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Phosphonium Salt Methodology for the Synthesis of Phosphoric Monoesters and Diesters and its Application to Selective Phosphorylation

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Abstract: The reaction of an alcohol with a trialkyl phosphite in the presence of pyridinium bromide perbromide and triethylamine afforded the phosphoric triester in good yield, which can be transformed to the phosphoric monoester or diester. The method was applied to selective phosphorylation aiming at a convenient synthesis of phosphatidyl *myo*-inositol derivatives.

Nucleic acid chemistry has stimulated the development of a variety of phosphorylation methods.[1] Phosphotriester approach which involves reactive phosphoryl [O=P(V)] species has been well documented in the synthesis of oligonucleotides[2] and more recently, the alternative phosphoramidite method employing [P(III)] derivatives[3] has been utilized widely. On the other hand, we have recently reported the phosphorylation method based on a phosphonium salt [P^{+}(IV)] reactive intermediate.[4] The method comprises the reaction of alkyl *o*-xylylene phosphite with alcohols in the presence of pyridinium bromide perbromide (PBP). Although there are some reports on the similar reactions of trialkyl phosphites with halonium ion type oxidants[5] and diethyl azodicarboxylate[6] in the presence of simple alcohols, its synthetic application to phosphorylation has been little considered so far, except for Mukaiyama's reports in which bromocyanoacetamide was utilized as the oxidant.[7] Such a tetracoordinate phosphonium salt is expected to show medium reactivity between P(III)- and O=P(V) species toward alcohol, consequently its reactivity might be utilized for selective phosphorylation of polyols. Keeping this consideration in mind, we have investigated a novel type of phosphorylation strategy based on the reaction of a phosphite with an alcohol in the presence of PBP and herein the realization of the idea will be described.

A representative procedure for the preparation of alkyl dimethyl or alkyl dibenzyl phosphate has been performed by the reaction of trimethyl or tribenzyl phosphite with an alcohol in the presence of PBP and triethylamine in dichloromethane at -42 °C (Table 1). The reaction at room temperature lowered the yield while the reaction conducted at 0 °C proceeded well as at -42 °C. The yield also decreased remarkably in the reaction of entry 4 in Table 1 where the alcohol was added later after stirring a mixture of the other reaction components for 5 min. Trimethyl phosphite was shown to be more reactive than tribenzyl phosphite as a larger molar amount of the latter reagent was required to obtain a good yield of the product (entry 4). When 2,2-dimethylpropan-1,3-diol was treated with nearly equimolar amounts of tribenzyl phosphite and PBP, the corresponding six-membered cyclic phosphate as well as diphosphate were not obtained accompanied by the monophosphate (entry 6). The dimethyl and dibenzyl products can be deprotected by the reaction with bromotrimethylsilane and hydrogenolysis for the latter case to afford the phosphoric monoesters.

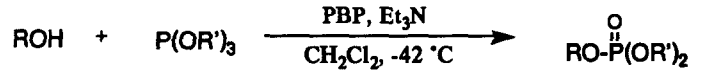
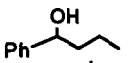
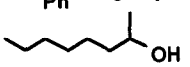
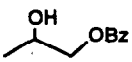
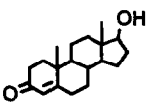
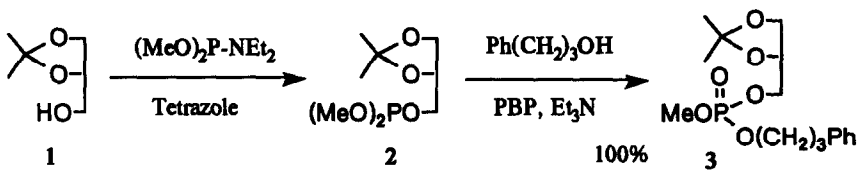


