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AN EFFECTIVE METHOD FOR THE PREPARATION OF O^6-SUBSTITUTED GUANOSINE AND N^3-SUBSTITUTED URIDINE DERIVATIVES VIA THE CORRESPONDING STANNYLATED INTERMEDIATES

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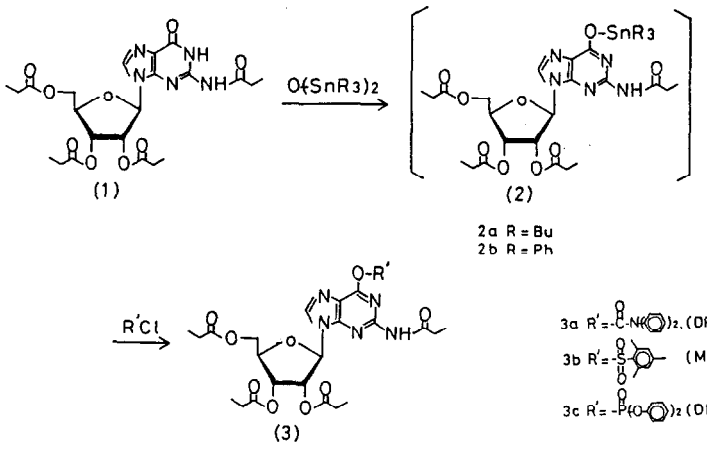
Abstract—O^6-substituted guanosine and N^3-substituted uridine derivatives were obtained in high yields by stannylation of the corresponding unsubstituted nucleosides with bis(tributyltin)-oxide followed by treatment with various electrophiles.

It is well known that the guanine and uracil moieties exist in the equilibrium between amide and imide forms substantially. When in oligonucleotide synthesis they are not masked with appropriate protecting groups,[1-15] base modifications at these residues occur at the chain elongation step.[16] Our previous paper[17] showed that dephenylthiolation of dinucleoside S-phenyl phosphorothioates could be performed with bis(tributyltin)oxide based on the strong affinity of tin for sulfur.[18] Tin is also known to have a strong affinity for oxygen. This property is widely applied to the selective acylation or alkylation in the sugar and nucleoside chemistry.[19]

In this paper, we wish to describe the synthetic utility of stannylated species of guanosine and uridine derivatives for their substitutions.

Stannylation of guanosine at the O^6-position was carried out by refluxing a mixture of 2N, 2', 3', 5'-O-tetrapropionyl guanosine (1) (508 mg, 1 mmol) and TBT(298 μl, 0.5 mmol) or TPT(358 mg, 0.5 mmol—716 mg, 1 mmol) in benzene (10 ml) for 15 min,[20,21] followed by successive azeotropic removal of water by coevaporation with pyridine (1 ml X 3) under reduced pressure.[17] To a solution of the resulting stannyl intermediate in pyridine (2 ml) was added an electrophile at room temperature. After the starting material disappeared on tlc, ice and 5% $NaHCO_3$ solution were added. The aqueous solution was extracted with $CHCl_3$ (50 ml X 3). The combined $CHCl_3$ extracts were evaporated to dryness under reduced pressure. The residue was chromatographed on a column of silica gel to give 3a-c.[22]

