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Phosphorylation of Alcohols and Phosphates by Oxidation-Reduction Condensation

Teruaki MUKAIYAMA and Mitsunori HASHIMOTO

Laboratory of Organic Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo

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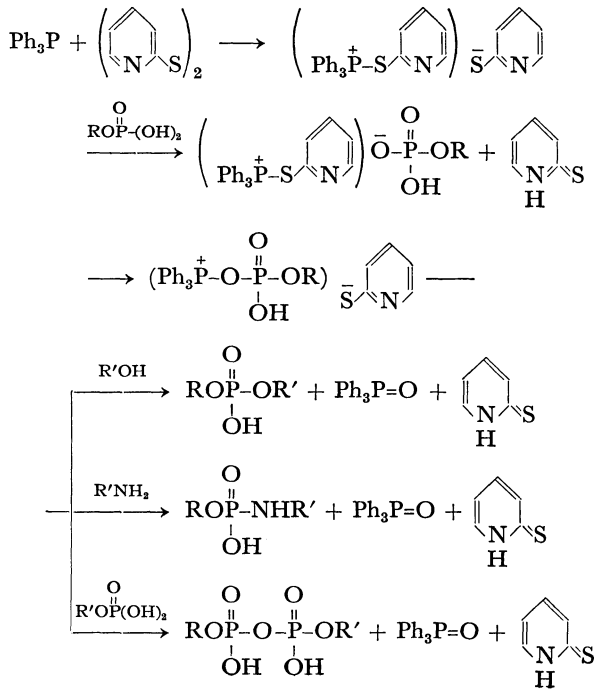
Phosphorylation of alcohols and phosphates forming mixed esters of phosphoric acid and pyrophosphate by the oxidation-reduction condensation with triphenylphosphine and 2,2′-dipyridyl disulfide has been investigated. *n*-Butyl *p*-nitrophenyl phosphate was obtained in 80% yield when *p*-nitrophenyl dihydrogen phosphate was treated with one equiv. each of triphenylphosphine and 2,2′-dipyridyl disulfide in the presence of three equiv. of anhydrous *n*-butyl alcohol at room temperature. It was found that P^1,P^2-bis(*p*-nitrophenyl)pyrophosphate was obtained in 91% yield when *p*-nitrophenyl dihydrogen phosphate was treated with 1.5 equiv. each of triphenylphosphine and 2,2′-dipyridyl disulfide.

Recently, it was reported that peptides are synthesized in high yields with optical purity by use of triphenylphosphine and 2,2′-dipyridyl disulfied as the coupling reagents.[1] Dehydration from free carboxylic components and free amino components proceeds by eliminating one oxygen atom (reduction) and two hydrogen atoms (oxidation) with triphenylphosphine and 2,2′-dipyridyl disulfide, respectively, to afford peptides, triphenylphosphine oxide and 2 mol of 2-mercaptopyridine.

In the present study the phosphorylation of alcohols and phosphate was investigated. It was considered that the reaction of triphenylphosphine, 2,2′-dipyridyl disulfied and phosphates would yield a reactive intermediate, phosphoryloxyphosphonium salt, which in turn would further react with alcohols of phosphate to give mixed esters of phosphates and pyrophosphate, respectively, according to the following equation.

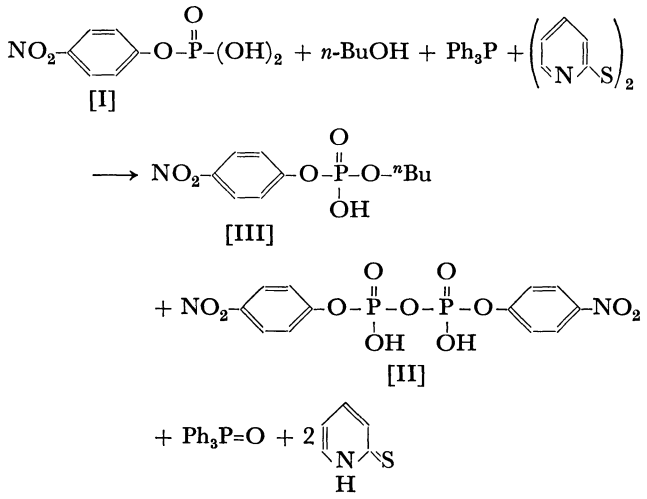
Selective phosphrylation can be effected successfully by this method without isolating the intermediate, since it reacts exclusively with nucleophilic reagents



1) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, **1970**, 1901.

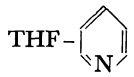
such as alcohols, amines and phosphates under mild conditions.

When *p*-nitrophenyl dihydrogen phosphate was treated with triphenylphosphine and 2,2'-dipyridyl disulfide in excess anhydrous *n*-butyl alcohol at room temperature, an instantaneous reaction took place and *n*-butyl *p*-nitrophenyl phosphate was obtained in high yield along with a small amount of symmetrical P^1,P^2-bis(*p*-nitrophenyl) pyrophosphate.



