5-FLUOROURACIL DERIVATIVES. VI.[1] ALKYLATION OF 5-FLUOROURACIL USING THE (OCTYLTHIO)CARBONYL GROUP AS A PROTECTING FUNCTION

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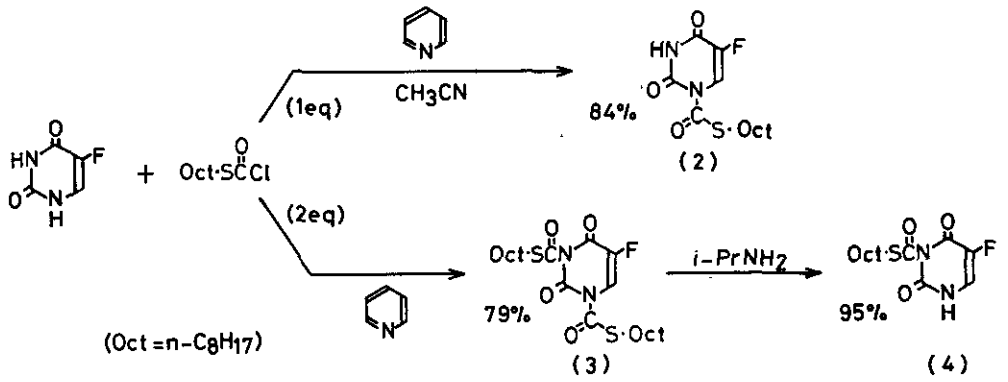
Abstract —— N_1- and N_3-alkyl-5-fluorouracils are prepared in good yields by the alkylation of 5-fluorouracil protected by the (octylthio)carbonyl group.

Alkylation of 5-fluorouracil (5-FU)[2] or its disilyl derivative,[3] 5-fluoro-2,4-bis-(trimethylsilyloxy)pyrimidine gives generally a mixture of 1- and 3-monoalkyl- and 1,3-dialkyl derivatives. Employment of a protecting group is a more promising way to get 1- or 3-alkyl-5-FU selectively. There have been known several protected 5-FUs such as sulfonyl,[4] acyl,[5] 2,2,2-trichloroethyloxycarbonyl,[6] and benzyl[7] derivatives. Some of these protecting groups are too labile to tolerate various reaction conditions. Deprotection of them requires reductive, alkaline, or acidic condition. These conditions are not always satisfactory, especially when the functional groups sensitive to such conditions exist in the same molecule. We have investigated a more sufficient protecting group which is introduced and removed effectively under mild conditions. We report here alkylation of 5-FU using the (octylthio)carbonyl group as a protecting one. Relating to this group, little attention has been paid to the use of S-substituted thiocarbonate derivatives[8] for protecting nitrogen and oxygen functions.

The (octylthio)carbonyl group was easily introduced at the N_1- and N_3-position in 5-FU respectively with high efficiency (Scheme I). Thus, treatment of 5-FU with S-octyl chlorothioformate in the presence of an equimolar amount of pyridine gave the corresponding N_1-protected 5-FU (2) in 84% yield. Protection of the N_3-position was achieved by way of the 1,3-bis(octylthio)carbonyl derivative (3) which was prepared by the reaction of 5-FU with a nearly stoichiometric amount of S-octyl chlorothioformate in pyridine. Isopropylamine effected the selective conversion of 1,3-disubstituted 5-FU (3) to the N_3-protected derivative (4), whereas alcoholic ammonia in place of the amine gave unselective results. The S-octyl group is better than the S-butyl, judging from the yield of the reaction leading to (3) from 5-FU.



Scheme I

The protected derivatives (2) and (4) were alkylated with various alkyl halides in the presence of ethyldiisopropylamine or trietylamine (Table 1 and 2).[9] The former amine is an effective base for alkylation of (2) and (4).

Selective and smooth deprotection was realized by two procedures based on utilizing typical properties of thioester. First choice is to employ a thiophile as lead (II) acetate[8c,f] for selective activation of the thioester function. The second method consists of aminolysis using isopropylamine or diethylamine. This procedure is based on the nucleophilic ability of amine to the thioester group. Thus, the protecting group was efficiently removed without injuring the alkyl substituent to give high yield of monoalkyl-5-fluorouracils (Table 1 and 2).[9]

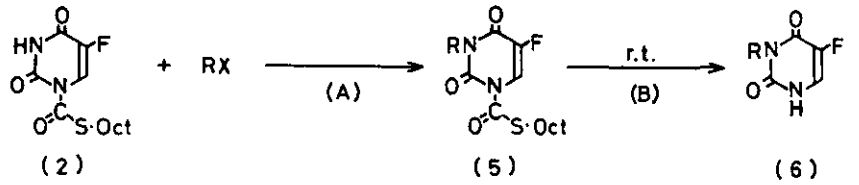
The (octylthio)carbonyl group is introduced and removed smoothly in good yields under mild conditions. The same function can be used to protect N_1- and N_3-nitrogen atoms respectively. S-octyl chlorothioformate used for preparation of the protected 5-FU derivatives (2), (4) is commercially available.[10] Furthermore, alkylation demonstrated here proceeds so cleanly that the isolation procedure is very simple. Consequently, the present alkylation procedure might be widely applicable to monoalkylation of pyrimidine derivatives such as uracil[11] and thymine as well as 5-FU.

