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NUCLEOPHILIC SUBSTITUTION OF ALCOHOL AT PHOSPHORUS OF SPIRO ACYLOXYPHOSPHORANE : TRANSPHOSPHORANYLATION

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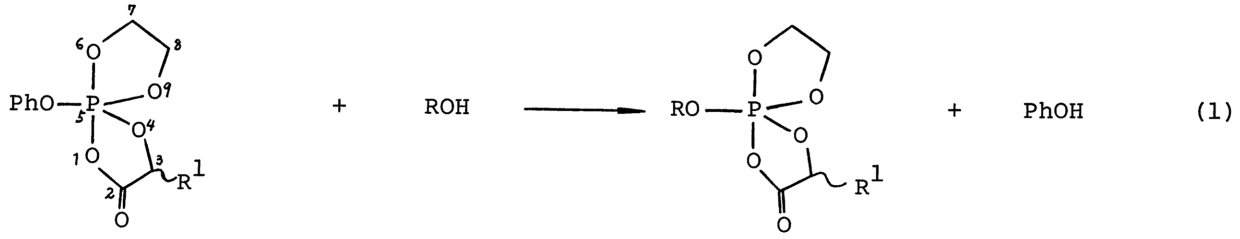
Spiro acyloxyphosphoranes (S-AOPs, **1** and **3**) underwent the nucleophilic substitution of alcohols at the phosphorus atom to give another S-AOPs (**2**) (Transphosphoranylation). Reaction mechanism and characteristics of the transphosphoranylation are described.

Oxyphosphoranes[1,2] are currently studied extensively in relation to the synthetic utility[1] as well as the biological importance of the hydrolysis mechanism of phosphates.[2] We have recently found new, versatile methods to prepare spiro acyloxyphosphoranes (S-AOPs) by the reactions of cyclic phosphorus (III) compounds with α-keto acids[3] and with acrylic acid or β-propiolactone.[4] More recently new spiro diacyloxyphosphoranes have been obtained by using a cyclic acyloxyphosphonite as a phosphorus(III) compound.[5] These S-AOPs can be taken as "orthophosphates" of cyclic acyl phosphates, which have been considered as reaction intermediates in the biological metabolism[6] and prepared in particular cases as reactive species.[7] The present paper deals with nucleophilic substitutions of an O-nucleophile of alcohols with S-AOPs (**1** and **3**), in which an alkoxyl group in S-AOP is replaced by another alkoxyl group at the phosphorus atom to yield new S-AOPs (**2**) (Transphosphoranylation, or Phosphorane Interchange).



(1)

1a, R^1=Me (-39.2, -39.6)
b, R^1=Ph (-39.0, -39.4)

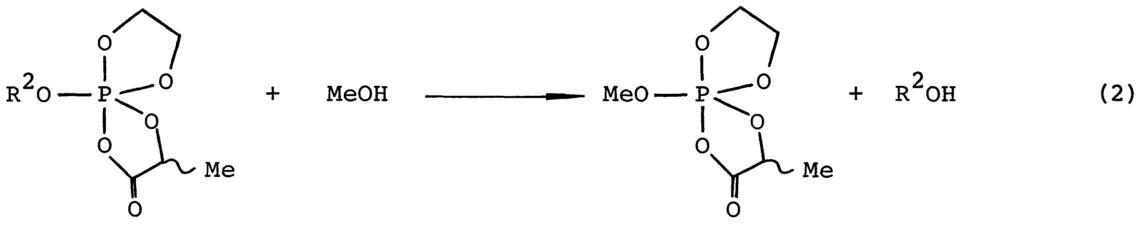
2a, R=R^1=Me (-35.4, -36.0)
b, R=Et; R^1=Me (-36.7, -37.4)
c, R=i-Pr; R^1=Me (-38.1, -38.6)
d, R=c-C_6H_{11}; R^1=Me (-37.9, -38.3)
e, R=Me; R^1=Ph (-34.7, -35.4)
f, R=Et; R^1=Ph (-36.1, -36.8)
g, R=i-Pr; R^1=Ph (-37.4, -37.9)