When I was treated with one equiv. each of triphenylphosphine and 2,2'-dipyridyl disulfide in the presence of ten equiv. of *n*-butyl alcohol, III was obtained in 80% yield. The results are nearly the same as those obtained when dicyclohexylcarbodiimide is used as a coupling reagent (see Table 1).

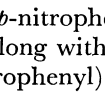
Table 1. Phosphorylation of *n*-butyl alcohol (10 equiv.) by means of triphenylphosphine (1 equiv.) and 2,2'-dipyridyl disulfide (1 equiv.)

Solvent (reaction at r.t.)	I(%)	II(%)	III(%)
THF	15	5	80
THF–  (2 : 1)	5	10	80
	5	15	80
Cf. DCC method			
THF	9	12	80

The effects of the solvent and base were examined in order to find a suitable condition for the preparation of III without accompanying the undesirable formation of II.

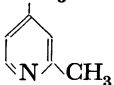
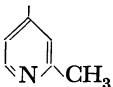
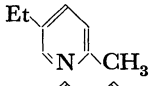
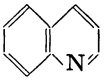
It was found that III was obtained in 50—70% yield together with 10—40% yield of II when phosphorylation was carried out in the presence of three equiv. of *n*-butyl alcohol (see Table 2). Of various solvents examined, it was found that the yield of II increased when pyridine is used as the solvent. However, when a catalytic amount of acetic anhydride was added to the pyridine solution, the formation of II decreased and III was obtained in fairly good yield.[2,3]

Table 2. Solvent effects in phosphorylation of *n*-butyl alcohol (3 equiv.) by means of triphenylphosphine (1 equiv.) and 2,2'-dipyridyl disulfide (1 equiv.)

Solvent	I(%)	II(%)	III(%)
THF	19	9	70
THF– 	5	30	65
	5	40	55
CH_3CN	24	25	49
DMF	40	25	35
	14	26	58
CH_2Cl_2	15	16	65
$CHCl_3$	18	20	62
	29	13	46
THF– (catalytic amounts)	17	2	80

Concerning the effect of bases, it was made clear that the reaction was accelerated in the presence of bases, but there was no remarkable difference on the products ratio of II to III (see Table 3).

Table 3. Effect of bases in phosphorylation of *n*-butyl alcohol (3 equiv.) by means of triphenylphosphine (1 equiv.) and 2,2'-dipyridyl disulfide (1 equiv.)

Base (Solvent THF)	I(%)	II(%)	III(%)
Et_3N (1 equiv.)	—	30	62
Bu_3N (1 equiv.)	—	25	65
$(HOCH_2CH_2)_3N$ (1 eqiuv.)	13	20	67
Me_2N–  (1 equiv.)	—	20	73
(1 equiv.)	—	30	60
 (1 equiv.)	—	25	65
 (1 equiv.)	—	30	57
 (1 eqiuv.)	—	30	60
 (1 equiv.)	10	20	70

When I was treated with just one eqiv. of *n*-butyl alcohol and 1.5 equiv. each of triphenylphosphine and 2,2'-dipyridyl disulfide, the result was almost

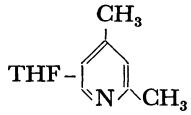
2) M. W. Moon and H. G. Khorana, *J. Amer. Chem. Soc.*, **88**, 1798 (1966).

3) H. G. Khorana and J. P. Vizasalyi, *ibid.*, **81**, 4660 (1959).

TABLE 4. PHOSPHORYLATION OF *n*-BUTYL ALCOHOL (1 equiv.) BY MEANS OF 1.5 equiv. EACH OF TRIPHENYLPHOSPHINE AND 2,2′-DIPYRIDYL DISULFIDE

Solvent	I(%)	II(%)	III(%)
THF	12	10	70
	17	30	52
DMF	24	25	45

TABLE 5. PHOSPHORYLATION OF *n*-BUTYL ALCOHOL (3 equiv.) BY MEANS OF TRIPHENYLPHOSPHINE AND 5,5′-DINITRO-2,2′-DIPYRIDYL DISULFIDE

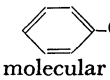
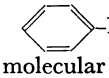
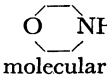
Condition (Solvent)	I(%)	II(%)	III(%)
THF	25	3	72
THF - (Py-Ac_2O) - (catalytic amounts)	19	—	70
THF - Et_3N (1 mol)	—	15	80
THF-  (1 mol)	10	5	71
	—	—	88
DMF	45	—	50

One equiv. each of reagents, triphenylphosphine and 2,2′-dipyridyl disulfide, were used.

the same as those obtained when 3 equiv. of *n*-butyl alcohol were used as shown in the above experiments. Thus, it can be said that the use of a small excess of the coupling reagents, triphenylphosphine and 2,2′-dipyridyl disulfied, is effective for this type of phosphorylation (see Table 4).

