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Nucleosides VII:[1] Synthesis of *N*-Triphenylphosphoranylidene Nucleosides by Mitsunobu Reaction. A Novel Protecting Group for Primary Amines of Nucleosides

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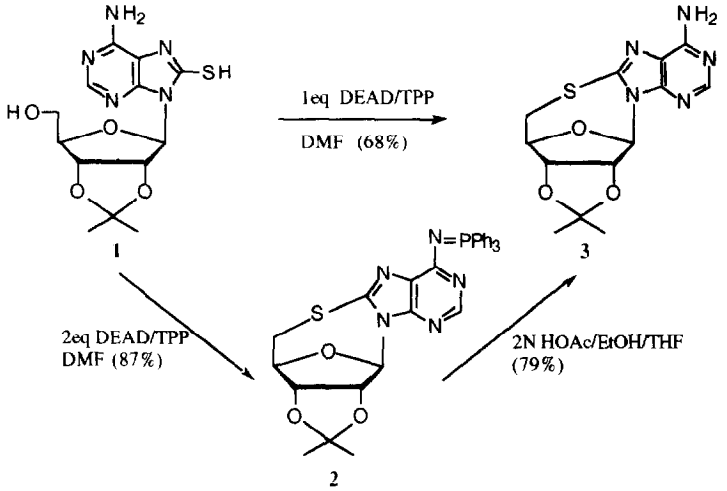
Abstract: N-Triphenylphosphoranylidene nucleosides synthesized by Mitsunobu reaction can be utilized for protecting the amino groups bearing on the base moieties of nucleosides.

Efficient functional group protection is one of the most fundamental and crucial problems in the synthesis of oligonucleotides.[2] Basically, it needs a mild condition to deprotect the protectors from the highly functionalized synthetic intermediates. During our investigations on the synthesis and identification of nucleosides and nucleotides, an alternative amine protecting group for use in the synthesis of nucleotide sequences containing isoguanosine is needed.[3]

Scheme 1



A perusal of literature illustrated that acylation is the most widely used method for amino group protection and the removal of the acyl group is accompanied by the cleavage of internucleotide linkage.[4] We now report herein a mild process to synthesize *N*-triphenylphosphoranylidene nucleosides in which *N*-triphenylphosphoranylidene

may serve as an useful amine protecting group in nucleosides and nucleotides synthesis. *N*-Triphenylphosphoranylidene nucleosides can be easily synthesized via Mitsunobu reaction[5] and is removable under weak acidic condition.

Iminophosphoranes which were first prepared by Staudinger[6] have been applied in organic synthesis. The most common use is the ring construction of nitrogen-containing heterocycles.[7] There are few iminophosphorane nucleosides reported in the literature, such as N^4-triphenylphosphoranylidene-5'-chloro-5'-deoxycytidine[8] which was the undesired major product instead of the 5'-chlorocytidine when cytidine was treated with carbon tetrachloride and triphenylphosphine in DMF. And, in a recent report from our laboratory,[1] we also obtained the *N*-triphenylphosphoranylidene nucleoside as a side product during the 8,5' cyclization of 2',3'-*O*-isopropylidene-8-mercaptoadenosine (**1**) under Mitsunobu reaction condition. (Scheme 1)

Scheme 2

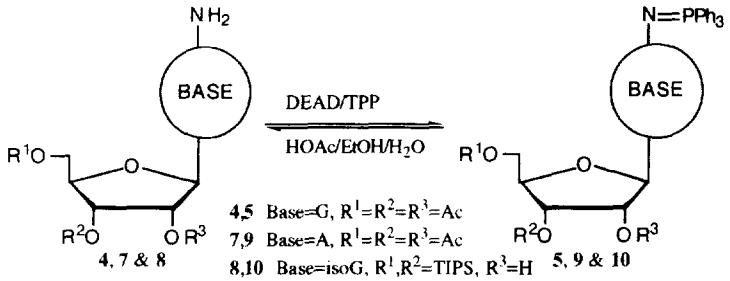
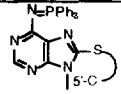
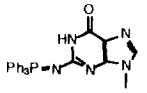
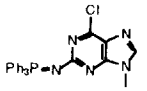
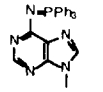
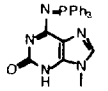
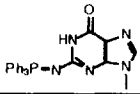