EXPERIMENTAL

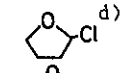
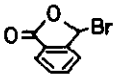
1-(Octylthio)carbonyl-5-fluorouracil (2): An acetonitrile (20 ml) solution of pyridine (10 mmol) was added to a suspension of 5-FU (10 mmol) in acetonitrile (10 ml) containing S-octyl chlorothioformate (10 mmol) at 0°C. The resulting mixture is stirred at the same temperature for 1 h and then at r.t. for 1 day. After addition of AcOEt the organic layer was washed successively with H_2O, dil. HCl, and H_2O and then dried. Recrystallization from benzene-hexane gave (2) in 84% yield, mp 111-112°C.

1,3-Bis(octylthio)carbonyl-5-fluorouracil (3): 5-FU (10 mmol) in pyridine (25 ml) was treated with S-octyl chlorothioformate (30 mmol) at 0°C for 1 h and then at r.t.

Table 1. Synthesis of 3-alkyl-5-FU

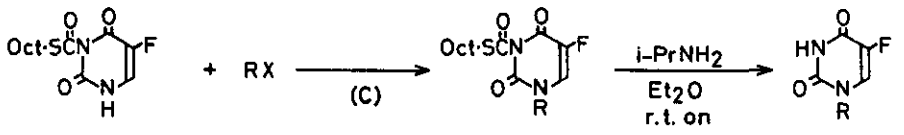


(2) (5) (6)

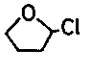
RX	Reaction coditions A base[a]	solv.	temp.	time[b]	B reag.[c]	solv.	time	Yield, % (5)	(6)	mp, °C (5)	(6)
$PhCH_2Br$	TEA	DMF	r.t.	on	LA	EtOH	1day	85	83		
	EDA	DMF	0°C	4h	DIA	CH_2Cl_2	3days	93	95	78.0-79.5	156.0-157.0
					DEA	CH_2Cl_2	20min		86		
 [d]	TEA	THF	r.t.	1h	IPA	Et_2O	10min	92	quant.	64.0-65.0	127.0-128.0
	EDA	DMF	r.t.	3h	IPA	Et_2O	20min	74	97	95.0-96.0	261.5-262.5
$MeOCH_2Cl$	EDA	DMF	0°C	30min	IPA	Et_2O	10min	92	quant.	62.5-63.5	124.0-125.0
n-BuBr	EDA	DMF	r.t.	1day	IPA	Et_2O	10min	83	98	52.0-54.0	88.0-89.0
$PhSCH_2Cl$	EDA	DMF	r.t.	1day	IPA	Et_2O	10min	56	99	80.5-82.0	131.0-132.5

a) TEA=triethylamine, EDA=ethyldiisopropylamine. b) on=overnight. c) LA=lead(II)acetate·$3H_2O$, DIA=diisopropylamine, DEA=diethylamine, IPA=isopropylamine. d) Prepared in situ according to the literature (ref. 1a).

Table 2. Synthesis of 1-alkyl-5-FU



(4) (7) (8)

RX	Reaction conditions C base	solv.	temp.	time	Yield, % 7	(8)	mp, °C (7)	(8)
	TEA[a]	THF	r.t.	on	78	95	oil	163.0-164.0
$MeOCH_2Cl$	EDA	DMF	0°C	1h	99	91	oil	129.0-130.5

a) In order to neutralize the reaction medium, excess triethylamine was used.

for 1 day. After addition of AcOEt and filtration, the filtrate was evaporated under reduced pressure (<40°C). The residue was washed with dil. HCl and H_2O, and dried. Disubstituted 5-FU (3) was isolated by SiO_2 column chromatography (CH_2Cl_2/hexane = 1), 79% yield, mp 60-61°C (from hexane).

3-(Octylthio)carbonyl-5-fluorouracil (4): Compound (3) (10 mmol) in Et_2O (100 ml) was treated with isopropylamine (10 mmol) at 0°C for 30 min. Removal of the solvent under reduced pressure gave the residue which was chromatographed on SiO_2 (AcOEt/hexane = 2/3) to give (4) in 95% yield, mp 120-121°C (from benzene-hexane).

Alkylation of (2) and (4): The protected 5-FU derivatives (2) and (4) (1 mmol) in DMF (3 ml) were treated with an alkyl halide (1.1-1.2 mmol) in the presence of a tert-amine (1.1-1.2 mmol) as shown in the tables.

Deprotection; a) with $Pb(OAc)_2 \cdot 3H_2O$: An alkylation product (1 mmol) was treated with $Pb(OAc)_2 \cdot 3H_2O$ (1 mmol) in ethanol (10 ml) as shown in the tables.

b) With an amine: Treatment of (2) or (4) (1 mmol) in Et_2O or CH_2Cl_2 (10 ml) with diethylamine or isopropylamine (1-1.2 mmol) gave (5) or (6) as ahown in the tables.

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9. All new compounds gave satisfactory spectral data (IR and NMR) and combustion analysis. The structures of the known compounds were determined by comparison of their melting points with that reported in literature and by spectral data.
10. This reagent was kindly presented by BASF Aktiengesellschaft.
11. The same sequential procedure afforded 3-alkyluracils in good overall yield.

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