New Boranophosphorylation Reagents, Dimethyl Boranophosphate Monopotassium Salt and Tetramethyl Boranopyrophosphate

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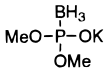
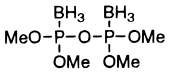
Boranophosphates, which have an isoelectronic relationship with phosphates, are useful compounds, like thiophosphates, in biochemical and molecular biological investigations.[2] They have also anticipated utility as carriers of ^{10}B in boron neutron capture therapy (BNCT) for the treatment of cancer.[3] This class of compounds, including borano derivatives of oligonucleotides, was previously synthesized by the reactions of phosphites and related substrates with borane.[4] Although the method affords the products in good yields, it essentially requires tricoordinate phosphorus compounds as the precursors.

We envisioned that various boranophosphates might be synthesized by a simpler procedure via an electrophilic or a nucleophilic substitution, as shown in Scheme 1. The methods would employ nucleophilic or electrophilic reagents containing a boranophosphate building block. To realize this idea, we prepared new reagents, dimethyl boranophosphate monopotassium salt (**1**) and tetramethyl boranopyrophosphate (**2**), and examined their reactivities toward various electrophiles or nucleophiles.



1



2

Potassium salt **1** was obtained as good crystalline solids by the hydrolysis of trimethyl boranophosphate with KOH in methanol, followed by recrystallization from acetonitrile.[5,6] This salt was stable under neutral or basic conditions, while it gradually decomposed on contact with hydrochloric acid with evolution of hydrogen. X-ray crystallographic analysis of **1** was undertaken, and its crystal structure is shown in Figure 1.[7] The boranophosphate anion interacts with the potassium ion as a monodentate ligand; no apparent coordinative interaction between the boranato group and the potassium ion is observed.[8]

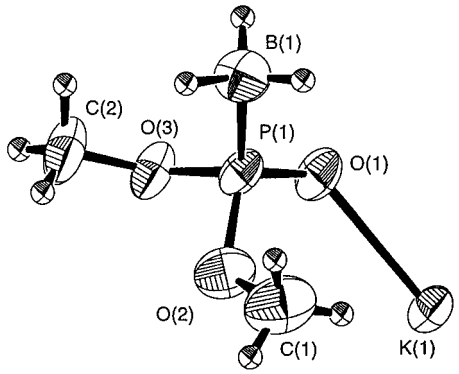
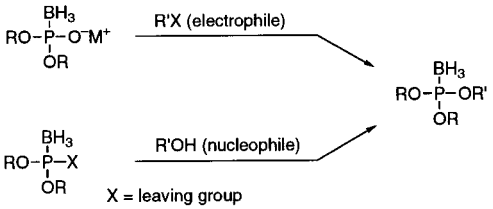


Figure 1. ORTEP drawing for compound **1**. Selected bond distances (Å) and angles (deg): P(1)−B(1), 1.895(6), P(1)−O(1), 1.490(3); P(1)−O(2), 1.597(4); P(1)−O(3), 1.612(3); O(1)−K(1), 2.656(3); B(1)−P(1)−O(1), 116.4(2); O(1)−P(1)−O(2), 110.2(2); O(2)−P(1)−O(3), 96.8(2); O(3)−P(1)−B(1), 113.4(2); B(1)−P(1)−O(2), 114.1(2); O(1)−P(1)−O(3), 103.6(2); P(1)−O(1)−K(1), 132.3(2).

Scheme 1



The reactivities of compound **1** toward alkyl halides, chlorosilanes, and acid chlorides were examined, and the results are summarized in Table 1. It is noted that compound **1** underwent facile S_N2 reactions with alkyl halides possessing an oxygen functional group at the α-position. Another notable fact is that carboxylic and boranophosphoric mixed anhydrides were readily obtained by the reactions with acid chlorides.

Compound **1** (2 mol) reacted with 1 mol of methanesulfonyl chloride in acetonitrile to give tetramethyl boranopyrophosphate **2** as an oil in excellent yield (eq 1).[9] The pyrophosphate **2** reacted with lithium alkoxides of simple alcohols to give the corresponding boranophosphates in good yields.[10] The utility of this method is substantiated by the synthesis of a borano functionalized nucleotide (eq 2).

