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FACILE ALKYLATION OF PURINES, PYRIMIDINES, NUCLEOSIDES AND NUCLEOTIDES USING TETRABUTYLAMMONIUM FLUORIDE

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Alkyl halides[1,2] and trialkyl phosphates[3] have been employed under a variety of conditions for the alkylation of purine and pyrimidine bases. With both reagents yields are often quite low (10-40%) and are usually under 60%[2,3] even though temperatures up to 220°C have been employed. With trialkyl phosphates in particular, only trimethyl phosphate gives good yields[3] and even here at temperatures of 25-60°C, long reaction times (10-48 hr) and with base catalysis yields are low, even with thymine and uracil.

We have previously described the use of tetrabutylammonium fluoride (TBAF) to produce quantitative acylation at the hydroxyl groups of pyrimidine nucleosides[4]. We wish to report here that TBAF causes rapid and often quantitative alkylation of purine and pyrimidine bases with alkyl halides and trimethyl phosphate at room temperature. Alkyl phosphates other than $(CH_3O)_3PO$ require higher temperatures to produce good yields of alkylated base (Table I).

The procedure can be illustrated by the reaction of uracil with either methyl bromide or trimethyl phosphate. One mmole of uracil is dissolved in 10 ml of tetrahydrofuran containing 5 mmole of TBAF. Methyl bromide (3 mmole) or trimethyl phosphate (1 ml) is then added and the solution is stirred at room temperature for 1 hr. Products can be isolated in a variety of ways including thick layer chromatography on silica gel. 1,3-Dimethyluracil is obtained in nearly quantitative yield from each reaction. Yields for a variety of alkyl halides and alkyl phosphates with purines and pyrimidines are shown in Table I. Guanine does not react with methyl bromide under these conditions since it is insoluble in the medium.

Recently nucleosides bridged through their bases have become of interest[5]. Such derivatives can easily be obtained from thymidine nucleotides. For example treatment of 5'-O-methoxytritylthymidine (I) with TBAF in methylene chloride yields the dimer 2a in 91% yield after 4 hr at 25°C. Similarly, compounds 2b and 2c were obtained in 27% and 35% yields respectively using 1,2-dichloroethane and 1,6-dichlorohexane.

Table I

Alkylation of Purines and Pyrimidines by Trialkyl Phosphates and Alkyl Halides with TBAF

Base	Alkylating Agent	Temp (°C)[*]	Products (%)
uracil	CH_3Br	25	1,3-dimethyluracil (99)
uracil	$(CH_3O)_3PO$	25	1,3-dimethyluracil (97)
uracil	ϕCH_2Cl	25	1,3-dibenzyluracil (96)
uracil	$CH_3CH_2CH_2CH_2Br$	25	1,3-dibutyluracil (90)
uracil	$(C_2H_5O)PO$	75	1-ethyluracil (10) 1,3-diethyluracil (60)
uracil	$(C_4H_9O)_3PO$	75	1-butyluracil (10) 1,3-dibutyluracil (60)
cytosine	CH_3Br	25	1,3-dimethylcytosine (85)
cytosine	$(CH_3O)_3PO$	25	1-methylcytosine (70) 1,3-dimethylcytosine (30)
adenine	CH_3Br	25	9-methyladenine (95)
adenine	$(CH_3O)_3PO$	25	9-methyladenine (80) 3-methyladenine (20)
adenine	ϕCH_2Cl	25	9-benzyladenine (93)
xanthine	CH_3Br	25	caffeine (85)
xanthine	$(CH_3O)_3PO$	25	caffeine (85)
guanine	$(CH_3O)_3PO$	25	no reaction[+]
guanine	CH_3Br	25	

