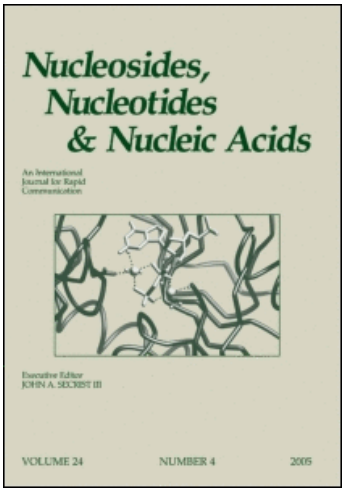

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O-Alkylation of Dialkyl Phosphates and O-Alkyl Phosphonates via the Stannyl Intermediates

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O-ALKYLATION OF DIALKYL PHOSPHATES AND *O*-ALKYL PHOSPHONATES *VIA* THE STANNYL INTERMEDIATES

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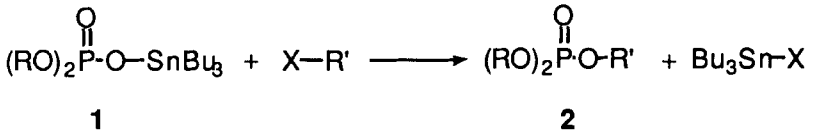
Abstract: A preparation of trialkyl phosphates and *O,O*-dialkyl phosphonates by means of alkylation of the corresponding tributylstannyl dialkyl phosphates and tributylstannyl *O*-alkyl phosphonates was described.

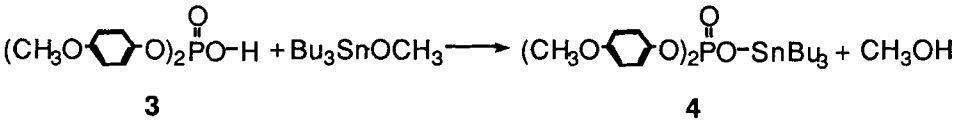
Attempts to prepare triesters of phosphoric acid starting from the corresponding diesters have been usually done by phosphorylation reaction by use of a suitable condensing reagent. The phosphotriesters may be also synthesized by alkylation of the diesters of phosphoric acid. The alkylation of phosphates has not been general except a few cases[1,2,3] because the reaction proceeds sluggishly due to the poor nucleophilicity of the phosphate ion. However, this type of reaction is important for the modification of oligo- and poly-nucleotides.[4,5] In this paper, we wish to describe the alkylation reaction of diesters of phosphoric acid by use of alkyl halides *via* the stannyl phosphate derivatives.

This paper is dedicated to the late Professor Tohru Ueda.

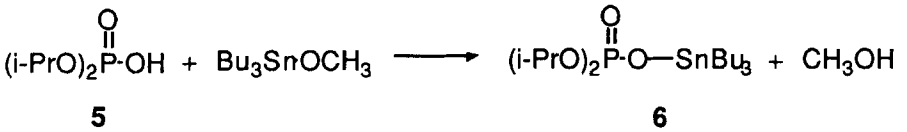


1 2

Tributylstannyl dialkyl and diaryl phosphates were prepared quantitatively by simple addition of stoichiometric amount of tributylstannyl methoxide.[6] The stannyl phosphate derivatives are soluble in DMF and acetonitrile, and even in xylene. They were identified as pure material by means of ^{31}P-NMR.



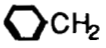
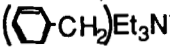
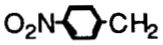
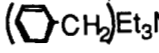
3 4



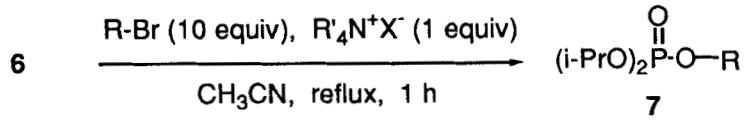
5 6

When tributylstannyl bis(p-methoxyphenyl) phosphate (**4**) (1 equiv) was treated with benzyl bromide (1 equiv) in xylene at a higher temperature (140 °C) for 10 h, benzyl bis(p-methoxyphenyl) phosphate was obtained in 58% yield. However, it was obtained almost quantitatively for 2 h when 10 equiv of benzyl bromide were employed under the similar conditions. Among benzyl halides, benzyl bromide is more suitable than that of chloride or iodide. It may be due to the stability of Sn-Br bond of tributylstannyl bromide formed from the alkylation reaction.[6,7] On the other hand, Vijayaraghavan[8] reported that the reaction of tributylstannyl carboxylates with phenacyl bromide in the presence of tetraalkylammonium halide as an additive afforded the corresponding phenacyl esters. Therefore, several tetraalkylammonium halides were tested in the present reaction and the addition of tetraalkylammonium halides was found to be effective. When tributylstannyl diisopropyl phosphate

