SELECTIVE SYNTHESIS OF 1-ALKOXYCARBONYLOXYMETHYL-5-FLUOROURACILS VIA 1,3-BIS(HYDROXYMETHYL)-5-FLUOROURACIL[1]

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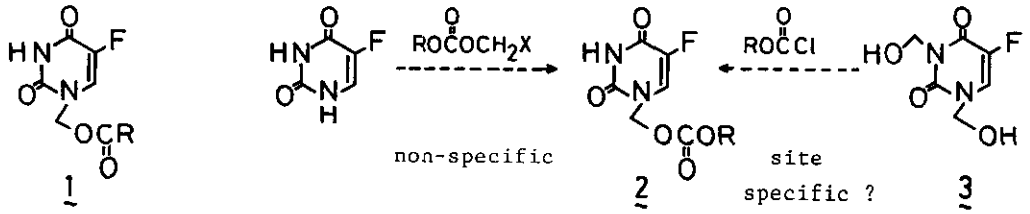
Abstract—Esterification of 1,3-bis(hydroxymethyl)-5-fluorouracil with various alkyl chloroformates in the presence of tert- or hindered sec-alkylamine selectively gave potentially antitumor active 1-alkoxycarbonyloxymethyl-5-fluorouracils in moderate to good yields.

During our studies on masked 5-fluorouracil derivatives, it was found that 1-acyloxymethyl-5-fluorouracils (1) had the stronger antitumor activity and the weaker toxicity.[2] This time we planned to prepare 1-alkoxycarbonyloxymethyl-5-fluorouracils (2) with the aim of obtaining less toxic derivatives than 1. Since direct alkylation of 5-fluorouracil are known to be non-site specific reaction,[3] we investigated the selective esterification of 1,3-bis(hydroxymethyl)-5-fluorouracil (3)[1] with alkyl chloroformates.



1 2 3

At first, 3 was treated with 1.0-1.2 eq of benzyl chloroformate in pyridine at room temperature to afford a mixture of 1-, 3-, and 1,3-bis(benzyloxycarbonyloxymethyl)-5-fluorouracils (4, 5, and 6) in 11, 11, and 6% yields, respectively. Even if the reaction was carried out with 1.27 eq of pyridine or 2,6-lutidine, products were also a mixture of 4, 5, and 6. When triethylamine (1.27 eq) was used as a base in place of pyridine, however, no trace of 5 was detected in the reaction mixture. After usual work-up, 85% yield of 4 accompanied with 7% yield of 6 was isolated. Using other tert-amines, for examples, ethyldiisopropylamine (EDA) and N,N-dimethylaniline, or hindered sec-amine (diisopropylamine) gave only 1-substituted compound 4 and a small amount of bis-compound 6 (see Table 1).

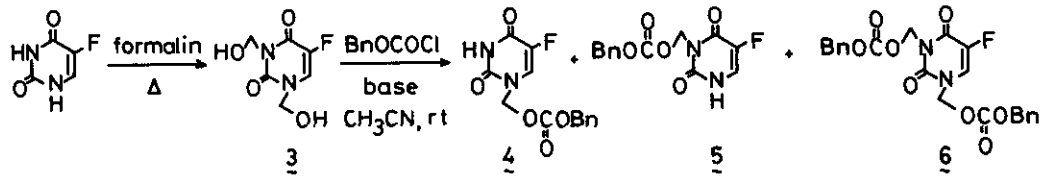


Table 1. Preparation of N-(Benzyloxycarbonyloxymethyl)-5-fluorouracils.

base	(eq)	yield (%)[a]			base	(eq)	yield (%)[a]		
		4	5	6			4	5	6
	(excess)[b]	11	11	6	EDA	(1.20)	68	-[c]	11
	(1.27)	13	47	23	Et_3N	(1.27)	85	-[c]	7
	(1.27)	24	17	14		(10)	9	9	-[c]
$NaHCO_3$	(1.27)	49	5	5	$^iPr_2NH$	(1.25)	75	-[c]	8
$PhNMe_2$	(1.20)	11	-[c]	1					

a: Isolated yield based on 5-fluorouracil after usual work-up and separation.

b: Pyridine was used as a solvent.

c: No product was obtained after usual work-up nor detected on TLC in the reaction mixture.

Subsequently, in order to examine whether bis-compound 6 was decomposed to 4 or 5 under the present reaction conditions, 6 was treated with various amines in acetonitrile at room temperature but in case of triethylamine, EDA, diisopropylamine, and pyridine no reaction occurred (Table 2).[4] In contrast 6 was treated with imidazole

Table 2. Stability of Compound 6 under Basic Conditions.

