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Facile synthesis of simple mono-alkyl phosphates from phosphoric acid and alcohols

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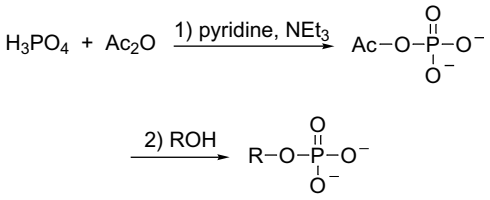
ABSTRACT

Simple aliphatic alcohols can be selectively converted into mono-alkyl phosphate esters at the laboratory scale using the acetic anhydride-mediated activation of inorganic phosphate.

Phosphate monoesters constitute simple models of membrane constituents or biological intermediates involved in many cell signaling and regulation pathways. For chemical purposes, phosphate or phosphoric acid can be introduced in the synthesis of phosphodiesters or other related species as a monoprotected phosphoric acid. Unfortunately, most monosubstituted phosphate esters derived from simple alcohols are not commercially available, which is probably in relation with their instability linked to a specific mechanism of degradation. Indeed, they can undergo a dissociative breakdown in acidic or neutral media through a resonance stabilized transition state related to metaphosphate ion.[1] There is a need for laboratory-scale syntheses of simple alkyl phosphate esters or phosphate derivatives carrying selectively removable groups. Together with well established procedures,[2–5] the ongoing publication of new reports[6,7] on this subject illustrates the need for laboratory scale methods for their preparation. Methods starting from phosphorus oxychloride, generally in the presence of pyridine, followed by hydrolysis suffer from a lack of selectivity, yielding mixtures of mono-, di-, and even tri-substituted derivatives.[5] The difficulty in their synthesis is to selectively stop the reaction at the stage of the monosubstituted derivative. A possibility is to start from activated phosphodiesters[8] and then to remove protecting groups. Alternatively, methods involving activated phosphates are likely to selectively induce monophosphorylation of alcohols through dissociative mechanisms resulting in the transfer of the equivalent of a metaphosphate ion (PO_3^-), whatever this species could be a reaction intermediate or not.[1] Polymetaphosphate has been used in this way,[2] but other methods involving monomeric metaphosphate[9] or the trichloroacetonitrile-promoted activation[3] of phoshoric acid have also been proposed. Alternatively, the formation of phosphate esters by azeotropic dehydration in the presence of catalyst has been performed. [7] Here, we report on a practical and efficient protocol for the conversion of simple alcohols into the corresponding monophosphate esters using acetic anhydride activation of inorganic phosphate.

This method of activation (see Scheme 1) involves the formation of acetyl phosphate a high energy biochemical intermediate capable of phosphorylating alcohols or other nucleophiles.[10] A one-pot procedure was carried out without inconvenient, starting from less acidic aliphatic alcohols (Table 1). But alcohols with a more pronounced acidic character were shown to lead to lower yields probably due to the inactivation of acetic anhydride through ester formation.

In those cases, the fact of performing the formation of acetyl phosphate mixed anhydride in an independent step in a non-reacting solvent (acetonitrile) before the introduction of the alcohol of



Scheme 1.

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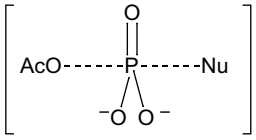
Table 1
Synthesis of phosphate monoesters[a]

Entry	R	Yield[b] (%)
1	Methyl	51
2	Ethyl	56
3	*t*-Butyl	63
4	Dodecyl	56[c]
5	Benzyl	38
6	2-Hydroxyethyl	56
7	Allyl	72
8	2-Cyanoethyl	56
9	2,2,2-Trichloroethyl	38[d]

[a] Prepared via method (a) unless otherwise mentioned (see Ref. 11 for experimental procedure).
[b] As recrystallized cyclohexylamine salts.
[c] Method (b).
[d] Method (c).

interest was shown to improve the overall yield. Another side-reaction identified in the course of this study consisted in pyrophosphate formation,[10b,c] which is inevitable even in the presence of large excess of the alcohol, but phosphodiester formation was not observed in our experiments. Though they must be much lesser nucleophiles than phosphate dianion, aliphatic alcohols compete favorably when using them in high excess, which can be accounted for by the dissociative character of the phosphoryl transfer reaction. As a result, the influence of the nucleophilic power of the attacking group is moderate since bond formation is limited at the transition state, which is resembling metaphosphate ion (PO_3^-).[1]