Scheme 1



Scheme 2

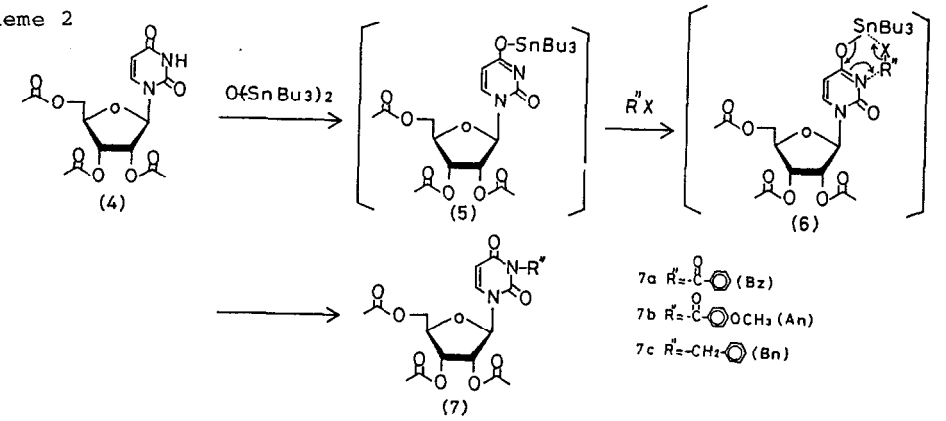


Table 1. Conditions and results of displacement of guanosine and uridine derivatives.

Entry	Compd.	Stannylating agent (equiv.)	Substituent group (equiv.)	Time	Product	Yield of 3 or 7 (%)
1)	1	TBT[a] (0.5)	DPC (1.2)	10 min	3a	88
2)	1	TPT[a] (0.5)	DPC (1.2)	8 h	3a	68[b]
3)	1	TPT (0.5)	DPC (3.0)	8 h	3a	60[b]
4)	1	TPT (1.0)	DPC (1.2)	30 min	3a	92
5)	1	TBT (0.5)	MS (2.0)	40 min	3b	85
6)	1	TBT (0.5)	DPP (2.0)	5 min	3c	83
7)	4	TBT (0.5)	Bz (2.0)	20 min	7a	94
8)	4	TBT (0.5)	An (2.0)	20 min	7b	88
9)	4	TBT (0.5)	Bn (2.0)	10 min	7c	81

a TBT; bis(tributyltin)oxide, TPT; bis(triphenyltin)oxide

b The starting material did not disappear after 8 h.

Entry 1 showed that the carbamoylation by the use of TBT was completed more rapidly than that described in the case of diisopropylethylamine as the activating reagent.[3,7,8,13] As shown in Entry 2 of Table 1, the starting material (1) remained unchanged to a degree of 30% when 0.5 equivalent of TPT was used. When the amount of DPC was increased to 3.0 equivalent, a similar result was obtained. (Entry 3) However, an optimum yield of 3a was obtained, when 1 equivalent of TPT and 1.2 equivalents of DPC were employed as shown in Entry 4. These results suggested that the stannylation of (1) was incomplete in the case of 0.5 equivalent of TPT probably owing to steric hidrance of the triphenylstannyl group. As a result, TBT was superior to TPT for obtaining stannylated nucleoside intermediates.

The products were analyzed by ^{1}H-NMR and ^{13}C-NMR to determine the position where the displacement occured.[23] The ^{1}H-NMR spectrum of 3a was identified with that of the authentic sample prepared by the use of diisopropylethylamine.[7,13] Especially, in the formation of 7a,c the benzoyl and benzyl groups were found to bind to the uracil residue of the N^3-position.[24]

In conclusion, the present approach by the use of stannylated nucleoside intermediates will provide a convenient method for introduction of a variety of substituents involving several new protecting groups, which are useful in oligonucleotide synthesis, to the guanine and uracil moieties. Moreover, this method facilitated the purification of O^6-substituted guanosine and N^3-substituted uridine derivatives, which could be obtained as colorless materials.

Acknowledgment

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22) Compound 3a (Entry 1): Calcd for $C_{35}H_{38}N_6O_{10}$: C, 58.02; H, 5.53; N, 15.38. Found: C, 57.65; H, 5.49; N, 15.52.
^{13}C-NMR ($CDCl_3$) (ppm): C^2, 154.39; C^4, 152.34; C^5, 121.22; C^6, 156.32; C^8, 141.69.
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24) ^{13}C-NMR of compound 7a ($CDCl_3$) (ppm): C^2, 149.24; C^4, 161.64; C^5, 103.14; C^6, 139.29. ^{13}C-NMR of compound 7c ($CDCl_3$) (ppm): C^2, 150.88; C^4, 162.11; C^5, 102.96; C^6, 137.07.

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