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A convenient method for phosphorylation using triallyl phosphite

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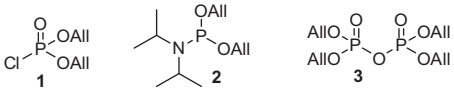
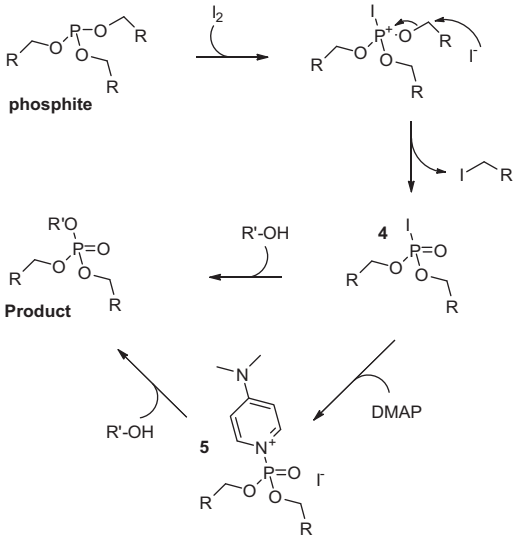
ABSTRACT

A direct method for the phosphorylation of alcohols, phenols, saccharides and nucleosides using triallyl phosphite is described. From primary or secondary alcohols, the corresponding diallyl-protected phosphorylated compounds are obtained in good to high yields. The method was found to be selective for primary alcohols and to be applicable to diverse simple and functionalized alcohols, including amino acids, carbohydrates and nucleosides.

Orthogonal allyl-based protecting groups are essential in peptide[1,2] and nucleotide[3,4] synthesis and, more generally, in total synthesis.[5] In particular, phosphorylation reactions leading to orthogonally allyl-protected phosphates are useful because their deprotection can be achieved in mild conditions by allylic transfer to a scavenger (butyl amine,[2–4,6] pyrrolidine[7,8] or others[9]), catalysed by tetrakis(triphenylphosphine)palladium)[1] or by using palladium chloride[10] in methanol.[11,12] Several methods have been reported for the synthesis of allyl-protected phosphates,[10] namely the use of diallyl chlorophosphate **1**,[12,13] phosphoramidite **2**[2,7–9,14,15] and, more recently, the catalytic Lewis acid phosphorylation with pyrophosphates such as compound **3**.[16] However, the combination of phosphite and iodine, a cheap, easy-to-handle method which does not require prior synthesis of the reagent, has never been reported for access to allyl phosphates whereas it is an established method for the introduction of methyl, ethyl or benzyl protected phosphates.[17] Moreover, triallyl phosphite is commercially available and quite inexpensive, or it can be easily prepared from phosphorus trichloride.[18] In this study, we report the results of our investigations into this method which offers a simple, direct and cheap alternative for accessing allyl phosphorylated alcohols, phenols, nucleosides and sugars.



The phosphite/iodine phosphorylation method is based on the sequence shown in Scheme 1, starting with an Arbuzov reaction of alkyl phosphite with iodine[19] leading to the formation of the corresponding dialkyl phosphoriodidate **4**. Once produced, this reactant reacts with alcohols or phenols directly or via its reaction with pyridine, as initially described.[17,20] DMAP can also



Scheme 1. Proposed mechanism of phosphorylation using phosphite: the dialkyl phosphoriodidate (**4**) and the 4-(dimethylamino)pyridin-1-ium (**5**) are the reactants for the phosphorylation process.[17,19,20]

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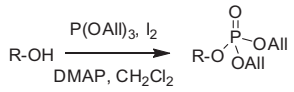
0040-4039/

Table 1
Conditions for the phosphorylation of *p*-cresol and benzyl alcohol (the phosphorylating reagent was prepared following the typical experiment)