Table 1. Phosphoric ester synthesis via the phosphonium salt approach

Entry	ROH	Phosphite R'	Phosphite equiv	PBP equiv	Et_3N equiv	Time, h	Yield, %
1		Bn	1.4	1.6	1.8	1.0	93
2		Me	1.4	1.5	1.6	1.5	85
3		Bn	1.5	1.8	1.9	2.0	89
4		Bn	2.4	2.5	2.6	3.0	85
		Me	1.2	1.3	1.4	2.0	87
5		Me	1.2	1.3	1.5	3.0	84
6		Bn	1.2	1.3	2.0	1.5	78[a]

[a]Monophosphate

The phosphonium salt procedure was then utilized for the synthesis of phosphoric diester. Racemic 2,2-dimethyl-1,3-dioxolane-4-methanol 1 was first allowed to react with dimethyl *N,N*-diethylphosphoramidite in the presence of 1*H*-tetrazole to afford the glyceryl dimethyl phosphite 2 which, after washing with water and without purification, was treated with 3-phenylpropanol as the another alcohol, PBP, and triethylamine in a similar manner described above, resulting in the formation of the phosphoric triester 3 in quantitative yield. Removal of the methyl group in 3 with thiophenol and triethylamine[8] may furnish the phosphoric diester.

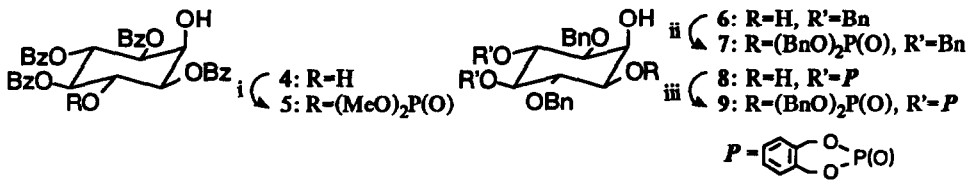


Scheme 1. A demonstration of the synthesis of protected mixed dialkyl phosphates

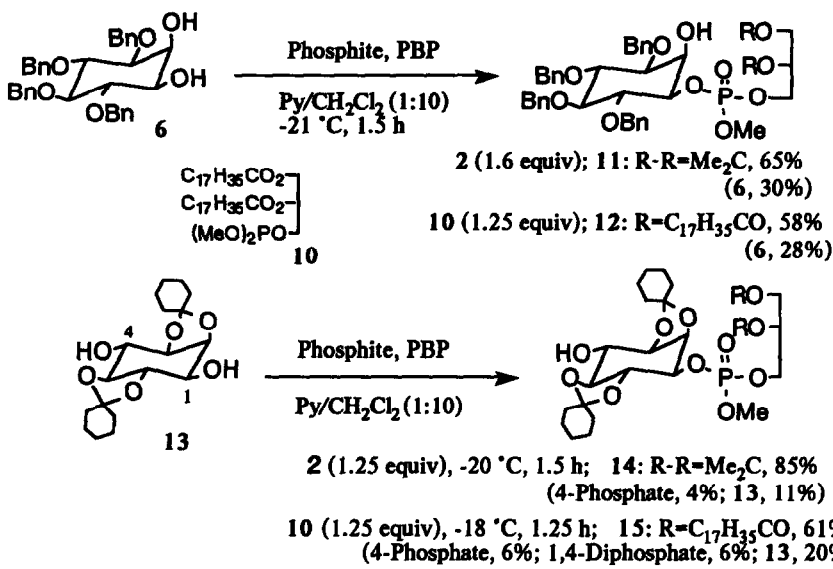
Compared with the Mukaiyama's procedure using bromocyanoacetamide,[7] ours may be practical since PBP is commercially available and easy-handling and the yield of testosterone 17-dimethyl phosphate (entry 5) was higher in our case than the reported yield[7b] (60%). Thus, the present phosphonium salt methodology has now been apparent to provide alternative methods for the synthesis of phosphoric monoesters and diesters.

