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A FACILE ACYLATION OF STERICALLY HINDERED HYDROXYLS AND A DIRECT REPLACEMENT OF SILYL GROUPS BY ACYL GROUPS IN NUCLEOSIDE CHEMISTRY

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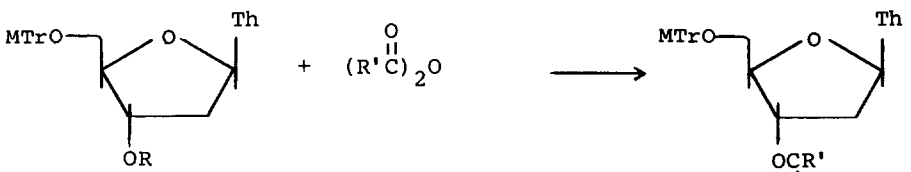
The routine acylation of hydroxyl groups in organic chemistry usually involves an acid chloride or an acid anhydride and usually in pyridine as a solvent. In the case of nucleosides these reagents often give poor yields[1,2] (seldom greater than 80%) and in the case of hindered alcohols sometimes fail to react[2]. Further, acid chlorides[2] and as shown below, acetic anhydride, often give side reactions with thymine and uracil nucleosides presumably through reaction at the base[2].

We wish to describe a procedure requiring fluoride ion catalysis which gives near quantitative yields on acylation using tetrahydofuran (THF) as solvent, results in no detectable side reactions, and gives high yields with pivalic anhydride even with highly hindered alcohols where other conditions give no reaction. Further these same conditions allow the direct replacement of a silyl protecting group by an acyl group. This latter feature permits the in situ replacement of an alkali resistant protecting group by an alkali sensitive protecting group and is thus a valuable synthetic tool.

To first illustrate the effectiveness using bulky acylating agents consider the reaction (Table I) of Ia with pivalic anhydride (IIb) in pyridine which after 24 hours at room temperature gives only 9% pivaloylation at the 3'-position (IIIb). This is in sharp contrast to the reaction of pivalic anhydride (25 eq.) with Ia in THF with 10 mmole of the tetra-(n-butyl)ammonium fluoride-(TBAF) which gives a 95% isolated yield of III b after 10 h. at room temperature.



I a, R = H

b, R = $(CH_3)_3C\,Si(CH_3)_2-$

II

III

for II & III

a, R' = CH_3-
b, R' = $(CH_3)_3C-$
c, R' = Ø-
d, R' = $CH_3(CH_2)_{12}-$

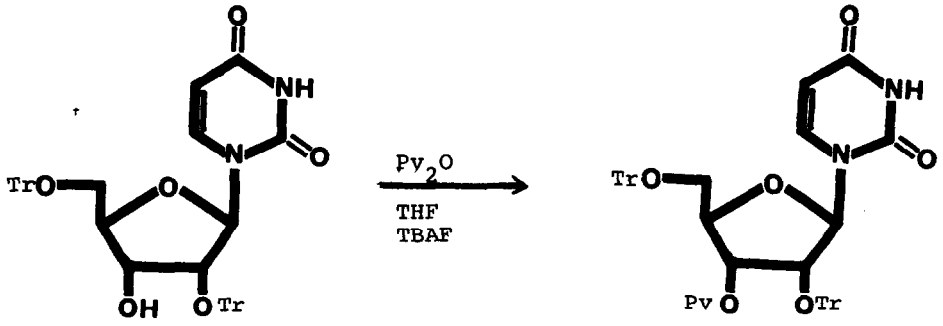
MTr = p-monomethoxytrityl

It should be noted that TBAF is required in these reactions since in the absence of TBAF anhydrides give very little reaction with Ia in THF even after 24 hr. Benzoic anhydride gives the highest yield (36% III) while acetic gives 9% of IVa and the others give less than 2% reaction.

A silyl group can be directly replaced by an acyl group using Ib and II in THF with TBAF. Yields including pivalic anhydride are 95% or better. No side products could be detected. In the absence of fluoride ion no reaction occurs even after 24 hr. Myristic anhydride is slow to react at the 3' position, even in refluxing THF. A disilylthymidine can be converted to the diacylthymidine under the standard conditions in nearly quantitative yields (using IIa-c, IId gives an 83% after reflux for 4 hr.).