In most cases, the monoester can be separated from unreacted phosphate, pyrophosphate, and other side-products by crystallization as a divalent cyclohexylamine salt. The stability of the base-labile 2-cyanoethyl ester to this purification method is noteworthy, and was attributed to the electrostatic effect of phosphate dianion likely to destabilize a negatively charged transition state. In subsequent synthetic transformations, the monophosphate esters prepared in this way can be reacted to give phosphodiesters or mixed anhydrides,[12] for instance by activation with dicyclohexylcarbodiimide. But any coupling step requires the conversion of the cyclohexylamine salt into the salt of a non-reactive tertiary amine or tetra-alkylammonium salt. This can be made readily on a cation exchange resin column (H^+ form) even in the case of acid-sensitive *t*-Bu-phosphate.[12]

In conclusion, a series of phosphate esters, including protecting groups removable through a variety of procedures, has been prepared through a simple procedure in convenient yields.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.083.

References and notes

1. Williams, N. H. *Biochim. Biophys. Acta* **2004**, *1697*, 279–287.
2. (a) Cherbuliez, E.; Rabinowitz, J. *Helv. Chim. Acta* **1956**, *39*, 1455–1461; (b) Cherbuliez, E.; Rabinowitz, J. *Helv. Chim. Acta* **1956**, *39*, 1461–1467; (c) Cherbuliez, E.; Rabinowitz, J. *Helv. Chim. Acta* **1958**, *41*, 1168–1175.
3. Cramer, F.; Rittersdorf, W.; Bohm, W. *Liebigs Ann. Chem.* **1962**, *654*, 180–188.
4. Khwaja, T. A.; Reese, C. B.; Stewart, J. C. M. *J. Chem. Soc. (C)* **1970**, 2092–2100.
5. Slotin, L. A. *Synthesis* **1976**, 737–752.
6. Weber, P.; Fonvielle, M.; Therisod, M. *Tetrahedron Lett.* **2003**, *44*, 9047–9049.
7. (a) Sakakura, A.; Katsukawa, M.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1999–2002; (b) Sakakura, A.; Katsukawa, M.; Ishihara, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1423–1426; (c) Sakakura, A.; Katsukawa, M.; Hayashi, T.; Ishihara, K. *Green Chem.* **2007**, *9*, 1166–1169.
8. Jones, S.; Smanmoo, C. *Tetrahedron Lett.* **2004**, *45*, 1585–1588.
9. (a) Ramirez, F.; Marecek, J. F.; Yemul, S. S. *J. Org. Chem.* **1983**, *48*, 1417–1420; (b) Iwamoto, N.; Okamoto, Y.; Takamuku, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1505–1508.
10. (a) Lipmann, F. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1946**, *6*, 231–267; (b) Di Sabato, G.; Jencks, W. P. *J. Am. Chem. Soc.* **1961**, *83*, 4393–4400; (c) Herschlag, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 7938–7946.
11. *Typical experimental procedure*: Method (a). To a stirred mixture of crystalline phosphoric acid (1.0 g, 10.2 mmol) and pyridine (4.15 mL, 51 mmol), the alcohol (102 mmol) and then triethylamine (2.8 mL, 20.4 mmol) were added via a dropping funnel. After complete dissolution, acetic anhydride (1.93 mL, 20.4 mmol) was added dropwise. The reaction mixture was stirred for 2 h at 90 °C, and then cooled to room temperature. After addition of water (5 mL), the reaction mixture was stirred at 90 °C for 1 h and cooled to room temperature. The solution was diluted with water (12 mL). The aqueous phase was washed three times with diethyl ether (25 mL) and concentrated. The oily liquid was dissolved in acetone/water (9:1). Then cyclohexylamine (2.1 mL, 30.6 mmol) was added. The mixture was cooled at 4 °C and allowed to crystallize for 12 h, and the white solid formed was collected by filtration and dried. The solid was heated in ethanol, the insoluble residue was filtered off, and the filtrate was cooled for 12 h at 4 °C. The white solid was filtered, washed with ethanol, and dried under vacuum. Method (b) as method (a) except that the workup was modified as follows. The phosphate ester was extracted from the aqueous phase as a triethylamine salt with CH_2Cl_2; the organic layer was concentrated and precipitated as previously. Method (c). The reaction was carried by performing the activation of phosphate in an independent stage: a mixture of crystalline phosphoric acid, pyridine, and triethylamine was stirred until complete dissolution in acetonitrile (10 mL). Acetic anhydride was added dropwise to the solution. Then the alcohol was added and the reaction mixture was stirred at 90 °C for 12 h. The workup was then carried out as mentioned in method (a).
12. Biron, J. P.; Pascal, R. *J. Am. Chem. Soc.* **2004**, *126*, 9198–9199.