

A NEW METHOD FOR THE SYNTHESIS OF 5'-AMINO-NUCLEOSIDES AND
THEIR PHOSPHORAMIDATE DERIVATIVES¹⁾

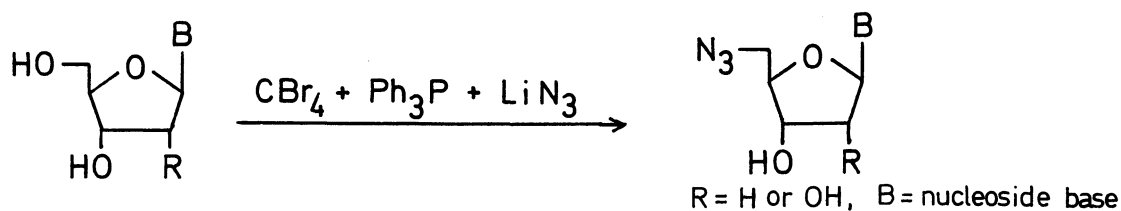
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The reaction of nucleoside azides with trimethylsilyl phosphites is described. By use of the reaction, amino-nucleosides were obtained in high yields. The reaction can be also applied to the synthesis of dinucleoside phosphoramidate and nucleoside cyclic phosphoramidate.

Amino-nucleosides having amino group on the sugar moiety are well recognized to be important substances in nucleoside chemistry and biochemistry. Among several procedures for the synthesis of amino-nucleosides, the method via azido-nucleoside intermediates²⁾ is known to be the most successful. Recently, we have found a convenient method for the synthesis of 5'-azido-5'-deoxyribonucleosides by the reaction of nucleosides with carbon tetrabromide and triphenylphosphine in the presence of lithium azide.³⁾



More recently, Letsinger⁴⁾ has reported that 5'-amino-5'-deoxythymidine was prepared by the reaction of 5'-azido-5'-deoxythymidine with triphenylphosphine.

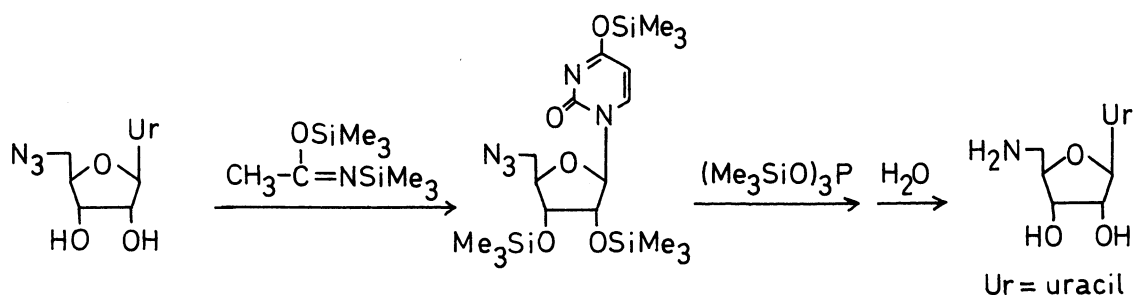
In this communication, we wish to report the reactions of 5'-azido-5'-deoxyribonucleosides with silyl phosphites⁵⁾ which are highly reactive trivalent phosphorus compounds.

First, the synthesis of 5'-amino-5'-deoxyribonucleosides is described.

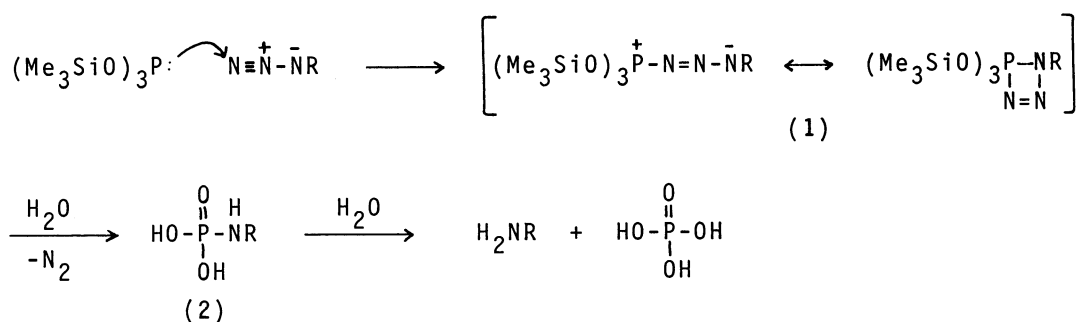
For example, 5'-azido-5'-deoxyuridine³⁾ was silylated with bis(trimethylsilyl)acetamide (BSA) in dry pyridine at room temperature for 45 min, and then it was treated with tris(trimethylsilyl) phosphite at room temperature. After continuous stirring for 4 hr, water was added at 0°C and the mixture was kept standing at room temperature for 1 hr for removal of the trimethylsilyl group. The mixture was concentrated to dryness under reduced pressure and the residue was applied to a column of DIAION SK-1B resin (pyridinium form).⁶⁾ After the column was washed with water, 5'-amino-5'-deoxyuridine was eluted with 0.5 N aqueous ammonia.

