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Application of the Benzyloxycarbonyloxymethyl Moiety to a Protective Group of 5-Fluorouracil. Selective Alkylation of Amide Nitrogen of the Uracil Ring$^{1)}$

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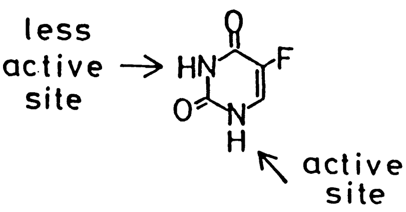
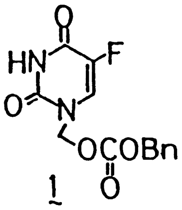
Selective alkylation of 5-fluorouracil using the benzyloxycarbonyloxymethyl moiety as a protective group of amide nitrogen of the uracil ring is described. Protection, alkylation and deprotection were carried out in high yields.

Site-specific substitution reaction of the N_1 or N_3 position of the uracil ring is very important for preparation of the desired N-mono-substituted derivatives. In order to solve the problem a suitable protective group has been used. In the field of 5-fluorouracil chemistry many protective groups, for example, sulfonyl,$^{2)}$ acyl,$^{3)}$ alkoxy- or aryloxy-carbonyl,$^{4)}$ and benzyl$^{5)}$ groups, have been proposed and used for protection of amide nitrogen. However, some of these groups are especially susceptible to usual reaction and work-up conditions and others are deprotected under basic, acidic, or strongly reductive conditions. In a previous paper we described selective preparation of 1-alkoxycarbonyloxymethyl-5-fluorouracils.$^{1)}$ Among these 5-fluorouracil derivatives we focused on 1-benzyloxycarbonyloxymethyl-5-fluorouracil (1) because 1 had the substituent characterized as follows: That a substituent attached to the uracil ring through a methylene caused to increase the stability of the N-C bond between the ring and the substituent under acidic or basic conditions. On the contrary, this substituent which involved a benzyloxycarbonyl moiety was easily removed by catalytic hydrogenolysis. Therefore, N-benzyloxycarbonyloxymethyl-5-fluorouracils (1, 2) seem to become facile protected compounds of 5-fluorouracil. We wish to describe here selective alkylation of 5-fluorouracil using this benzyloxycarbonyloxymethyl moiety as a protective group.

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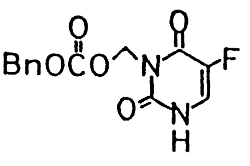
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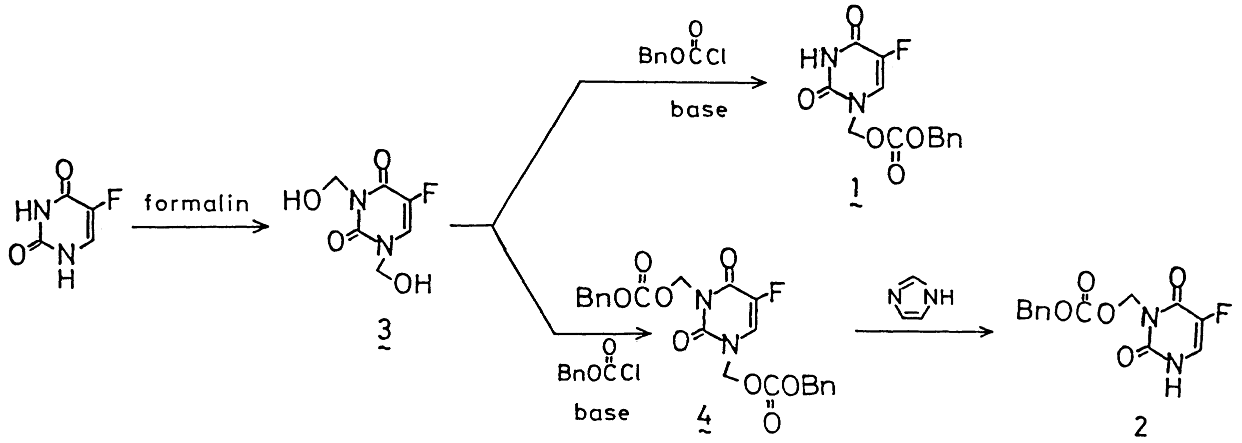
Bn : $PhCH_2$-