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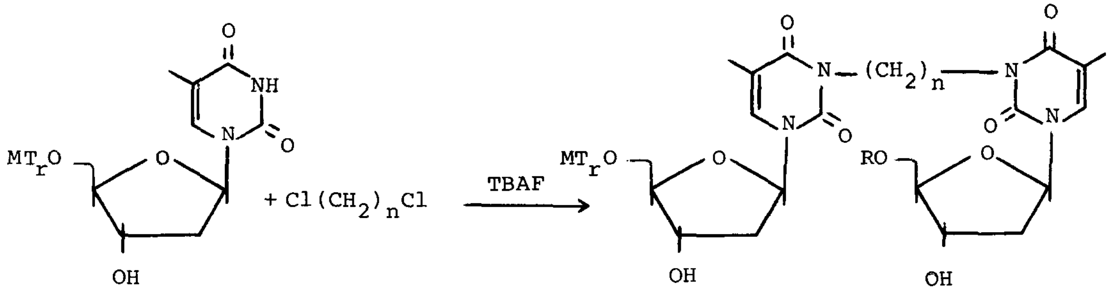
[*] All reactions at 25°C were for 1 hr duration. Those at 75°C were for 16 hr. Other conditions are those described in the text.

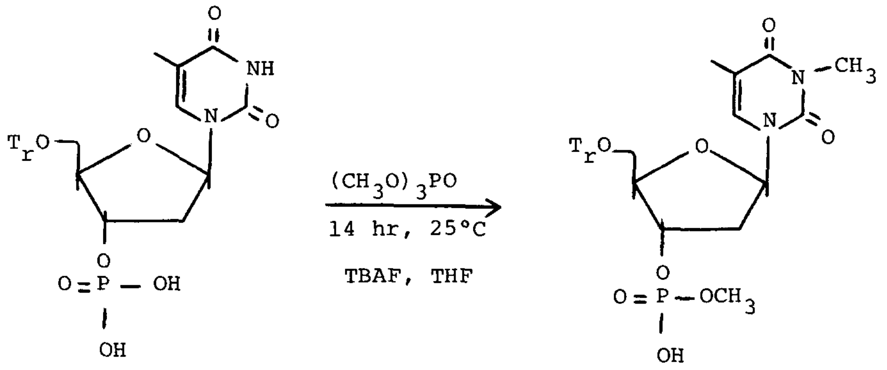
[+] Guanine is insoluble in the reaction media.



1

2 a,n=1, R=MT_r
b,n=2*, R=H
c,n=6*, R=H

We have also studied the alkylation of nucleotides and find that trimethyl phosphate will produce high yields of diesters from mononucleotides along with alkylation at the base. Thus the treatment of 5'O-tritylthymidine-3'



3

4

phosphate (3) with trimethyl phosphate for 14 hr at room temperature produced 4 in 95% yield.

Alkyl halides produce triesters along with diesters from nucleotides. Thus when MT_r-T_pT (5) is treated with methyl bromide and TBAF for 24 hr at room temperature a 55% yield of the fully methylated triester 6a is obtained along with 42% of the diester 6b. On the other hand trimethyl phosphate produces 95% of 6b.

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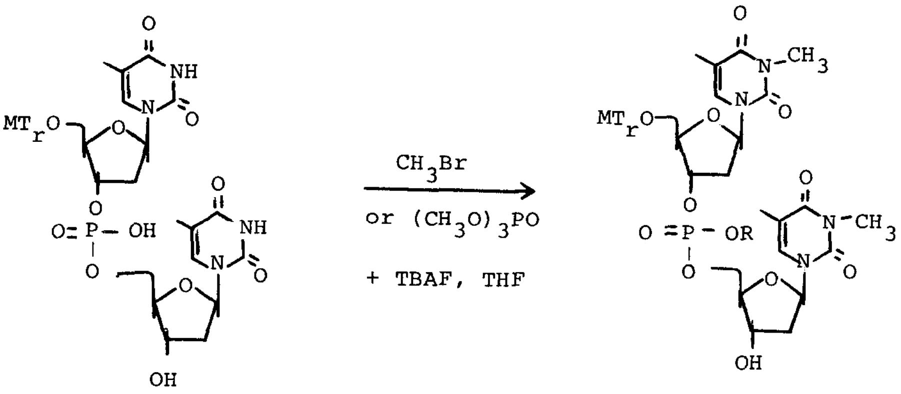
*In these cases the product of N-3 alkylation of 1 is isolated in quantitative yield and then condensed with thymidine in TBAF-THF to yield the products 2b and 2c.



5

6 a, R=CH_3
b, R=H

All new compounds reported here have been fully characterized.

Acknowledgement

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