A New and Rapid Synthesis of Phospholipids

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Reaction of 2-chloro-3-methyl-1,3,2-oxazaphosphacyclopentane with long chain alcohols gives cyclic alkyl phosphoramidites, which yield alkyl phosphoryl *N*-methylethanolamines on dinitrogen tetroxide oxidation and acid hydrolysis.

Phospholipids are major components of cell membranes;[1] their amphipathic structure confers on such membranes a bi-layer structure.[2] Phospholipids have also been implicated in a number of physiological processes,[3] and their synthesis is of interest not only in model membrane studies,[4] but also as enzyme inhibitors,[5] as drug carriers,[6] and as drugs in their own right.[7]

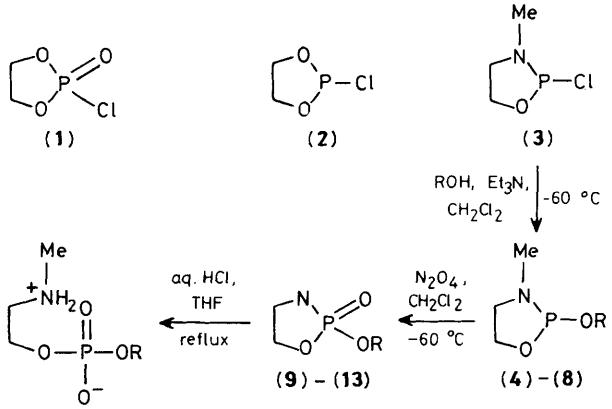
A new synthesis of alkyl phosphoryl cholines was recently presented by Magolda and Johnson.[8] Long chain alcohols were treated with phosphoryl chloride to give alkyl phosphorodichloridates $ROPOCl_2$ which were cyclised with ethane-1,2-diol. Prolonged treatment of this phosphate triester with trimethylamine gave the required alkyl phosphoryl cholines in moderate (46—50%) yield. However, the method is wasteful in terms of the long chain alcohol, which would prevent its application to the synthesis of more complex phospholipids. Moreover, the reactions take several days to complete and, in particular the final stage is rather tedious and is likely to cause modificaton of more labile phospholipid derivatives.

A synthetic strategy more acceptable in terms of the use of the alcohol would be to use a pre-constructed phosphorus heterocycle. Indeed, 2-chloro-1,3,2-dioxaphosphacyclopentane 2-oxide (**1**) has been used in this context.[9] However, this is unreactive towards hindered alcohols. It was considered that this disadvantage might be overcome by the use of the more reactive phosphite,[10] 2-chloro-1,3,2-dioxaphosphacyclopentane (**2**). Furthermore, since the introduction of the required nitrogen atom into these oxygen containing heterocycles is rather troublesome, it would be advantageous to use a nitrogen containing heterocycle, such as 2-chloro-3-methyl-1,3,2-oxazaphosphacyclopentane (**3**).[11]

The reaction of *N*-methylethanolamine with phosphorus trichloride in chloroform at low temperature gives (**3**) in a purified yield of 48%.[12] This reacts with (long chain) alcohols at low temperature to give phosphite triesters (**4**)—(**8**) in almost quantitative yield.

Attempted iodine oxidation of the long chain alkyl phosphites by the procedure of Letsinger[13] was unsuccessful. However, oxidation to the phosphates (**9**)—(**13**) was highly successful using dinitrogen tetroxide.[14] The resulting phosphate triesters (crude yield 97—100%) were hydrolysed without purification, to give the acyclic phospholipids in 76—86% yield.

Thus, the alkyl phosphoryl *N*-methylethanolamines (**14**)—(**18**) were prepared from the corresponding alcohols in an overall yield of 73—86% in a rapid three-stage procedure. The



(**14**) R = Et (73%)
(**15**) R = C_6H_{13} (73%)
(**16**) R = C_8H_{17} (86%)
(**17**) R = $C_{18}H_{37}$ (76%)
(**18**) R = 9Δ-$C_{18}H_{37}$ (80%)

THF = tetrahydrofuran

final products, and their phosphite precursors, were characterised by ^{1}H and ^{31}P n.m.r. spectroscopy.†

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† Selected ^{31}P n.m.r. data (in $CDCl_3$): (**4**) 138.75, (**5**) 138.68, (**6**) 138.71, (**7**) 138.76, (**8**) 138.75, (**14**) −3.2, (**15**) −1.5, (**16**) −1.1, (**17**) −1.0, (**18**) −1.4. p.p.m. Positive shifts are downfield from external 85% H_3PO_4.