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p-Methoxybenzyl as a New N^3-Imide Protecting Group of 5-Fluorouridine and Its Application to the Synthesis of 5'-O-Acryloyl-5-fluorouridine[1)]

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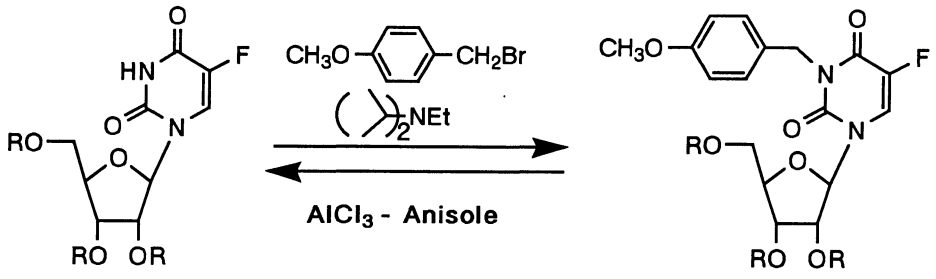
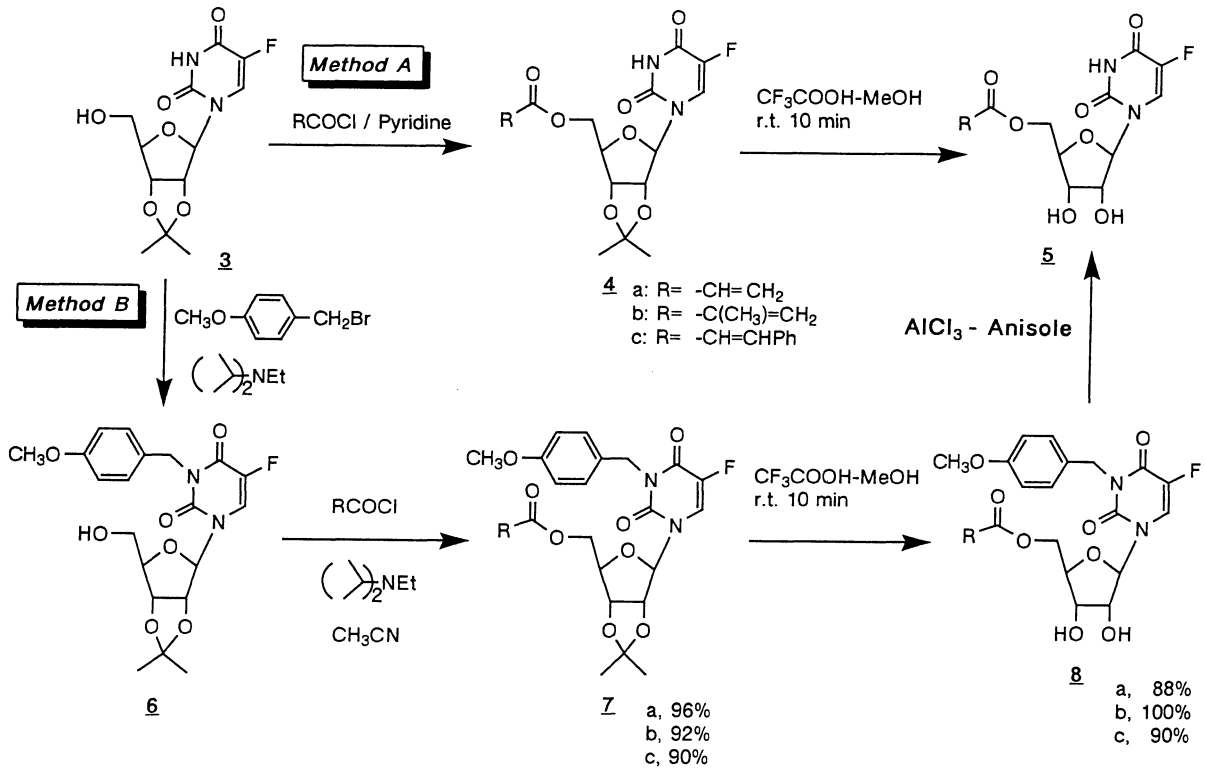
5'-O-Acryloyl-5-fluorouridine was prepared by use of p-methoxybenzyl(PMB) group as a new N^3-imide protecting group of 5-fluorouridine. A chemoselective method for protection has been developed by use of ethyldiisopropylamine as a base and deprotection was effected by $AlCl_3$-anisole system.

In the course of synthetic studies on 5-fluorouracil derivatives having antitumor activity, we have found that 5'-O-acyl-5-fluorouridines showed strong antitumor activity against L-1210 leukemia in mice.[2)] In order to synthesize 5'-O-acryloyl and 5'-O-methacryloyl-5-fluorouridines efficiently, protection of the N^3-imide function was necessary. In this paper, we report a new protecting group for the N^3-imide function of 5-fluorouridine, p-methoxybenzyl group, which can be introduced selectively and removed under mild conditions by treatment with $AlCl_3$ in anisole,[3)] and its application to the synthesis of 5'-O-acryloyl-5-fluorouridine.