A mixture of methanol (7.5 mmol) and **1a** (3.0 mmol), which had been produced from 2-phenoxy-1,3,2-dioxaphospholane and pyruvic acid,[3] in 3.0 ml of chloroform was kept at -30°C for 3 hr under nitrogen. The ^{31}P NMR spectrum of the reaction mixture showed that **1a** (-39.2 and -39.6)[8] completely disappeared and was converted to another S-AOP **2a** (-35.4 and -36.0)[9] in 92% yield, in which a phenoxyl group in **1a** was replaced with a methoxyl group. The similar reactions carried out at 0°C and at room temperature for 1 hr gave **2a** in 90 and 92% yields, respectively. Analogously, ethanol reacted with **1a** and gave transphosphoranylated product **2b** in high yields at 0°C and at room temperature.

Secondary alcohols of isopropanol and cyclohexanol were less reactive toward **1a** than primary alcohols. At room temperature the complete consumption of **1a** took 3 hr and transphosphoranylated products **2c** and **2d** were formed in 75 and 78% yields, respectively. A phosphate-type product (from ^{31}P NMR) was formed in each case as a by-product which has not been identified.

Tertiary alcohols such as tert.-butanol showed a very reduced reactivity toward S-AOP. The transphosphoranylated product of tert.-butanol was not stable enough at room temperature and gradually decomposed to give a dehydrated product of isobutylene[10] and polyphosphate diester.[11]

In the reaction of eq (1), phenoxyl group is the leaving group. In relation to this reaction, the transphosphoranylations of other species of S-AOP having electron-withdrawing alkoxyl groups were examined (eq (2)).



(2)

3a; $R^2O=CF_3CH_2O$ (-38.2, -38.7)
b; $R^2O=CCl_3CH_2O$ (-38.4, -38.8)

2a

At 0°C reactions of **3a** and **3b** with methanol gave **2a** in yields of 93 and 90%, respectively. Thus, 2,2,2-trifluoro- and 2,2,2-trichloroethoxyl groups are as reactive as phenoxyl group.

The above reactions may be explained as follows. There are two courses conceivable for the attack of alcohol onto S-AOP. The nucleophilic attack of alcohol takes place at the phosphorus of **1** and leads to the production of **2** and phenol probably through a hexacoordinated intermediate **4**,[12] which might be in equilibrium with phosphorane **5**. Another possible course is the nucleophilic attack of alcohol onto the phosphorus atom of the phosphonium-carboxylate zwitterion **6**, which is present in equilibrating with **1**, leading to phosphorane intermediate **5**. Then, **5** gives rise to the production of **2** and phenol.

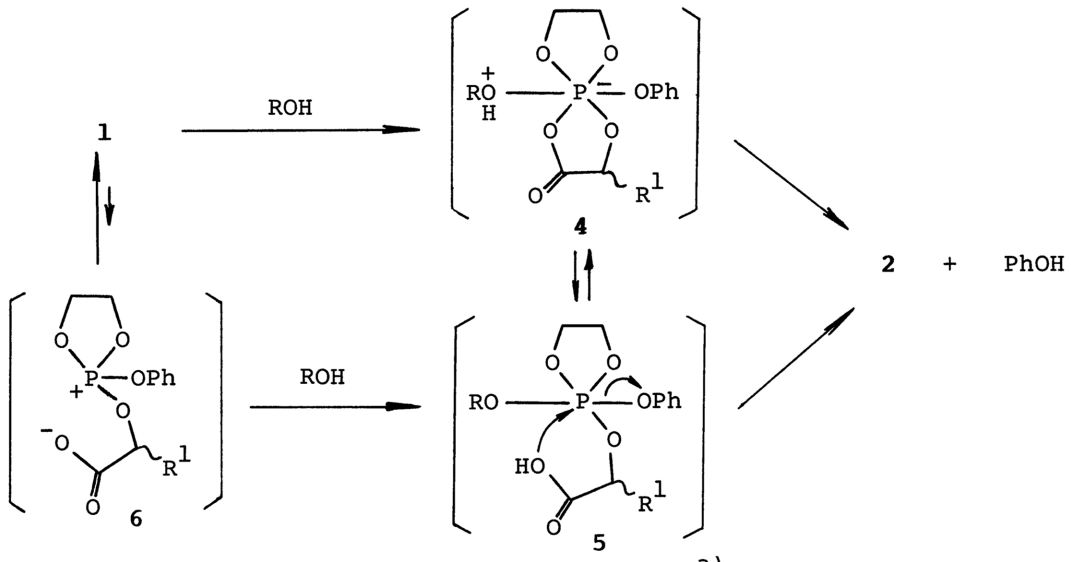
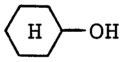