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(2) For representative reviews on chemically modified phosphates, see: (a) Eckstein, F. *Acc. Chem. Res.* **1979**, *12*, 204−210. (b) Frey, P. A. *Tetrahedron* **1982**, *38*, 1541−1567. (c) Eckstein, F. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 423−439. (d) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543−584. (e) Stein, C. A.; Cheng, Y.-C. *Science* **1993**, *261*, 1004−1012. (f) Baraniak, J.; Stec, W. J. *Rev. Heteroatom Chem.* **1993**, *8*, 143−164.

(3) For representative reviews on BNCT, see: (a) Hawthorne, M. F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 950−984. (b) Nemoto, H. *Synth. Org. Chem. Jpn.* **1994**, *52*, 1044−1052.

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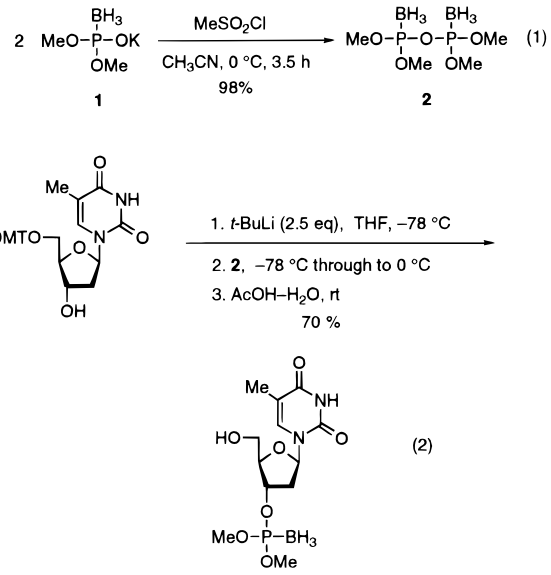
(5) Preparation of compound **1**: To an ice-cold solution of 13.8 g (0.1 mol) of trimethyl boranophosphate in methanol (50 mL) was added 8.5 g of powdered potassium hydroxide. The mixture was stirred at 0 °C for 30 min, and it was gradually warmed to 60 °C. After the mixture was stirred at the same temperature for 5 h, the solvent was removed under reduced pressure and the residual solid was recrystallized from acetonitrile to give 14.2 g (87%) of compound **1** as colorless needles: mp 169.5−170.5 °C; ^1H NMR (D_2O, TSP) δ −0.2∼0.8 (br q, 3H), 3.54 (d, $^3J_{PH}$ = 10.2 Hz); ^{13}C NMR (D_2O, TSP) δ 53.2 (d, $^2J_{CP}$ = 4.9 Hz); ^{31}P NMR (D_2O, H_3PO_4) δ 94.5 (q, J_{PB} = 144 Hz); ^{11}B NMR (128 MHz, D_2O, $B(OMe)_3$) δ −60.7 (d, J_{BP} = 144 Hz); IR (KBr) 2920, 2380, 1080, 1015, 785 cm^{-1}. Anal. Calcd for $C_2H_9BKO_3P$: C, 14.83; H, 5.60. Found: C, 14.92; H, 5.55.

(6) Other potassium salts ($(RO)_2P(BH_3)OK$: R = Et, $PhCH_2$) were also obtained in high yields. On the other hand, the corresponding lithium or sodium salts were not obtained as good crystalline solids, although the trialkyl boranophosphates were subjected to hydrolysis on treatment with LiOH or NaOH.

(7) Crystal data of **1**: orthorhombic, *Pccn*; a = 11.4209(8) Å, b = 19.957(3) Å, c = 6.681(2) Å; V = 1522.8(5) Å^3; D_{calc} = 1.413 g cm^{-3}; $F(000)$ = 672; μ(Cu Kα) = 75.86 cm^{-1}; λ(Cu Kα) = 1.54178 Å; 1357 reflections measured, 924 observed ($I > 1.5\sigma(I)$); 73 variables; R = 0.049, Rw = 0.064, GOF = 1.55.

