Communications to the Editor

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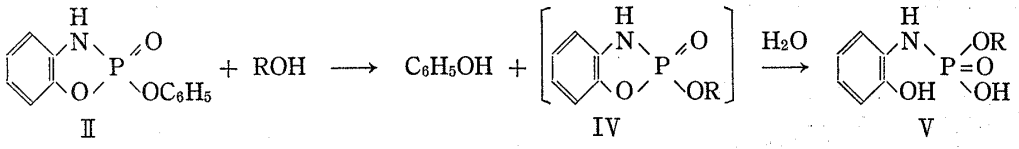
2-Phenoxy-benzoxazaphosphole-2-oxide, a Novel Phosphorylating Agent of Alcohols

Presented is a novel phosphorylating reagent of alcohols, 2-phenoxy-benzoxazaphosphole-2-oxide, which reacts quite easily with ordinary alcohols to give, in fair yields, alkyl N-(2-hydroxyphenyl)phosphoroamidates potentially useful for further modification.

We introduced previously a novel phosphorylating agent of alcohols, 2-phenoxy-benzodiazaphosphole-2-oxide (I),[1] whose characteristic feature was the use of the intrinsic reactivity of the strained benzophosphole-2-oxide ring.[2,3] During further investigation on the reaction of various kinds of 2-phenoxy-benzophosphole-2-oxides, we found that[4] oxaza derivative (II) was much more reactive towards hydrolysis than I to give exclusively N-(2-hydroxyphenyl)phosphoroamidate and phenol.[5] This observation prompted us to investigate the application of II for the phosphorylation of alcohols. The present communication reports the results along this line and provides a valuable method for the preparation of alkyl phosphoroanilidates as shown in equation 1.



Equation 1

As a general procedure, an alcohol (1—2 m moles) listed in Table I was treated with an equivalent amount of freshly distilled 2-phenoxy-benzoxazaphosphole-2-oxide II[7] in anhydrous tetrahydrofuran (THF) at room temperature for 24 hrs. After the reaction three equivalents of water was added to effect the hydrolysis of the intermediate IV[8] and THF was evaporated *in vacuo*. To the ether solution of the residue 6 equivalents of cyclohexylamine was added. Cyclohexylammonium salt of alkyl N-(2-hydroxy-phenyl)phosphoroamidate[9] (V) was separated out and was purified by the recrystallization. The results are summarized in Table I. In all cases the yields are better than those obtained with I. Since the reaction condition is

1) T. Koizumi, Y. Arai, and E. Yoshii, *Tetrahedron Letters*, **1973**, 4763.
2) Principle of this phosphorylation is quite unique, and one might call the method as the ring strain promoted phosphorylation.
3) F. Westheimer, *Accounts of Chem. Research*, **1**, 70 (1968); P. Gillespie, F. Ramirez, I. Ugi, and D. Marquarding, *Angew. Chem. Intern. Edit.*, **12**, 91 (1973).
4) T. Koizumi, Y. Watanabe, and E. Yoshii, "in preparation"; Presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April, 1974.
5) These products are formed by the ring retention process (see ref. 3), whereas I gave both ring retention and ring cleavage products.[6]
6) T. Koizumi, Y. Arai, and E. Yoshii, *Chem. Pharm. Bull.* (Tokyo), **21**, 202 (1973).
7) T. Koizumi, Y. Watanabe, Y. Yoshida, and E. Yoshii, *Tetrahedron Letters*, **1974**, 1075.
8) The formation of the intermediate IV is not confirmed but is most likely from the interpretation of the result of the hydrolysis of II. The details of the mechanism will be discussed in a full paper.
9) The structure of V was established in the case of ethyl derivative (V: R=Et) by the treatment with diazomethane. The methylated product was identified as methyl ethyl N-(2-methoxyphenyl)phosphoroamidate by nuclear magnetic resonance (NMR) and infrared (IR). NMR (in $CDCl_3$) τ: 8.7 (3H t J=7 Hz p-$OCH_2\underline{CH_3}$), 6.25 (3H d J=11 Hz, p-$O\underline{CH_3}$), 6.17 (3H s phenyl-$O\underline{CH_3}$), 5.9 (2H quintet like multiplet p-$O\underline{CH_2}CH_3$), 2.8—3.2 (4H aromatic). IR ν_{max}^{film} cm^{-1}: 3400 (PONH), 2920, 1600, 1240, 1025, 750.

Table I. Reaction of 2-Phenoxy-benzoxazaphosphole-2-oxide with Various Alcohols

Alcohol (ROH)	Yield of alkyl N-(-2-hydroxyphenyl)-phosphoroamidate as cyclohexylammonium salt[a]	Alcohol (ROH)	Yield of alkyl N-(2-hydroxyphenyl)-phosphoroamidate as cyclohexylammonium salt[a] (%)
CH_3	64	*sec*-C_4H_9	70
C_2H_5	87	*tert*-C_4H_9	—[b]
n-C_3H_7	68	$C_6H_5CH_2$	70
iso-C_3H_7	69	CH_2=$CHCH_2$	79
n-C_4H_9	73	cholesteryl	71
iso-C_4H_9	71		

a) All compounds gave satisfactory elemental analyses and spectral data.
b) Only the hydrolysis product, N-(2-hydroxyphenyl)phosphoroamidate was isolated.

much milder (24 hrs at room temperature for II *vs.* 24 hr reflux in THF for I), II is much more useful for the phosphorylation of alcohols than I. Furthermore the reagent has an advantage of yielding, in one step, the hydroxyanilidates of monoalkyl phosphates which might be convertible to other phosphates analogues by the known methods.[10,11] The application of the present method to more complex alcohols such as nucleosides and the conversion to other phosphate derivatives are now in progress and will be reported elsewhere.

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10) E. Ohtsuka, K. Murao, M. Ubasawa, and M. Ikehara, *J. Amer. Chem. Soc.*, **92**, 3441 (1970); E. Ohtsuka, S. Morioka, and M. Ikehara, *Tetrahedron Letters*, **1972**, 2553.
11) T. Koizumi, Y. Arai, and E. Yoshii, *Chem. Pharm. Bull.* (Tokyo), **22**, 468 (1974).