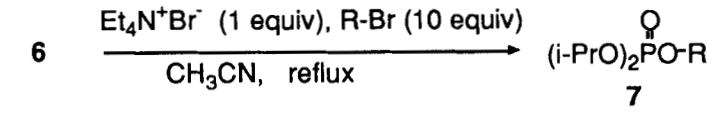
Table 1. *O*-Alkylation of **6** with alkyl bromide in the presence of tetraalkylammonium halide

R	$R'_4N^+X^-$	yield (%)
	none	50
	$Bu_4N^+F^-$	84
	$Bu_4N^+Br^-$	83
	$Et_4N^+Br^-$	89
	$Me_4N^+Br^-$	84
		84
	$Bu_4N^+F^-$	94
	$Bu_4N^+Br^-$	94
	$Et_4N^+Br^-$	99
	$Et_4N^+I^-$	98
		93

(**6**) (1 equiv) was allowed to react with benzyl or p-nitrobenzyl bromide (10 equiv) in the presence of an appropriate tetraalkylammonium halide (see Table 1) in acetonitrile under refluxing for 1 h, the corresponding benzyl esters were obtained in 84-99% yields.

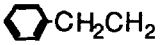


The reaction was examined by use of several alkyl halides. It was found that primary alkyl bromides gave much better results than secondary or tertiary alkyl bromides as shown in Table 2.



The reaction was applied to the alkylation of dinucleosidyl phosphate: One equiv of tributylstannyl methoxide

Table 2. *O*-Alkylation of **6** by use of alkyl bromide

R	time (h)	yield (%)
	1	89
	1	99
	1	99
	1	73
CH_2=$CHCH_2$	1	48
n-C_5H_{11}	1	30
	1	4
$(CH_3)_2CH$	3	16
	6	0
$(CH_3)_3C$	3	0

was added to thymidylyl(3'-5')thymidine in methanol to convert into the stannyl phosphate (**9**). It was treated with p-nitrobenzyl bromide (10 equiv) in the presence of tetraethylammonium bromide in acetonitrile under refluxing for 2 h. p-Nitrobenzyl thymidylyl(3'-5')thymidine (**10**a) was obtained in 64% yield and the structure was confirmed by ^{31}P-NMR.

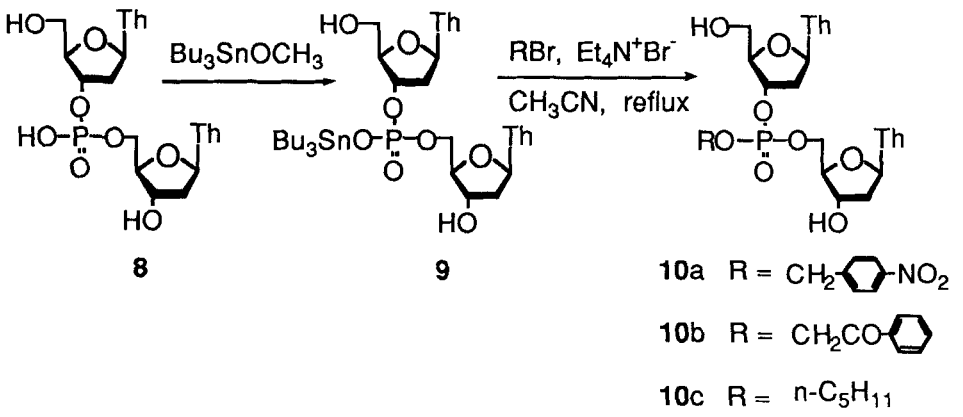


Table 3. *O*-Alkylation of **11** with alkyl bromide under various conditions

R	equiv.	solvent	additive	time (h)	yield (%)
O_2N-C$_6$H$_4$-CH_2	5	CH_3CN	none	6	58
	5	CH_3CN	$Et_4N^+Br^-$	1	73
	5	CH_3CN	$Et_4N^+Br^-$	3	88
	5	DME[a)]	$Et_4N^+Br^-$	3	46
C$_6$H$_5$-CH_2	10	CH_3CN	$Et_4N^+Br^-$	1	58
C$_6$H$_5$-CH_2CH_2	10	CH_3CN	$Et_4N^+Br^-$	3	46
	10	CH_3CN	$Et_4N^+Br^-$	3	87
n-C_5H_{11}	10	CH_3CN	$Et_4N^+Br^-$	3	50
i-C_3H_7	10	CH_3CN	$Et_4N^+Br^-$	3	19
t-C_4H_9	10	CH_3CN	$Et_4N^+Br^-$	3	16