Table 1 Synthesis and Deprotection of *N*-Triphenylphosphoranylidene Nucleosides

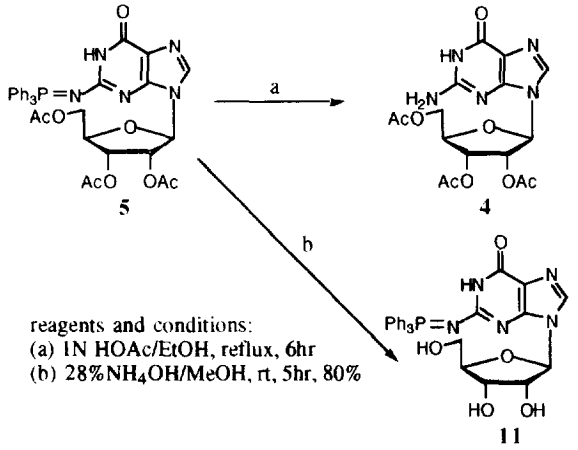
	Compound	R^1	R^2	R^3	Solvent	Yield (%)	^{31}P NMR	Hydrolysis condition
2		-----	$C(CH_3)_2$		DMF	87[a,d]	21.7[f]	2N HOAc/EtOH /THF = 2:1:2
5		Ac	Ac	Ac	DMF	76[a]	18.2[g]	1N HOAc/EtOH = 1:1
6		Ac	Ac	Ac	CH_3CN	30[b]	18.4[g]	----------
9		Ac	Ac	Ac	DMF	70[a]	18.7[g]	1N HOAc/EtOH = 1:1
10		TIPS		H	Toluene	56[c,e]	18.3[g]	1N HOAc/EtOH = 1:1[h]
11		H	H	H	-------	-------	20.8[f]	----------

[a] 2eq DEAD/TPP/DMF/rt; [b] 4eq TPP/CCl_4/CH_3CN/80 °C/5h; [c] 1.1eq DEAD/TPP/Toluene/80°C/1.5h; [d] Ref. 1; [e] The low yield may be caused by the free hydroxy group of 2'-position; [f] DMSO-d_6; [g] $CDCl_3$; [h] Deprotection caused partial deprotecting on sugar moiety.

The triphenylphosphoranylidene protecting group in all of the above iminophosphorane nucleosides show unusual stability toward mild acidic or basic condition in contrast with those which are located on non-aromatic moiety. Recently, it has been reported that iminophosphoranes generated in situ can be used as practical and efficient protecting group for primary amines.[9] We reasoned that the iminophosphoranes might be also used for the protection of amino groups on base of nucleosides. Thus we extend to the applicability of *N*-triphenylphosphoranylidene as an amine protecting group in nucleosides.

There are several approaches for the synthesis of iminophosphoranes including, Staudinger reaction[6] (the reduction of azides with phosphorus (III)), and conversion of primary amines to iminophosphoranes by the following reagents such as PPh_3/CCl_4,[10] PPh_3/Br_2,[11] Br_2PPh_3,[12] and DEAD/PPh_3.[13] For the synthesis of *N*-triphenylphosphoranylidene nucleosides, we thought that PPh_3/CCl_4 and DEAD/PPh_3 might be suitable to achieve our goals. At the outset, 2',3',5'-tri-*O*-acetylguanosine (**4**) was treated with PPh_3 and CCl_4 in dichloromethane at reflux for 5 hours, a single product was isolated and characterized by ^1H ,^{13}C and ^{31}P NMR, and mass spectral data as the desired product, 2',3',5'-tri-*O*-acetyl-N^4-triphenylphosphoranylidene-guanosine (**5**). Interestingly, it shall be noted that repeating the same reaction in acetonitrile afforded the 6-chlorinated product, 6-chloro-4-(triphenylphosphoranylideneamino)-9-(2,3,5-tri-*O*-acetyl-1-β-D-ribofuranosyl)purine (**6**) accompanied with compound **5**. A survey of literature demonstrated that the same chlorination has been recently reported.[14] To avoid such chlorination reaction, Mitsunobu reaction was chosen for further studies. Two equivalents of each of PPh_3 and DEAD in DMF were added to a solution of OH-protected nucleosides (**4**, **7** & **8**) in DMF. The reaction was carried out at room temperature for 24 hours. After removing the solvent *in vacuo*, the reaction mixture was purified by column chromatography and gave *N*-triphenylphosphoranylidene nucleosides (**5**, **9** & **10**) with reasonable yield. (Table 1) As for the hydrolysis of iminophosphoranes using hydrochloric acid, it has also been well documented.[9,15] Treatment of *N*-triphenylphosphoranylidene nucleosides with dilute aqueous acetic acid in ethanol at reflux temperature furnished the deprotected products in quantitative yield without any side products. (Scheme 2)

Scheme 3



It shall be noted that the *O*-acetyl groups of compound **5** can be selectively deprotected to afford N^2-triphenylphosphoranylideneguanosine (**11**) in mild basic condition. When compound **5** was treated with ammonia water/methanol mixture (1:1, *v/v*) at room temperature, after 5 hours the reaction mixture was evaporated *in vacuo* following chromatography to give compound **11** in 80% yield. (Scheme 3)

The synthesis of *N*-triphenylphosphinylidene nucleosides can be accomplished at reasonable yield by a mild and one-pot process via Mitsunobu reaction and can be quantitatively and selectively deprotected by refluxing in HOAc/H_2O/Ethanol. Compared with the conventional methods (including *N*-acetyl-, *N*-benzoyl-, *N*,*N*-dibenzoyl-[4] and *N*-(dimethylamino)methylene-[16]), the use of iminophosphoranes as amine protecting groups on nucleosides not only provides base-stable products (except compound **9**), but also increases the solubility by decreasing the intermolecular hydrogen bonding of the nucleosides. This method is extended further to the protection of nucleosides and nucleotides synthesis in our laboratory.

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