R	Conditions	Temperature (°C)	Yield (%)
CH_3Ph–	$P(OAll)_3$ (1.2 equiv), I_2 (1 equiv), DMAP (1 equiv)	RT	52
CH_3Ph–	$P(OAll)_3$ (1.2 equiv), I_2 (1 equiv), DMAP (1 equiv)	0	52
CH_3Ph–	$P(OAll)_3$ (1.2 equiv), I_2 (1 equiv), DMAP (1 equiv)	−10	49
CH_3Ph–	$P(OAll)_3$ (1.2 equiv), I_2 (1 equiv), DMAP (1 equiv)	−30	47
CH_3Ph–	$P(OAll)_3$ (2.2 equiv), I_2 (2 equiv), DMAP (2 equiv)	0	75
Bn–	$P(OAll)_3$ (1.2 equiv), I_2 (1 equiv), DMAP (1 equiv)	RT	75
Bn–	$P(OAll)_3$ (1.2 equiv), I_2 (1 equiv), DMAP (1 equiv)	0	75
Bn–	$P(OAll)_3$ (1.2 equiv), I_2 (1 equiv), DMAP (1 equiv)	−10	75
Bn–	$P(OAll)_3$ (1.2 equiv), I_2 (1 equiv), DMAP (1 equiv)	−30	73
Bn–	$P(OAll)_3$ (2.2 equiv), I_2 (2 equiv), DMAP (2 equiv)	0	82

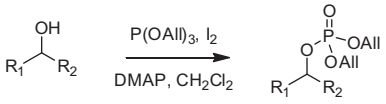
be used, as shown by Soulère et al.,[21] with triethylphosphite leading to the production of 1-(bis(alkyl)phosphoryl)-4-(dimethylamino)pyridin-1-ium (**5**) (Scheme 1).[20]

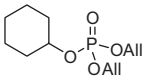
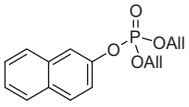
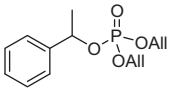
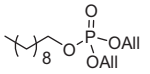
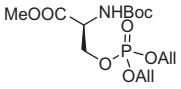
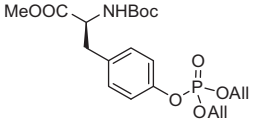
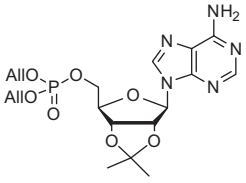
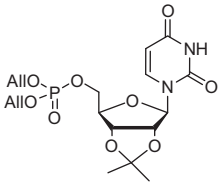
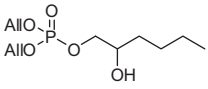
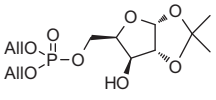
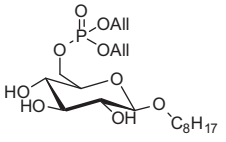
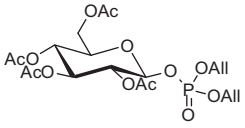
To screen several reaction conditions, benzyl alcohol was used as a model primary alcohol and *p*-cresol as a model phenol. We then examined the influence of temperatures, (0 °C, −10 °C, −30 °C or RT) and of different amounts of iodine (1 or 2 equiv) and triallyl phosphite (1.2 or 2.2 equiv). The phosphite was always used in excess to ensure complete consumption of iodine (Table 1). Though the role of DMAP can be catalytic, it is used in stoichiometric amount for neutralizing the hydrogen iodide formed in the process, in order to prevent undesired acid catalyzed side reactions on more fragile functions of the substrates and products. The reaction was efficient, with comparable yields for both alcohols at 0 °C, −10 °C, −30 °C or RT. As expected, the yields increased in both cases when 2 equiv of the phosphorylating agent were used.

In a typical experiment for the phosphorylation of benzyl alcohol, iodine (2 equiv) was added at 0 °C to a solution of triallyl phosphite (2.2 equiv) in anhydrous DCM (5 mL). After 10 min at 0 °C, the solution was warmed up to room temperature and added, drop-wise for 5 min, to a solution of benzyl alcohol (0.5 mmol) and DMAP (2 equiv) in anhydrous DCM (5 mL) at RT. After 4 h, the solution was diluted with DCM and washed with saturated $NaHSO_4$, saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The diallylbenzylphosphate was purified by flash chromatography and characterized by standard analytical procedures.