The reaction conditions work well even for the nucleosides which are not normally soluble in THF but which dissolve readily when TBAF is added. For example, using the standard 22°C conditions in THF, deoxycytidine is converted in 90% yield to the N,3',5'-tribenzoyldeoxycytidine. With deoxyguanoxine an 81% yield of the dibenzoyl derivative is obtained while deoxyadenosine yields 78% of 3',5'-dibenzoyldeoxyadenosine and 17% of N,3',5'-tribenzoyldeoxyadenosine.

To conclusively demonstrate the effectiveness of this acylation procedure, 2',5'-dityrituridine (IV) was treated with pivalic anhydride (25eq) in THF at 80°C with TBAF and a 95% yield of the 3'-pivaloylated compound V was obtained. This contrasts to the previously reported[2] reaction in pyridine where no reaction occurred.



Tr = triphenylmethyl

Pv_2O = pivalic anhydride

To illustrate the elimination of side products compare the reaction of Ia in pyridine with pivaloyl chloride which gives only 22% of the desired III b but yields 78% of a material containing two pivaloyl groups.[3] Using pivalic anhydride in THF with TBAF produces no such side product but gives 95% of the desired III b. To further illustrate this point note that acetic anhydride in pyridine reacts with the completely protected I b to add an acetyl group (20%) to the molecule[3] while acetic anhydride in THF with TBAF gives a 96% replacement of the silyl group by an acetyl group (III a, no side reaction occurs even after 24 hr).

TABLE I

Nucleoside (1 mmole)	Acylating Agent	(mmole)	Solvent	TBAF[2] mmole	Temp. °C	Time	Yield of III
Ia	IIa	(25)	THF	10	22	30 min.	IIIa 99%
Ia	IIb	(25)	THF	10	22	5 hr.	IIIb 100%
Ia	IIb	(25)	pyridine	0	22	24 hr.	Ia 91% IIIb 9%
Ia	[ii]PvCl	(25)	pyridine	0	22	24 hr.	[iii]IIIb 22%
Ia	IIc	(25)	THF	10	22	2 hr.	IIIc 98%
Ia	IIc	(25)	pyridine	0	22	24 hr.	Ia 35% IIIc 65%
Ia	IId	(25)	THF	10	22	8 hr.	Ia 44% IId 55%
Ia	IId	(25)	THF	10	reflux	4 hr.	Ia, 36% IIId, 64%
Ib	IIa	(25)	THF	10	22	10 hr.	IIIa 96%
Ib	IIa	(25)	THF	0	22	24 hr.	Ib 100%
Ib	IIa	(25)	pyridine	0	22	24 hr.	[iii]Ib 80%
Ib	IIb	(25)	THF	10	22	10 hr.	IIIb 95%
Ib	IIc	(25)	THF	10	22	10 hr.	IIIc 97%
Ib	IId	(25)	THF	10	22	10 hr.	Ia 60% IIId 40%
Ib	IId	(25)	THF	10	reflux	4 hr.	Ia 48% IIId 52%

i TBAF = tetra-(n-butyl)ammonium fluoride

ii PvCl = pivaloyl chloride

iii In these reactions the remainder of the material contained an additional acyl group[2,3].

Fluoride ion does not appear to have the same effect on pyrophosphates. For example, tetraethyl pyrophosphate does not react with either I(a or b) or thymidine under the conditions described in this report.

Thus the procedures described in this report permit the facile acylation of hindered alcohols under very mild conditions. Further, silyl groups can be directly replaced by an acyl group. This result permits considerable flexibility in synthetic schemes requiring, as in nucleotide synthesis, the temporary protection of hydroxyl groups.

Acknowledgement

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References

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2. J. Baker, M. Jarman, and J.A. Stock, J. Chem. Soc. 665 (1973).
3. The position of the additional acyl group has been postulated to be on the ring[2]. These compounds will be fully described in a complete publication.