1- or 3-Benzyloxycarbonyloxymethyl-5-fluorouracil (1, 2) was prepared in the following manner. 5-Fluorouracil was directly allowed to react with 30% formalin (2.5 equiv.) below 70 °C. Within 15 min 5-fluorouracil reacted with formalin and dissolved in water. After complete removal of water and excess formalin in vacuo, 1,3-bis(hydroxymethyl)-5-fluorouracil (3) was obtained as viscous oil$^{6)}$ in almost quantitative yield. Compound 3, which was used without further purification, was dissolved in dry acetonitrile and allowed to react with 1.2 equiv. of benzyl chloroformate in the presence of triethylamine (1.2 equiv.) to afford the 1-protected 5-fluorouracil 1[7] in 85% yield (mp 144-146 °C) based on 5-fluorouracil, while 3 was at first allowed to react with 3.0 equiv. of benzyl chloroformate to give the 1,3-bis(protected) derivative 4 (80% yield based on 5-fluorouracil), which was treated with 1.1 equiv. of imidazole in acetonitrile to afford the 3-protected 5-fluorouracil 2[8] quantitatively (mp 130-132 °C)(Scheme 1). Compounds 1 and 2 were well soluble in usual polar organic solvents and very stable under strongly acidic conditions. Under basic conditions 1 and 2 were relatively stable.[9]



Scheme 1.

Alkylation of 1 and 2 was carried out in acetonitrile in the presence of tertiary amine, for example, triethylamine or ethyldiisopropylamine (EDA) at room temperature (EDA was the most effective as a base). Reaction smoothly occurred within several hours and yields of alkylation were almost quantitative. Both 1 and 2 sufficiently reacted with alkyl halides (1.1-1.5 equiv.) described in the Tables 1 and 2, but 2 was more reactive than 1 toward the less reactive halides.

Deprotection of the benzyloxycarbonyloxymethyl group was carried out as described below. Alkylated 5-fluorouracil 5 or 7 was dissolved in methanol and stirred at room temperature under hydrogen atmosphere (under stmospheric pressure) in the presence of 5-10% (w/w) of 5% palladium carbon as catalysts. Deprotection usually completed within 30 min. After simple filtration of catalysts and removal of solvent, the alkylated compound was obtained in almost quantitative yield as a pure and sole product without further purification. The results of alkylation and deprotection are summarized in Tables 1 and 2. Under these conditions the N-benzyl group was not cleaved at all, but in the case of the N-allyl group hydrogenation into the propyl group occurred at the same time that hydrogenolysis of the protective group proceeded. Some exchanges of the hydrogenolytic conditions were not effective for selective deprotection of the benzyloxycarbonyloxymethyl moiety. However, ammonolysis with concentrated aqueous ammonia succeeded in selective and quantitative deprotection of the benzyloxycarbonyloxymethyl group within a few minutes.[10]

On the basis of the experimental results presented above, we proposed that the advantages of this benzyloxycarbonyloxymethyl moiety to a protective group of 5-

fluorouracil as follows: (1) This group is easily introduced to 1- or 3-position of 5-fluorouracil by the use of commercially available and inexpensive reagents under mild conditions; (2) Protected compounds are quite stable under acidic conditions and relatively stable under basic conditions, and have well solubility in usual polar solvents and sufficient reactivity toward various alkyl halides; (3) This group is smoothly and completely deprotected under very mild conditions. Since the protective moiety decomposes into volatile materials, no further purification except for filtration of catalysts and evaporation of solvent is required during the work-

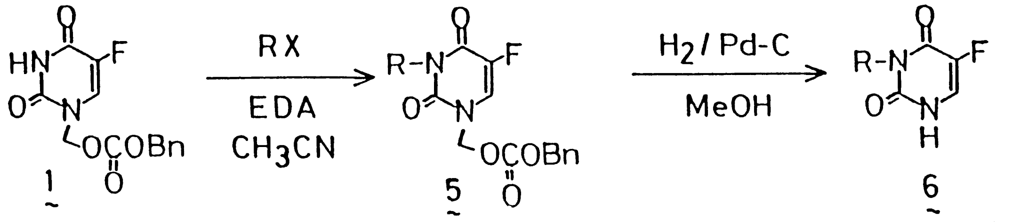


Table 1. Alkylation and Deprotection of 1-Protected 5-Fluorouracil 1 a)

