Anal.* Calcd for $C_{11}H_{16}FN_3O_6$: C, 43.28; H, 5.28; N, 13.77. Found: C, 43.43; H, 5.40; N, 13.63. PMR: 6.12 (d, J_{HF}=2.5 Hz). **7b**; mp 148—149°C (EA–H). PMR: 5.32 (d, J_{HF}=2.5 Hz). **7c**: mp 97—98°C (C–H). *Anal.* Calcd for $C_{13}H_{20}FN_3O_6$: C, 46.85; H, 6.05; N, 12.61. Found: C, 47.07; H, 6.09; N, 12.48. PMR ($CDCl_3$): 6.30 (d, J_{HF}=2.5 Hz). **7d**: mp 136—137°C (C–H). *Anal.* Calcd for $C_{13}H_{20}FN_3O_6$: C, 46.85; H, 6.05; N, 12.61. Found: C, 46.83; H, 6.05; N, 12.61. PMR ($CDCl_3$): 6.38 (d, J_{HF}=2.5 Hz). **7e**: mp 111—112°C (B–H). *Anal.* Calcd for $C_{15}H_{16}FN_3O_6$: C, 50.99; H, 4.56; N, 11.89. Found: C, 51.13; H, 4.47; N, 11.82. PMR ($CDCl_3$): 6.33 (d, J_{HF}=2.5 Hz). **7f**: mp 121—122°C (EA–H). *Anal.* Calcd for $C_{15}H_{22}FN_3O_6$: C, 50.14; H, 6.17; N, 11.69. Found: C, 50.18; H, 6.08; N, 11.64. PMR ($CDCl_3$): 6.19 (d, J_{HF}=2.5 Hz). **7g**: mp 111—112°C (B–H). *Anal.* Calcd for $C_{16}H_{18}FN_3O_6$: C, 52.32; H, 4.94; N, 11.44. Found: C, 52.42; H, 4.80; N, 11.37. PMR ($CDCl_3$): 6.50 (d, J_{HF}=2.5 Hz). **7h**: oil. *Anal.* Calcd for $C_{16}H_{26}FN_3O_6$: C, 51.19; H, 6.98; N, 11.19. Found: C, 51.40; H, 7.01; N, 10.98. PMR ($CDCl_3$): 6.49 (d, J_{HF}=2.5 Hz). **7i**: mp 176—177°C (B–H). *Anal.* Calcd for $C_{24}H_{26}FN_3O_6$: C, 61.01; H, 5.55; N, 8.89. Found: C, 61.27; H, 5.39; N, 8.85. PMR ($CDCl_3$): 5.86 (d, J_{HF}=3 Hz).

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References and Notes

1) Part II: O. Miyashita, K. Matsumura, T. Kasahara, H. Shimadzu, and N. Hashimoto, *Chem. Pharm. Bull.*, **30**, 887 (1982).
2) A. Hoshi, M. Iigo, A. Nakamura, M. Inomata, and K. Kuretani, *Chem. Pharm. Bull.*, **26**, 161 (1978); T. Kametani, T. Okada, and M. Nakayama, *J. Med. Chem.*, **23**, 1324 (1980) and references cited therein.
3) The following abbreviations are used in this note: HFU, 5-fluoro-5,6-dihydrouracil skeleton; AcO-, RO-, RS-, and Y, substituents at C-6; -COOR, alkoxycarbonyl group at C-5.