a) dimethoxyethane

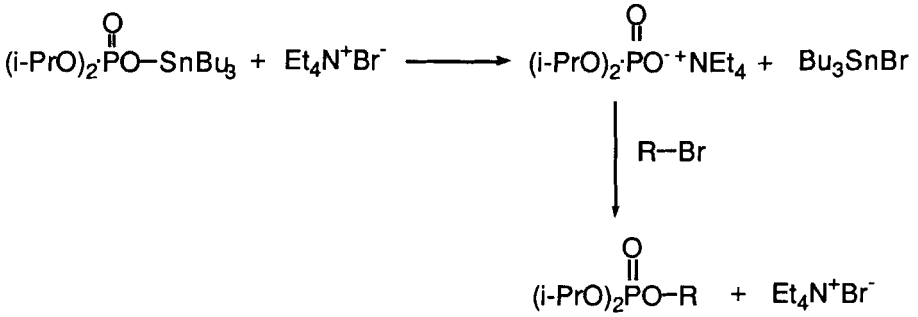
In a similar manner, the phenacyl (**10**b) and 1-pentyl (**10**c) esters were obtained in 53% and 36% yields, respectively.[9] According to this method, the alkylation of the base moiety, namely, N^3-alkylation of thymine moiety was not observed on thin layer chromatography.

This method can be also applied to so-called H-phosphonate derivatives: When tributylstannyl *O*-isopropyl-phosphonate (**11**) was allowed to react with alkyl bromides in the presence of tetraethylammonium bromide, the corresponding *O*-alkyl *O*-isopropyl phosphonates (**12**) were obtained as shown in Table 3.

11 **12**

The present reactions seem to proceed *via* the tetraalkyl-ammonium phosphates. Although they were not isolated, the

mechanism was supported by the reaction of the authentic sample of tetraalkylammonium phosphate with alkyl halides.[10,11]



Remarkable feature of the tributylstannyl phosphates is ester-like character. They do not dissociate under neutral conditions and are converted into the free acids *via* the trimethylsilyl esters by use of trimethylsilyl chloride.[12] The stannyl phosphates are not electronic charged form whereas the ammonium salts are highly polarized ion form. This means that the stannyl phosphates are more stable against moisture than the ammonium salts and the tributylstannylation increases lipophilicity of the phosphates.

EXPERIMENTAL

Solvents and reagents were purified by standard method. Melting points were determined on a Mitamura Riken melting point apparatus and were uncorrected. ^{1}H-NMR spectra were recorded at 60 MHz on a Hitachi R-24B or at 270 MHz on JEOL GX-270 spectrometer with tetramethylsilane as the internal standard in $CDCl_3$ or methanol-d_4. ^{31}P-NMR spectra were measured at 40.5 MHz on JEOL FX-100 spectrometer with 85% H_3PO_4 as the external standard. UV absorption spectra were recorded by use of Hitachi 220A spectrophotometer. Elemental analyses were done by Research Laboratory of Resources Utilization, Tokyo Institute of Technology. Analytical and preparative thin layer chromatography was performed on

Kieselgel 60 F_{254} precoated plates (Merck) using the following eluents; dichloromethane / hexane 10:1 (v/v), dichloromethane / methanol 12:1 (v/v), 2-propanol / 35% aqueous ammonia / water 7:1:2 (v/v/v). Silica gel column chromatography was performed using Wakogel C-200 (Wako Junyaku).