Table 1. Transphosphoranylation[a)]

S-AOP	Alcohol	Reaction		Product	
		Temp. (°C)	Time (hr)	structure	Yield (%)[b)]
1a	MeOH	-30	3	**2a**	92
1a	MeOH	0	1	**2a**	90
1a	MeOH	r.t.	1	**2a**	92
1a	EtOH	0	1	**2b**	88
1a	EtOH	r.t.	1	**2b**	94
1a	i-PrOH	r.t.	3	**2c**	75
1a		r.t.	3	**2d**	78
1b	MeOH	-30	3	**2e**	96
1b	MeOH	0	1	**2e**	96
1b	EtOH	0	1	**2f**	93
1b	i-PrOH	r.t.	3	**2g**	81
3a	MeOH	0	1	**2a**	93
3b	MeOH	0	1	**2a**	90

a) S-AOP=3.0 mmol and alcohol=7.5 mmol in 3.0 ml of $CHCl_3$ under nitrogen.
b) Determined by ^{31}P NMR of the reaction mixture based on S-AOP.

The present reaction is characterized by high selectivity and reactivity of S-AOP toward a nucleophile of alcohol. S-AOP is regarded as a mixed acid anhydride derivative of phosphoric and carboxylic acids. It is to be noted that an O-nucleophile of alcohol attacks selectively onto the phosphorus atom and not onto the carbonyl carbon atom of S-AOP. The reactivity of S-AOP is very much enhanced by the strong electron-withdrawing acyloxy group in forming **4** from **1** and alcohol. It is also possible that the acyloxy group enables the P-OC(O) bond to polarize into zwitterion form **6**. Previous studies by two groups of

Ramirez[12] and of Denny[13] are to be mentioned in relevant to the present investigation. They used various phosphoranes, mainly ene-diol type phosphoranes. Reactions of these phosphoranes with alcohols were carried out usually at room temperature up to 100°C. Sometimes a base-catalyst was necessary for these phosphoranes.[12] S-AOPs, on the other hand, are quite reactive even at -30°C.

The detailed mechanistic study and quantitative investigation of reactivity of spiro as well as cyclic AOPs are currently under progress.

References and Notes

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8) Chemical Shifts are in parts per million with negative values upfield from external 80% H_3PO_4. The values are indicated in the parentheses throughout this paper. The spectra were recorded with proton-decoupling at 35°C.
9) The structure of **2a** was supported by the following data. The ^{31}P NMR spectrum of the authentic sample **2a** prepared by the reaction of 2-methoxy-1,3,2-dioxaphospholane with pyruvic acid[3] showed two peaks (-35.4 and -36.0) with equal intensity, being identical with that of the reaction mixture. The ^{1}H NMR spectrum of the reaction mixture was also identical with that of the authentic **2a** except for signals due to phenol. Similarly, structural determinations of **2b-2g** were made by comparing ^{31}P and ^{1}H NMR spectra of the respective reaction mixture with those of the corresponding authentic sample of S-AOP. Two peaks of ^{31}P NMR are due to the existence of two stereo-isomers of the five-membered ring involving the C-3 carbon. These observations are specific to the spiro-structure of all AOPs. The detailed arguments of the stereochemistry will be published elsewhere.
10) S-AOP is a good dehydrating agent. This point is currently under investigation and will be reported soon.
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