Regioselective introduction of a phosphate function at C-1 in 1,2-free inositol derivatives is quite difficult,[9] although selective reactions such as alkylation,[10] silylation,[11] and acylation[12] have been known. This difficulty is attributed mainly to the reactivities of the known phosphorylating agents which consist of the phosphoryl [O=P(V)] compounds and phosphorous [P(III)] ones. In general, the reactivity of the former are not satisfactory to react with the inositols and that of the latter is so high. These facts prompted us to apply the phosphonium salt

strategy to selective phosphorylation of polyols. According to the method, 1,3,4,5-tetra-*O*-benzoyl-*myo*-inositol **4** was subjected to the reaction with trimethyl phosphite and the equatorial hydroxyl group was regioselectively phosphorylated to give dimethyl phosphate **5** in 75% yield together with the recovered starting diol (13%). Inositol derivatives having vicinal diol moieties **6** and **8** was also selectively phosphorylated at the C-1 positions respectively by the similar reaction using tribenzyl phosphite to give the corresponding 1-dibenzyl phosphates **7** and **9** in excellent yields (Scheme 2).[13] These products are valuable and protected derivatives of *myo*-inositol 1-phosphate and *myo*-inositol 1,4,5-trisphosphate ($InsP_3$)[11a] The latter was also the key intermediate for 2-acyl analogues of $InsP_3$[14] which were prepared previously in longer steps.[15]



Scheme 2. Regioselective phosphorylation. *Reaction conditions*: CH_2Cl_2, -42 °C, 1.5 h; i) $(MeO)_3P$ (1.2 equiv), PBP (1.4 equiv), Et_3N (1.6 equiv), 75% yield, SM: 13% yield, ii) $(BnO)_3P$ (1.2 equiv), PBP (1.3 equiv), Et_3N (1.4 equiv), 94% yield, iii) $(BnO)_3P$ (2.1 equiv), PBP (2.2 equiv), Et_3N (2.4 equiv),93% yield.



Scheme 3. Synthesis of protected 1-phosphatidyl-*myo*-inositol derivatives

The regioselective phosphorylation based on the phosphonium salt was extended to the synthesis of phosphatidyl inositols. Treatment of tetrabenzyl *myo*-inositol **6** with glyceryl phosphates **2** and **10** in a similar manner afforded the 1-phosphatidyl inositols **11** and **12** in good yields. Pyridine was suitable for solubilization of glyceryl phosphite **10** in addition to its role as a base. The equatorially disposed dihydroxy compound **13** was similarly phosphorylated by using **2** and **10** to give 1-phosphates **14** and **15** with excellent regioselectivities.[16]

The regioselective phosphorylation opens the short synthesis of inositol phospholipids.[17] Thus, the deprotection of 15 was accomplished by treatment with 1) PhSH/Et_3N and then 2) aqueous CF_3CO_2H. The 1-*O*-*rac*-phosphatidyl *myo*-inositol was also derived from 12 by demethylation (PhSH/Et_3N) and subsequent hydrogenolysis (H_2/5% Pd-C).

In summary, the phosphonium salt process presented here will provide a novel phosphorylation methodology for the synthesis of phosphoric monoesters and diesters which facilitates the selective phosphorylation, resulting in the development of a quite convenient strategy for phosphoinositide synthesis.

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13. Typical procedure: A solution of 1,4,5,6-tetra-*O*-benzyl-*myo*-inositol (**6**, 77.6 mg, 0.144 mmol), tribenzyl phosphite (60.6 mg, 0.172 mmol), and Et_3N (20.3 mg, 0.201 mmol) in dichloromethane (2.0 mL) with powdered 4A MS was cooled to -42 °C and then PBP (59.8 mg, 0.187 mmol) was added. The mixture was stirred at the same temperature for 1.5 h, AcOEt was added after a short treatment with H_2O at room temperature for a few minute. The organic layer was washed successively with H_2O, aqueous $NaHCO_3$, and brine, dried, and concentrated. The residue was recrystallized from AcOEt and hexane to give **7** (108 mg, 94% yield), mp 127-9 °C, δ_P (109 MHz, $CDCl_3$, external ref.=80% H_3PO_4) -1.02. Anal. Calcd for $C_{48}H_{48}O_9P \cdot 1/2H_2O$: C, 71.27, H, 6.11. Found: C, 71.61, H, 6.19.
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