The scope of the reaction was investigated using various alcohols, including secondary and functionalized alcohols such as BocSerOMe, BocTyrOMe, 2′,3′-isopropylideneadenosine and 2′,3′-isopropylideneuridine. We also used 1,2-hexanediol, 1,2-*O*-isopropylidene-α-D-xylofuranose and octyl β-D-glucopyranoside as polyols to examine the selectivity toward primary alcohols (Table 2). The phosphorylation reaction was less effective on secondary alcohols, such as cyclohexanol or α-methylbenzyl alcohol, with 39% and 42% yields, respectively. For all other alcohols, the reaction was found to be efficient with yields ranging from 62% to 98%. As shown for the reaction with tribenzyl phosphite,[20] the reaction proved to be selective for primary alcohols with good to excellent yields when conducted on 1,2-hexanediol, 1,2-*O*-isopropylidene-α-D-xylofuranose and octyl β-D-glucopyranoside.

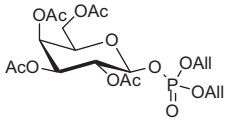
Table 2
Phosphorylation of various alcohols using triallyl phosphite[a]



Entry	Alcohols	Products	Yield (%)
1	Cyclohexanol		39
2	2-Naphtol		98
3	α-Methylbenzyl alcohol		42
4	Decan-1-ol		94
5	BocSerOMe		64
6	BocTyrOMe		77
7[b]	2′,3′-Isopropylidene adenosine		62
8[b]	2′,3′-Isopropylidene uridine		68
9	1,2-Hexanediol		72
10	1,2-*O*-Isopropylidene-α-D-xylofuranose		67
11	Octyl β-D-glucopyranoside		67
12[c]	2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose		73

(*continued on next page*)

Table 2 (*continued*)

Entry	Alcohols	Products	Yield (%)
13[c]	2,3,4,6-Tetra-*O*-acetyl-D-galactopyranose		55

[a] All reactions were conducted using the standard procedure except for nucleosides and the synthesis of β-glycosyl-1-phosphates: triallyl phosphite (2.2 equiv), I_2 (2 equiv) and DMAP (2 equiv) and DCM as solvent.

[b] Nucleosides were dissolved with DMAP (4 equiv) in THF and the phosphorylating agent prepared in DCM was added at −30 °C. The reaction was stirred overnight at RT.

[c] For the synthesis of β-glycosyl-1-phosphates, triallyl phosphite (7.8 equiv), I_2 (7.5 equiv) and DMAP (10 equiv) were used according to the standard procedure. The reaction was stirred overnight at RT.

Table 3
Phosphorylation of benzyl alcohol in various solvents[a]

Entry	Solvents	Yield (%)
1	DCM	82
2	THF	56
3	Pyridine[b]	84
4	Acetonitrile	85
5	DMF	41
6	DMSO	24

[a] All reactions were conducted with triallyl phosphite (2.2 equiv), I_2 (2 equiv) and DMAP (2 equiv) at RT. The solution of the phosphorylation reagent was prepared in DCM.

[b] Without DMAP.

Most reactions were performed using the conditions optimized for benzyl alcohol (2.2 equiv of phosphite, 2 equiv of iodine, 2 equiv of DMAP, DCM). However, some substrates required alternative conditions, such as the nucleosides (entries 7 and 8) which were dissolved in THF instead of DCM and for which a larger excess of DMAP was required to obtain an acceptable yield. The reaction was finally applied to 2,3,4,6-tetra-*O*-acetyl-D-gluco and -galactopyranose (entries 12 and 13, Table 2) leading, selectively, to the corresponding β-phosphates with similar selectivity, yields and conditions (7.8 equiv of phosphite, 10 equiv of DMAP) to those recently reported by Vincent and co-workers, who used diallyl chlorophosphate **1** as the phosphorylating agent.[12]

To further investigate the solvent scope of the reaction, the phosphorylation was performed on solutions of benzyl alcohol in THF, pyridine, acetonitrile, DMF and DMSO, in the presence of DMAP (except for pyridine). The phosphorylating agent was prepared in anhydrous DCM, as described above. These reactions showed that DCM, pyridine and acetonitrile were all appropriate solvents, with yields of approximately 80%, thus widening the choice when substrates are not soluble enough in DCM (Table 3).

In summary, a convenient direct phosphorylation method for providing fair to excellent yields of allyl-protected phosphorylated compounds from cheap and readily available triallylphosphite is reported. The method was applied to simple primary and secondary alcohols, as well as to more complex substrates, such as nucleosides or carbohydrate derivatives. Diols or polyols possessing both primary and secondary alcohol functions can be selectively phosphorylated at their primary position.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.030.

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