In the same manner, 5'-amino-5'-deoxythymidine was obtained in 94% yield.

In the case of adenosine and cytidine derivatives, the amino-nucleosides were separated by silica gel column chromatography (3 cm X 2.5 cm). Elution was performed by use of tetrahydrofuran containing 5 N ammonia (97:3 v/v). The results are summarized in Table 1.



The reaction seems to proceed through an addition compound (1) which in turn reacts with water to form the corresponding phosphoramidate (2) with the elimination of nitrogen⁷⁾ and 2 was further hydrolyzed to the amino-nucleoside and phosphoric acid as described in the following scheme.



In the above experiments, the phosphoryl group was found to be easily removed from the nucleoside phosphoramidate (2) by simple treatment with water, however, in earlier stage of the hydrolysis, the phosphoramidate (2) was detected by thin-layer chromatography.

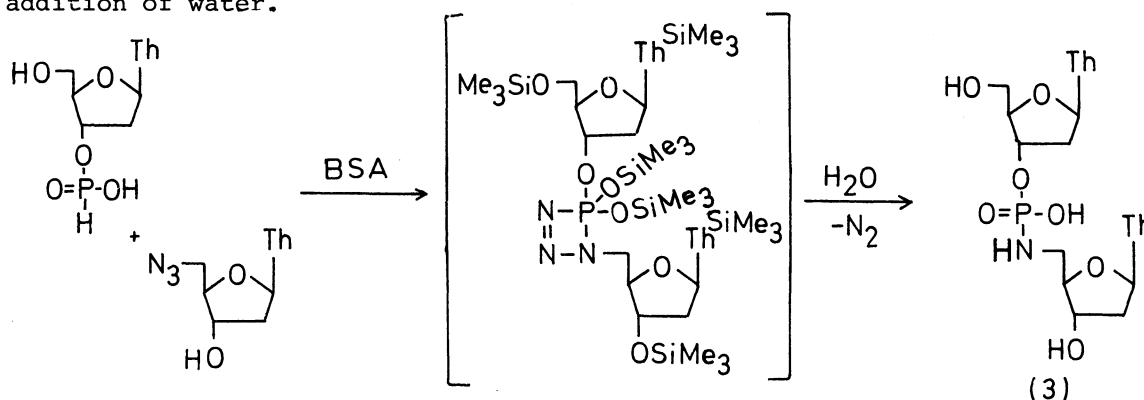
Table 1. Synthesis of 5'-Amino-5'-deoxyribonucleosides

5'-azido-nucleoside	(mmol)	Step 1			Step 2		5'-Amino-nucleoside	
		BSA (mmol)	pyridine (ml)	time (min)	P(OSiMe ₃) ₃ (mmol)	time (hr)	yield (%)	m.p. (°C)
N ⁶ -benzoyl-adenosine	0.5	1.88	2.50	60	1.0	6	79	125-128
N ⁴ -benzoyl-cytidine	0.5	1.88	2.50	60	1.0	6	57	143(dec.)
uridine	1.0	4.00	1.25	45	2.0	4	85	70(dec.)*
thymidine	1.0	2.50	5.00	30	2.0	5	94	175-177

* Methanol adduct.

