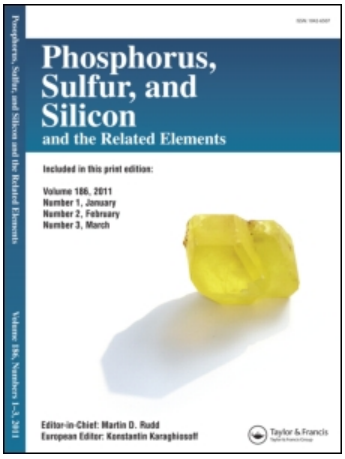

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PHOSPHORYLATIONS WITH $ROP(X)Cl_2$: A NEW MECHANISTIC PATHWAY

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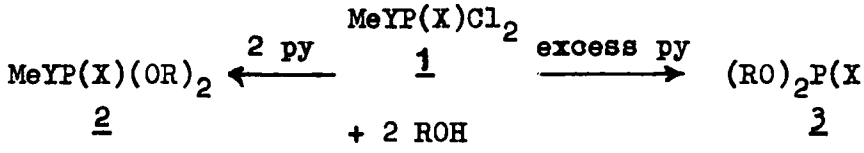
Abstract $MeYP(X)Cl_2$ (X,Y = O,S) reacts with equimolar as well as with excess amounts of pyridine below room temperature to form pyridinium betaines which act as strong bifunctional phosphorylating agents. Isolation of quite stable crystalline betaines can be accomplished by using 4-dimethylaminopyridine. The concept of donor-mediated phosphorylation is also applicable to monofunctional systems and can even be made more convenient by in situ generation of the reagents.

Whilst pyridine as a base is widely used in phosphorylations like 1 → 2, with 1a (and, to some extent, with $EtOP(O)Cl_2$, too,) in excess pyridine an "anomalous course of phosphorylation" [1], leading to diesters 3 instead of the expected 2, repeatedly has been observed and applied for preparative purposes. [1-3]



1-6	a	b	c	d
X	O	S	O	S
Y	O	O	S	S

From the presence of the N-methylpyridinium cation it was concluded [1] that 4a is the active phosphorylating bifunctional agent, generated as a result of a simple dealkylation step. [1-3] Moreover, elemental analysis of the isolated precipitate corresponded to what was regarded as 1:1 adduct of 4a and pyridine. [1]

$$C_5H_5N + \underset{\underline{1}}{MeYP(X)Cl_2} \longrightarrow \underset{\underline{4}}{C_5H_5\overset{+}{N}\text{-}Me\ \ Cl_2P(X)Y^-}$$

$MeOP(S)Cl_2$ (1b) acts, as we found, in quite the same manner forming high yields of 3b. Mixed compounds are also accessible, e.g., $(4\text{-}ClC_6H_4O)(4\text{-}O_2NC_6H_4O)PSO^-$ (isolated as dicyclohexylammonium salt in 75% yield). Excess amounts of pyridine, however, prove not to be essential, neither in reactions of 1a nor of 1b. Powerful phosphorylating bifunctional agents arise from mixing equimolar amounts of 1 and pyridine. Such 1:1 mixtures release methyl chloride far below room temperature, even by C-S bond fission in case of 1c and 1d, and to an extent that allows formation of 4 only to become a minor side reaction. This dramatic increase in the alkylating properties of 1 indicates that the interaction with pyridine obviously produces a highly active species, probably 5, by attack of the donor pyridine at phosphorus. What would remain of this "activated ester" after loss of methyl chloride is a betaine 6 that may be regarded as a kind of donor-stabilized metaphosphate species. Betaines 6a and 6b and, preferentially investigated, 6d, are known to be strong bifunctional phosphorylating agents [4] and have been prepared so far in a two step sequence starting from P_4S_{10}. [5,6] The reaction of 1 with pyridine thus constitutes a new, simple, one step synthetic route to betaines 6, by manifestation of both, phosphorylating plus alkylating properties, in a combined donor-mediated action.

$$:D + MeYP(X)Cl_2 \longrightarrow \underset{\underline{5}}{D\text{-}\overset{+}{\underset{\displaystyle Y\text{-}Me}{\overset{\displaystyle X}{\underset{|}{\overset{\|}{P}}}}}\text{-}Cl\ Cl^-} \longrightarrow \underset{\underline{6}}{D\text{-}\overset{+}{\underset{\displaystyle Y^-}{\overset{\displaystyle X}{\underset{|}{\overset{\|}{P}}}}}\text{-}Cl} + MeCl$$

$D = C_5H_5N$

With excess pyridine, of course, the latter will dealkylate 5 to give an equimolar mixture of 6 and N-methylpyridinium chloride having the same elemental composition

as the alleged 1:1 adduct of 4 and pyridine. The presence of 6 in 1:1 mixtures as well as in excess pyridine (along with minor amounts of $Cl_2P(X)Y^-$ as by-product from some dealkylation) is confirmed by ^{31}P-NMR spectra (6a: δ -8,4; 6b = 6c: δ 46,2; 6d: δ 97,4 ppm in $MeNO_2$). Since in the thiophosphate series the sulfur atom represents another nucleophile competing with pyridine and the chloride ion in the dealkylation of 5, reaction products of 1b may include, in addition to the main product 6 and some dichlorothiophosphate anion (δP 41,3 ppm), also some thiolo isomer 1c (δP 40,2 ppm), depending on the reaction conditions.

To obtain stabilized crystalline betaines, a donor quite superior to pyridine itself is its 4-dimethylamino derivative. With equimolar amounts of 1 it forms betaines 7 (table I) which were fully characterized spectroscopically and by elemental analyses. Of 7c an x-ray structure determination was performed which reveals a high degree of dearomatization to favour an exocyclic immonium resonance structure.[7]

TABLE I Betaines $4\text{-}Me_2\overset{+}{N}\text{-}C_5H_4N\text{-}P(X)(\overset{-}{Y})R$ (=7)

7	X	Y	R	%	F.°C	$\delta^{31}P$ a)
a	O	O	Cl	95	125-28	-8,6
b	S	O	Cl	87 b)	138-40	44,7
c	S	S	Cl	76	160-62	93,3
d	O	O	Ph	63	225	9,2

a) solvent $MeNO_2$ b) from 1b; from 1c: 84%

The presence of m/z = 130 corresponding to $ClPS_2$ in the mass spectra of 7c may indicate the possible release of a metaphosphate type moiety under appropriate conditions, as this was concluded before[8] from the thermal behaviour of intermediate sulfonium betaines analogous to the pyridinium betaines 6 and 7. Similarly like the betaines 6

and 7 dichloro(thio)phosphate ions, too, may be regarded as donor-stabilized chlorometa(thio)phosphates able to expel the donor chloride ion: with 4-dimethylaminopyridine Ph_4P^+ $Cl_2P(S)O^-$ undergoes complete conversion to Ph_4P^+ Cl^- and 7b.

The concept of donor-mediated phosphorylation via betaine formation is not restricted to bifunctional examples and can be applied as well to compounds containing only one leaving group bound to phosphorus. Furthermore, for preparing the betaines it is possible to generate the leaving group in situ as was demonstrated by the synthesis of 7d from PhP(O)(H)(OR) (R = Me, Me_3Si) and CCl_4 in presence of the pyridine donor.

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