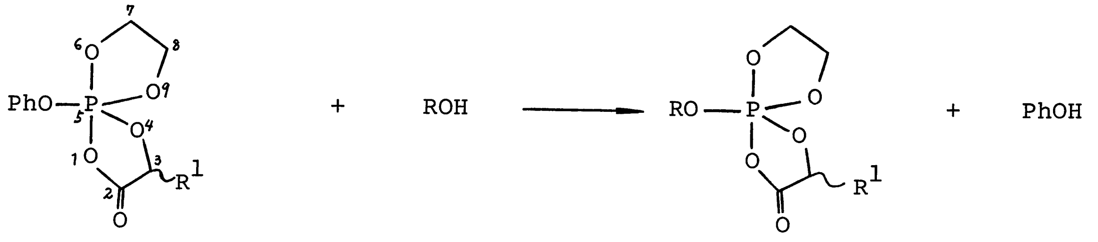
CHEMISTRY LETTERS, pp. 1599-1602, 1980.

NUCLEOPHILIC SUBSTITUTION OF ALCOHOL AT PHOSPHORUS OF SPIRO ACYLOXYPHOSPHORANE : TRANSPHOSPHORANYLATION

Shiro KOBAYASHI, Yukitoshi NARUKAWA,
Takatsugu HASHIMOTO, and Takeo SAEGUSA
Department of Synthetic Chemistry, Faculty of Engineering,
Kyoto University, Kyoto 606

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)

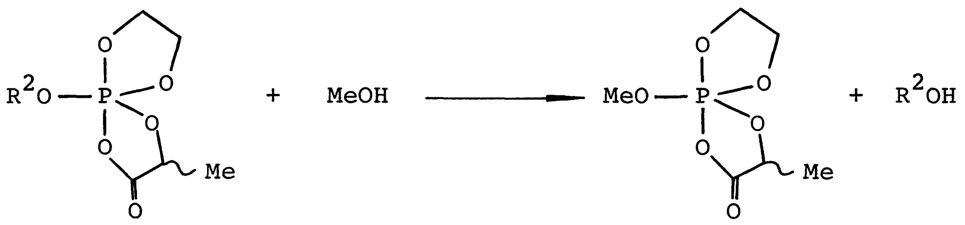
2a, R=R^1=Me (-35.4, -36.0)
b, R=Et; R^1=Me (-36.7, -37.4)
c, R=i-Pr; R^1=Me (-38.1, -38.6)
d, R=c-C_6H_{11}; R^1=Me (-37.9, -38.3)
e, R=Me; R^1=Ph (-34.7, -35.4)
f, R=Et; R^1=Ph (-36.1, -36.8)
g, R=i-Pr; R^1=Ph (-37.4, -37.9)

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 isobutylene10) 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.

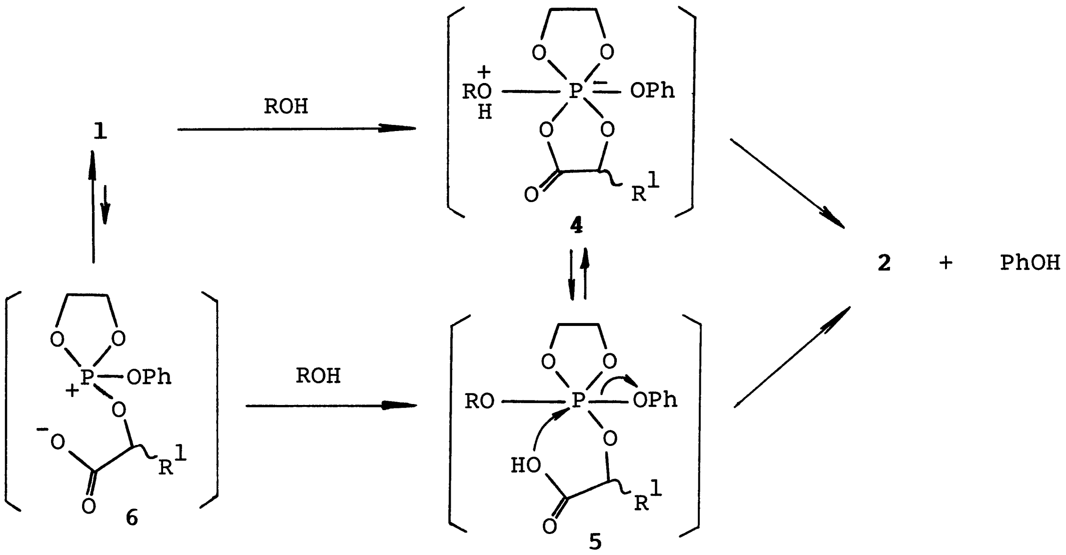
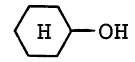


Table 1. Transphosphoranylation[a)]

S-AOP	Alcohol	Reaction Temp. (°C)	Reaction Time (hr)	Product 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

1) F. Ramirez, Synthesis, 90 (1974).
2) F. H. Westheimer, Acc. Chem. Res., 1, 70 (1968); F. Ramirez, ibid., 1,168 (1968).
3) T. Saegusa, S. Kobayashi, Y. Kimura, and T. Yokoyama, J. Am. Chem. Soc., 98, 7843 (1976).
4) T. Saegusa, S. Kobayashi, and Y. Kimura, J. Chem. Soc., Chem. Commun., 443(1976).
5) S. Kobayashi, T. Kobayashi, and T. Saegusa, Chem. Lett., 1979, 393.
6) V. M. Clark and A. J. Kirby, J. Am. Chem. Soc., 85, 3705 (1963); K. J. Schray and S. J. Benkovic, ibid., 93, 2522 (1971).
7) J. D. Chanley and E. Feageson, J. Am. Chem. Soc., 77, 4002 (1955); F. Ramirez, S. L. Glaser, and P. Stern, Tetrahedron, 29, 3741 (1973).
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.
11) S. Kobayashi, T. Hashimoto, and T. Saegusa, Macromolecules, in press.
12) F. Ramirez, K. Tasaka, N. B. Desai, and C. P. Smith, J. Am. Chem. Soc., 90, 751 (1968); F. Ramirez, A. J. Bigler, and C. P. Smith, Tetrahedron, 24, 5041 (1968); F. Ramirez, G. V. Loewengart, E. A. Tsolis, and K. Tasaka, J. Am. Chem. Soc., 94, 3531 (1972); F. Ramirez, K. Tasaka, and R. Hershberg. Phosphorus, 2, 41 (1972).
13) D. B. Denney and L. Saferstein, J. Am. Chem. Soc., 88, 1839 (1966); B. C. Chang, W. E. Conrad, D. B. Denney, D. Z. Denney, R. Edelman, R. L. Powell, and D. W. White, ibid., 93, 4004 (1971).

(Received September 27, 1980)