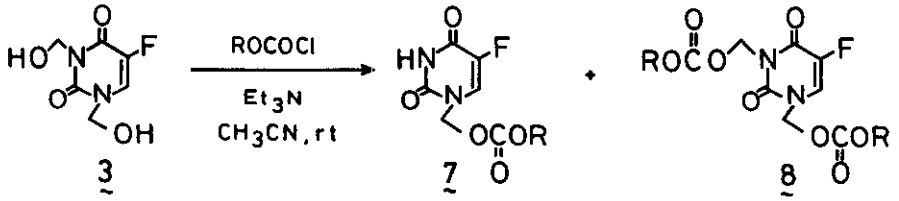
base	(eq)	reaction time	yield (%)[a]		
			4	5	6 (recovery)
	(10)	2 days	-	-	100
Et_3N	(10)	2 days	-	-	100
$PhNMe_2$	(5)	2 days	-	-	100
NH_3[b]	(16)	7 days	7	56	c
28% aq.NH_3	(10)	1 day	4	35	c
	(5)	5 days	-	99	-
$^iPrNH_2$	(10)	1 h	-	11	c

a: Isolated yield; b: Use the saturated dry ethanol solution of dry ammonia gas; c: 5-Fluorouracil was detected in the reaction mixture but not isolated.

(5 eq) at room temperature for 5 days to afford 3-substituted compound 5 selectively. This degradation of the N-1 substituent will become a promising route for the selective synthesis of 3-substituted compounds like 5.

According to the above experimental results, highly site-selective substitution of the present procedure could be explained as follows: In case of the effective base (triethylamine, EDA, diisopropylamine) 3 was activated enough to react with chloroformate at the N-1 position to afford 4. In the later stage of the reaction, the resulting 4 reacted with the remained benzyl chloroformate at the N-3 position to give bis-substituted compound 6 as a minor product. When pyridine or 2,6-lutidine was used as a base, the low basicity of these bases could not smoothly complete the desired alkoxycarbonylation, while the decomposition of the hydroxymethyl group of 3 into formalin and NH group competitively occurred.[5] Therefore the use of pyridine or 2,6-lutidine decreased the yield and the selectivity of the present alkoxycarbonylation. Details of the chemical properties of the hydroxymethyl group of 3 is now under investigation.

Following the conditions described above, 3 was allowed to react with various alkyl chloroformates. In all cases 3-substituted derivatives like 5 were not detected in the reaction mixture. Results are summarized in Table 3. All 1-alkoxycarbonyloxymethyl-5-fluorouracils have moderate antitumor activity against leukemia L-1210.[6] Further experiments of antitumor activity are under way.



3 → 7 + 8

Table 3. Preparation of Other 1-Alkoxycarbonyloxymethyl-5-fluorouracils.

R	yield (%)[a]		R	yield (%)[a]	
	7	8		7	8
	65	3	Et	47	17
	65	19	n-$C_{16}H_{33}$	62	16
sec-Octyl	59	3	Me 	68	20

a: Isolated yield based on 5-fluorouracil, not optimized.

In conclusion, the present method affords 1-alkoxycarbonyloxymethyl-5-fluorouracils without a trace amount of 3-substituted derivatives even if the procedure involves esterification of the bifunctional intermediate, 1,3-bis(hydroxymethyl)-5-fluorouracil.

Direct alkylation and acylation of 5-fluorouracil are known to non-site specific reaction,[3] and, moreover, selective (mono) esterification of 3 with acid halides and acid anhydrides has not been reported, therefore these results seem to be worth noting.

REFERENCES AND NOTES

1. 5-Fluorouracil Derivatives. XIV. Part XIII: S. Ahmad, S. Ozaki, T. Nagase, M. Iigo, and A. Hoshi, Chem. Pharm. Bull., 1987, 35, 4137.
2. Antitumor activity: A. Hoshi, M. Inomata, F. Kanzawa, M. Iigo, and K. Kuretani, J. Pharm. Dyn., 1982, 3, 208; synthesis: S. Ozaki, Y. Watanabe, T. Hoshiko, H. Mizuno, K. Ishikawa, and H. Mori, Chem. Pharm. Bull., 1984, 32, 733.
3. For example, H. Nomura, Y. Yoshioka, and I. Minami, Chem. Pharm. Bull., 1979, 27, 899.
4. Compound 3 was easily soluble in pyridine and acetonitrile, and slightly in dichloromethane. In the present work acetonitrile was used as a solvent without any description in the text.
5. Decomposition of 3 into 5-fluorouracil could be observed under the reaction conditions by use of pyridine or lutidine as a base. Two elimination mechanisms of formalin from 3 are considered. The first one is a base-induced mechanism. This is supported the following data: When 3 was stirred in the presence of 1.27 eq of pyridine in dry acetonitrile at room temperature for 13.5 h, and then treated with benzyl chloroformate, the yields of 4, 5, and 6 were 19, 18, and 17%, respectively. On the other hand, a proton-induced mechanism is also presumed because of the presence of pyridinium or lutidinium chloride in the reaction mixture. A small amount of proton deprotonated from onium salt may accelerate the degradation of N-C bond of 3. However, the exact mechanism can not be decided by the present experimental data. Further investigations are in progress.
6. A. Hoshi, personal communication. All the new compounds show the reasonable ^{1}H-NMR, IR, and elemental analysis (C,H,N) data supported the proposed structures.

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