Tributylstannyl bis(p-methoxyphenyl) phosphate (**4**)

A mixture of tributylstannyl methoxide[6] (0.96 g, 3.0 mmol) and bis(p-methoxyphenyl) phosphate[13] (**3**) (0.93 g, 3.0 mmol) in dichloromethane (20 ml) was concentrated and the resulting solid was recrystallized from ethanol.
m.p.: 57-58°C. The yield was almost quantitative (1.80 g). ^{31}P-NMR ($CDCl_3$) δ -10.86. ^{1}H-NMR ($CDCl_3$) δ 0.60-1.90 (m, 27H, butyl), 3.85 (s, 6H, CH_3O), 6.90 (dd, 8H, ArH, J = 6 Hz and 15 Hz). Anal. Calcd. for $C_{26}H_{41}O_6P_1Sn_1$: C, 52.11; H, 6.90. Found: C, 51.68; H, 7.39.

Tributylstannyl diisopropyl phosphate (**6**)

Compound **6** was also obtained from tributylstannyl methoxide[6] (1.61 g, 5.0 mmol) and diisopropyl phosphate[14] (**5**) (0.91 g, 5.0 mmol) in dichloromethane (15 ml). After complete removal of volatile substance *in vacuo*, an oily material was obtained . It was used for the successive reaction without further purification. The yield was almost quantitative (2.40 g). ^{31}P-NMR ($CDCl_3$) δ -11.24, (pyridine-d_5) d -7.80. ^{1}H-NMR ($CDCl_3$) δ 0.70-1.90 (m, 27H, butyl), 1.20 (d, 12H, CH_3 of isopropyl, J = 6 Hz), 3.90-4.55 (m, 2H, CH of isopropyl). Anal. Calcd. for $C_{18}H_{41}O_4P_1Sn_1$: C, 45.88; H, 7.77. Found: C, 46.14; H, 7.69.

O-Alkylation of tributylstannyl diisopropyl phosphate

Typical procedure: To a mixture of **6** (1.07 g, 2.3 mmol) and benzyl bromide (2.70 ml, 23 mmol) in acetonitrile (20 ml) was added tetraethylammonium bromide (0.48 g, 2.3 mmol). It was refluxed for 1 h and the resulting mixture was cooled to room temperature and then concentrated to a small volume (*ca.* 5 ml). The turbid solution was filtered and the precipitate was washed with dichloromethane (5 ml). The filtrate was concentrated and applied to silica gel column chromatography.

The column was washed with a mixture of dichloromethane and hexane (4:1, v/v). Elution was performed with a mixture of dichloro-methane and methanol (100:1, v/v). Eluent was concentrated *in vacuo*. Benzyl diisopropyl phosphate was 9.5 mmol) prepared by partial hydrolysis of diisopropyl phosphonate, was added tributylstannyl chloride (2.93 g, 9.0 mmol) in ethanol (20 ml) and it was stirred at room temperature for 2 h. The mixture was concentrated to remove the ethanol, and extraction was performed with a mixture of dichloromethane (30 ml) and water (15 ml). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated *in vacuo*. Compound **11** was obtained quantitatively (3.72 g) as oily material. ^{31}P-NMR ($CDCl_3$) δ -5.67 ($^1J_{PH}$ = 644 Hz and $^3J_{PH}$ = 9.8 Hz). ^{1}H-NMR ($CDCl_3$) δ 0.70-1.90 (m, 27.5H, butyl and PH), 1.75 (d, 6H, CH_3 of isopropyl, J = 6 Hz), 4.00-4.50 (m, 1H, CH of isopropyl), 12.90 (s, 0.5H, PH).

O-Alkylation of tributylstannyl isopropyl phosphonate

Typical procedure: To a mixture of **11** (0.71 g, 1.7 mmol) and p-nitrobenzyl bromide (1.84 g, 8.5 mmol) in acetonitrile (20 ml) was added tetraethylammonium bromide (0.36 g, 1.7 mmol). It was refluxed for 1 h. The resulting mixture was treated in a similar manner as described in the case of benzyl diisopropyl phosphate. Isopropyl p-nitrobenzyl phosphonate was obtained in 73% yield (0.32 g). ^{31}P-NMR ($CDCl_3$) δ 6.25 ($^1J_{PH}$ = 703 Hz, $^3J_{PH}$ = 7.8 Hz and 9.8 Hz). ^{1}H-NMR ($CDCl_3$) δ 1.35 (d, 6H, CH_3 of isopropyl), 4.50-5.10 (m, 1H, CH of isopropyl), 5.25 (d, 2H, CH_2 of benzyl, J = 9 Hz), 7.05 (d, 1H, PH, J = 708 Hz), 7.90 (dd, 4H, ArH, J = 9 Hz and 30 Hz).

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