(8) X-ray crystallographic analysis of $(MeO)_2P(O)OK$ was also carried out in order to compare its structure with compound **1**. Both compounds exhibit an analogous crystal structure except that two anionic oxygen atoms of $(MeO)_2P(O)OK$ interact with the potassium atom.

S0002-7863(97)02276-2 CCC: $14.00

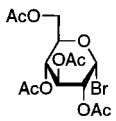
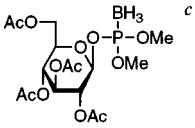
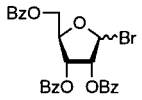
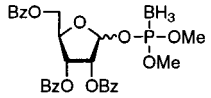


In summary, we have prepared new reagents, dimethyl boranophosphate monopotassium salt and tetramethyl boranopyrophosphate, and have demonstrated that these reagents react with reactive organic halides or lithium alkoxides in a nucleophilic or electrophilic manner. These facts open new and simple synthetic routes to various boranophosphates derivatives including borano analogues of naturally occurring phosphates.

(9) Preparation of compound **2**: Methanesulfonyl chloride (0.93 mL, 12 mmol) was added to a solution of **1** (3.24 g, 20 mmol) in acetonitrile (30 mL) at 0 °C, and the mixture was stirred at room temperature for 4 h. The precipitated solid was removed by filtration, and the filtrate was concentrated under reduced pressure. The residual oil was passed through a short column of silica gel with ethyl acetate to give compound **2** (2.26 g, 98%) as a colorless oil: $R_f = 0.23$ (silica gel, ethyl acetate−hexane 1:5); ^{1}H NMR ($CDCl_3$) δ −0.1 to −1.2 (br q, 6H), 3.85 (d, $^3J_{HP} = 11.5$ Hz); ^{31}P NMR ($CDCl_3$) δ 110.6−111.8 (m); ^{11}B NMR ($CDCl_3$) δ −62.4 (d, $J_{BP} = 87.3$ Hz); IR (neat) 2960, 2440, 1040, 860 cm^{-1}; HRMS (FAB) calcd for $C_4H_{17}B_2O_5P_2$ (M − H) 229.074, found 229.074. This compound violently decomposed at about 130 °C.

(10) A mixed anhydride, 2,4,6-$Me_3C_6H_2COOP(BH_3)(MeO)_2$, also reacted with lithium alkoxides to give the corresponding boranophosphates.

Table 1. Reactions of Compound **1** with Electrophiles

substrate	time (h)[a]	product	yield (%)[b]
$MeOCH_2Cl$	0.5	$MeOCH_2OP(BH_3)(OMe)_2$	69
p-$BrC_6H_4COCH_2Br$	15	*p*-$BrC_6H_4COCH_2OP(BH_3)(OMe)_2$	66
	13	 [c]	82
	24		71
t-$BuMe_2SiCl$	1	*t*-$BuMe_2SiOP(BH_3)(OMe)_2$	79
t-$BuPh_2SiCl$	15	*t*-$BuPh_2SiOP(BH_3)(OMe)_2$	87
MeCOCl	0.2	$MeCOOP(BH_3)(OMe)_2$	74
t-BuCOCl	3	*t*-$BuCOOP(BH_3)(OMe)_2$	81
PhCOCl	1	$PhCOOP(BH_3)(OMe)_2$	87
p-$O_2NC_6H_4COCl$	1	*p*-$O_2NC_6H_4COOP(BH_3)(OMe)_2$	81
2,4,6-$Me_3C_6H_2COCl$	1	2,4,6-$Me_3C_6H_2COOP(BH_3)(OMe)_2$	78

[a] All reactions were carried out in acetonitrile at room temperature. [b] Isolated yield. [c] The structure of this compound was unequivocally determined by single crystal X-ray analysis.

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Supporting Information Available: Spectral data of new boranophosphates (4 pages). See any current masthead page for ordering and Internet access instructions.

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