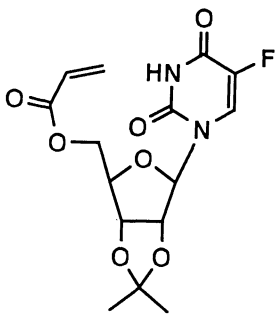
1 **Scheme 1.** 2

We have already synthesized various kinds of 5'-O-acyl-5-fluorouridines (5) by the following method (Method A in Scheme 2); 2',3'-O-isopropylidene-5-fluorouridine[4)] (3) was treated with acyl chloride in pyridine to afford 5'-O-acyl-2',3'-O-isopropylidene-5-fluorouridines (4) followed by deprotection of the 2',3'-O-isopropylidene moiety by use of trifluoroacetic acid to give 5 in good yields. However when methacryloyl and acryloyl chlorides were used as acyl components, the corresponding 5'-O-methacryloyl (**4b**) and 5'-O-acryloyl compounds (**4a**) were obtained



Scheme 2.

in very low yields. **4a** was too labile to purify by column chromatography. **4a** and **4b** were anomalously unstable in 5'-O-acyl-5-fluorouridine derivatives. When the 2',3'-hydroxyl group is protected by an isopropylidene group, 2-carbonyl oxygen of uracil is known to approach 5'-carbon compared to 2',3' free compound.[5] We speculated that this unusual lability was due to the presence of the N^3 proton and so, **4a** would be stabilized by protecting the N^3-imide function. As a protecting group for the uracil residue, benzoyl group is used commonly,[6] and new types of protecting groups have appeared.[7] But some of them need protection of hydroxyl group in advance and some need basic conditions to deprotect. In our case however, acryloyl ester function is labile under basic conditions, so protecting group deprotected under nonbasic conditions is desirable. We found the p-methoxybenzyl (PMB) group as a new protecting group for the imide function of the 5-fluorouridine residue, which could be deprotected under mild conditions.



4a

The PMB group was selectively introduced to 5-fluorouridine smoothly as ethyldiisopropylamine as a base and was deprotected by $AlCl_3$ in anisole at room temperature. 2',3'-O-Isopropylidene-3-(4-methoxybenzyl)-5-fluorouridine (**3**) was treated with p-methoxybenzyl bromide in the presence of ethyldiisopropylamine in acetonitrile at room temperature for 5 h to obtain 2',3'-O-isopropylidene-3-(4-

methoxybenzyl)-5-fluorouridine (6) in a quantitative yield. p-Methoxybenzyl bromide reacted selectively at the N^3 position in the presence of the 5'-OH group. 6 was allowed to react with acryloyl chloride in CH_3CN ethyldiisopropylamine as a base to afford 5'-O-acryloyl-2',3'-O-isopropylidene-3-(4-methoxybenzyl)-5-fluorouridine (**7a**) in 96% yield. As expected, **7a** was stable at room temperature and the stability of **4a** was dramatically improved by protection of the N^3-imide group. The 2',3'-O-isopropylidene moiety was removed by 80% trifluoroacetic acid in methanol to give **8a** in 88% yield. The deprotection of the PMB moiety was carried out as follows. An anisole solution of $AlCl_3$ (10 equiv.) was added to **8a** in anisole at room temperature. After stirring at that temperature for 2 h, MeOH was added to the reaction mixture at 0 °C. The solution was concentrated in vacuo to give an oil, which was purified by SiO_2 (CH_2Cl_2 : MeOH, 10: 1) to afford 5'-acryloyl-5-fluorouridine (**5a**) in 96% yield. $AlCl_3$ selectively cleaved the p-methoxybenzyl group without harming the N-glycosidic bond. Table 1 shows the results of this deprotection method. 5'-O-Methacryloyl and 5'-O-cinnamoyl derivatives were also obtained in good yields by this method.(Runs 2,3) It is noted that the 2',3'-O-isopropylidene moiety was not affected under these conditions.(Runs 4,5)

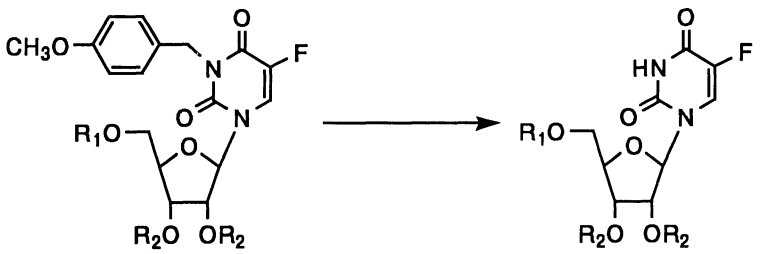


Table 1. Deprotection of the p-methoxybenzyl group[a)]

Run		R_1	R_2	R_3	Product	Yield / %
1	**8a**	-COCH=CH_2	H	H	**5a**	96
2	**8b**	-COC(CH_3)=CH_2	H	H	**5b**	81
3	**8c**	-COCH=CHPh	H	H	**5c**	93
4	**7c**	-COCH=CHPh	$C(CH_3)_2$		**5c**	81
5	**6**	H	$C(CH_3)_2$		**3**	82

a) 10 equiv. of $AlCl_3$ was used in anisole at room temperature.

As expected, **5a** thus obtained was much more stable than **4a** and we concluded that protection of 2',3'-hydroxyl groups with the isopropylidene group cause the imide moiety to come close to the 5'-O-acyl function and that the imide group would have intramolecularly catalyzed decomposition of the acryloyl derivative.

Consequently, PMB was found to be a good protecting group of the N^3-imide function of 5-fluorouridine. It should be noted that chemoselective introduction to

the N^3-imide function in the presence of hydroxyl groups is possible and that the PMB group was cleaved under mild conditions by treatment with $AlCl_3$ in anisole without affecting the N-glycosidic bond. By use of this method, hitherto inaccessible 5'-O-acryloyl-5-fluorouridine was obtained effectively. The antitumor activity of this compound will be reported later.

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