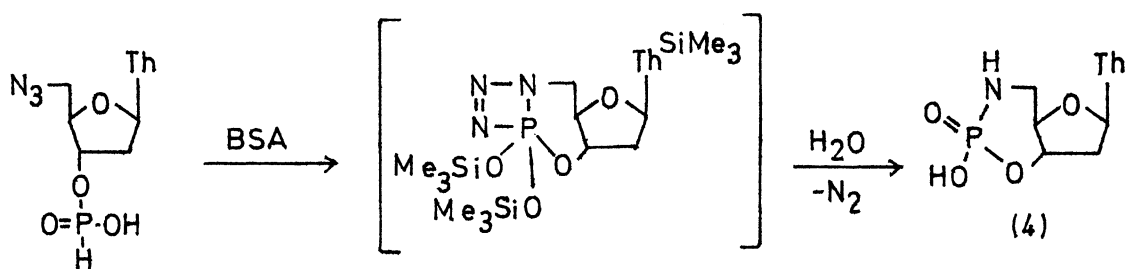
The same reaction was applied to the synthesis of a dinucleoside phosphoramidate having a P-N internucleotidic bond.^{4,8)}

When a mixture of thymidine 3'-phosphite⁹⁾ (0.05 mmol) and 5'-azido-5'-deoxythymidine (0.102 mmol) was treated with BSA (0.45 mmol) in dry pyridine (0.2 ml) at room temperature for 20 hr, 3'-O-thymidine-5'-N-thymidine phosphoramidate (3) was obtained in 49% yield after the reaction was quenched by addition of water.



This reaction was further applied to the synthesis of nucleoside 5'-cyclic phosphoramidate.

When a solution of 5'-azido-5'-deoxythymidine 3'-phosphite¹⁰⁾ (0.05 mmol) in dry pyridine (1 ml) was added to a solution of BSA (4.03 mmol) in dry pyridine (3 ml) with vigorous stirring at 110°C for 2.5 hr, the corresponding 5'-amino-5'-deoxythymidine 3',5'-cyclic phosphoramidate¹¹⁾ (4) was obtained in 66% yield. It was separated by paper electrophoresis using sodium carbonate (0.05 M)-sodium bicarbonate (0.1 M) buffer (pH 9.95).



References and Notes

- 1) This paper participates as Part IV in the series of Silyl Phosphites. A preliminary communication by T.Hata, M.Sekine, and N.Ishikawa, *Chemistry Letters*, 645(1975) is paper III in this series.
- 2) J.P.Horwitz, A.J.Tomson, J.A.Urbanski, and J.Chua, *J.Org.Chem.*, **27**, 3045 (1962).
- 3) T.Hata, I.Yamamoto, and M.Sekine, *Chemistry Letters*, 977(1975).
- 4) W.S.Mungall, G.L.Greene, G.A.Heanner, and R.L.Letsinger, *J.Org.Chem.*, **40**, 1659(1975).
- 5) T.Hata and M.Sekine, *J.Amer.Chem.Soc.*, **96**, 7363(1974); *Tetrahedron Lett.*, 3943(1974); M.Sekine and T.Hata, *Tetrahedron Lett.*, 1711(1975); T.Hata, M.Sekine, and N.Kagawa, *Chemistry Letters*, 635(1975); T.Hata, M.Sekine, and N.Ishikawa, *ibid.*, 645(1975).
- 6) DIAION SK-1B (Mitsubishi Chemical Industries Ltd.) is a commercially available ion exchange resin having sulfonic acid groups on cross-linked polystyrene.
- 7) Evolution of nitrogen gas was observed when the mixture was treated with water.
- 8) B.Jastorff and H.Hettler, *Chem.Ber.*, **102**, 4119(1969); R.L.Letsinger and W.S.Mungall, *J.Org.Chem.*, **35**, 3800(1970); R.L.Letsinger and G.A.Heavner, *Tetrahedron Lett.*, 147(1975).
- 9) Thymidine 3'-phosphite was prepared by the reaction of 5'-isobutyloxy-carbonylthymidine (1 mmol) with phosphorous acid (4 mmol) in the presence of tosylimidazolidine (4 mmol). The isobutyloxycarbonyl group was easily removed by treatment with concentrated ammonia. 5'-Isobutyloxycarbonyl-thymidine was prepared by the procedure of Letsinger: K.K.Ogilvie and R.L.Letsinger, *J.Org.Chem.*, **32**, 2365(1967).
- 10) 5'-Azido-5'-deoxythymidine 3'-phosphite was prepared in 83% yield by the reaction of 5'-azido-5'-deoxythymidine (0.5 mmol) with phosphorous acid (2 mmol) in the presence of tosylimidazolidine (2 mmol) at room temperature for 24 hr.
- 11) A.Murayama, B.Jastorff, F.Cramer, and H.Hettler, *J.Org.Chem.*, **36**, 3029(1971).

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