Run	RX	5	Yield/%b)	6	Yield/%b)
a	$MeOCH_2Cl$	5a	82	6a	quant.
b	n-BuBr	5b	64	6b	99
c	$BrCH_2COOEt$	5c	quant.	6c	92
d	$CH_2=CHCH_2Br$	5d	96	6d	96c) (quant.)d)
e	MeI	5e	93	6e	84
f	$PhCH_2Br$	5f	96	6f	quant.

a)All the new compounds showed the reasonable ^1H NMR, IR and analytical data supported the described structures. b) Isolated yield after chromatographic purification, if necessary. c) N-Allyl group was reduced to n-propyl group under the present hydrogenolysis, see text. d) Yield by the use of 28% aq. ammonia in the acetonitrile at room temperature for 10 min.

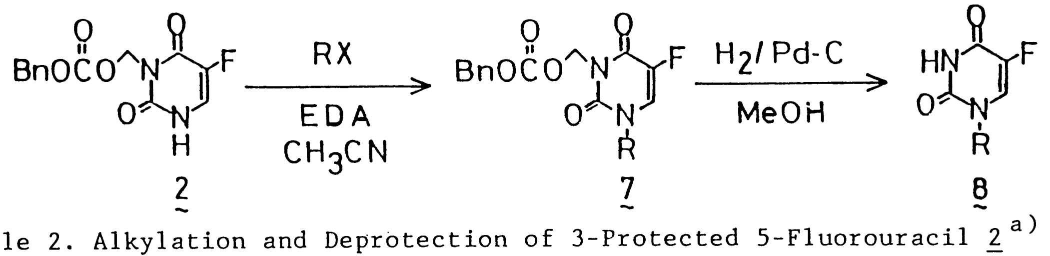


Table 2. Alkylation and Deprotection of 3-Protected 5-Fluorouracil 2 a)

Run	RX	7	Yield/%b)	8	Yield/%b)
a	$MeOCH_2Cl$	7a	90	8a	77
b	n-BuBr	7b	85	8b	90
c	$BrCH_2COOEt$	7c	quant.	8c	83
d	$CH_2=CHCH_2Br$	7d	quant.	8d	quant.c) (81)d)
e	MeI	7e	95	8e	93
f	$PhCH_2Br$	7f	97	8f	96

a) All the new compounds showed the reasonable ^1H NMR, IR,and analytical data supported the described structures. b) Isolated yield after chromatographic purification, if necessary. c) N-Allyl group was reduced to n-propyl group under the present hydrogenolysis, see text. d) Yield by the use of 28% aq. ammonia in the acetonitrile at room temperature for 10 min.

up procedure. Protection, alkylation, and deprotection proceed smoothly at room temperature. Application of this protective group to other uracil and thymine derivatives are now in progress.

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7) Spectral data for 1: ^{1}H NMR (DMSO-d_6):δ(ppm) 5.16 (s, 2H, -CH$_2$Ph), 5.64 (s, 2H, N-CH$_2$-O), 7.20-7.44 (5H, aromatics), and 7.88 (d, J_F = 6.4 Hz, 1H); IR (nujol): 3200, 1750, 1700, and 1660 cm^{-1}. Found: C, 53.09; H, 3.96; N, 9.50%. Calcd for $C_{12}H_{11}FN_2O_5$: C, 53.07; H, 3.77; N, 9.52%.
8) Spectral data for 2: ^{1}H NMR (DMSO-d_6):δ(ppm) 5.18 (s, 2H, -CH$_2$Ph), 5.94 (s, 2H, N-CH$_2$-O), 7.12-7.40 (5H, aromatics), and 7.48 (d, J_F = 5.2 Hz, 1H); IR (nujol): 3100, 1760, 1680, and 1650 cm^{-1}. Found: C, 52.85; H, 3.59; N, 9.51%. Calcd for $C_{12}H_{11}FN_2O_5$: C, 53.07; H, 3.77; N, 9.52%.
9) In the reaction medium compounds 1 and 2 were tolerant of tertiary amine (triethylamine, EDA), pyridine, 2,6-lutidine, or diisopropylamine.
10) In this case aminolysis of the benzyloxycarbonyloxymethyl group by the use of isopropylamine in ether or acetonitrile solution could not afford even a trace amount of deprotected compound.

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