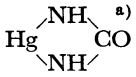
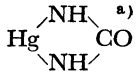
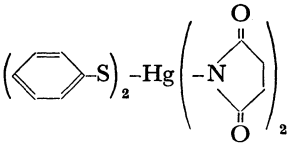
Phosphorylation of *n*-butyl alcohol was attempted with the use of 5,5′-dinitro-2,2′-dipyridyl disulfide in place of 2,2′-dipyridyl disulfide in oder to know the effect of the substituents of the disulfide component. It is worth mentioning that the undesirable by-pro-

TABLE 6. PHOSPHORYLATION OF ALCOHOL AND AMINES BY MEANS OF TRIPHENYLPHOSPHINE AND 2,2′-DIPYRIDYL DISULFIDE

Condition (Alcohol or amine) (Solvent THF)	I(%)	II(%)	III(%)
 (3 molecular equivalents used)	—	—	90
 (3 molecular equivalents used)	10	—	80
 (3 molecular equivalents used)	—	—	90
 (3 molecular equivalents used)	15	—	75

One equiv. each of reagents, triphenylphosphine and 2,2′-dipyridyl disulfide, were used.

TABLE 7. P^1,P^2-BIS(*p*-NITROPHENYL) PYROPHOSPHATE SYNTHESIS

Conditions (Solvent, reagent)		I(%)	II(%)
THF	reagent Ph_3P-  0.5 mol	55	45
THF,  (0.5 mol)	reagent Ph_3P-  0.5 mol	55	45
	reagent Ph_3P-  0.5 mol	19	81
 ,  (0.5 mol)	reagent Ph_3P-  0.5 mol	20	80
CH_3CN	reagent Ph_3P-  0.5 mol	40	60
DMF	reagent Ph_3P-  0.5 mol	38	62
THF	reagent Ph_3P-  0.75 mol	10	85
	reagent Ph_3P-  0.75 mol	9	91
THF	Ph_3P-  0.75 mol	7	93

a) mercaptan scavenger

duct, pyrophosphate II, was scarcely formed when 5,5′-dinitro-2,2′-dipyridyl disulfide was used as the disulfide component as shown in Table 5.

In a similar way, various disubstituted phosphates and phosphoramidates were prepared from I and benzyl alcohol or amines by using triphenylphosphine and 2,2′-dipyridyl disulfide as the coupling reagents. The results are summarized in Table 6.

Finally, the preparation of symmetrical pyrophosphate II was attempted. When a solution of one eqiuv. of I was treated with 1.5 equiv. each of triphenylphosphine and 2,2′-dipyridyl disulfide at room temperature, the reaction started instantly and symmetrical P^1,P^2-bis(*p*-nitrophenyl) pyrophosphate II was obtained in 91% yield. (see Table 7).

In conclusion, phosphorylation of alcohols and phosphates by oxidation-reduction condensation with triphenylphosphine and 2.2′-dipyridyl disulfide affords the corresponding mixed esters of phosphoric acid and pyrophosphate, respectively, in good yields under mild condition.

Differing from the case of the phosphorylation with the use of dicyclohexylcarbodiimide, the oxidation-reduction condensation proceeds rapidly even in the presence of strong bases such as triethylamine and tributylamine[4] to afford the phosphorylated products in good yields.

Experimental

Reagents. *p*-Nitrophenyl dihydrogen phosphate was prepared by hydrolysis of *p*-nitrophenyl phosphorodichloridate. *p*-Nitrophenyl phosphorodichloridate was prepared by an improved procedure, of which an example is given below. A mixture of 1 mol of *p*-nitrophenol, 3 mol of phosphorus oxychloride and 0.2 mol of potassium chloride was heated at 110°C for 28 hr. After removal of hydrogen chloride and excess phosphorus oxychloride, 179 g (70%) of *p*-nitrophenyl phosphorodichloridate bp 135°C/0.6 mmHg, was obtained. 2,2′-Dipyridyl disulfide[5,6] and 5,5′-dinitro-2,2′-dipyridyl disulfide[7,8] were prepared by procedures given in literature. Triphenylphosphine was obtained from a commercial source and purified by recrystallization.

General Methods. *Reaction of* n-*Butyl Alcohol and* p-*Nitrophenyl Dihydrogen Phosphate with Triphenylphosphine and 2,2′-Dipyridyl Diculfide*: To a solution of anhydrous *n*-butyl alcohol (111 mg, 1.5 mmol), *p*-nitrophenyl dihydrogen phosphate (110 mg, 0.5 mmol) and *2,2′*-dipyridyl disulfide (110 mg, 0.5 mmol) in anhydrous tetrahydrofuran 5 m*l*, triphenylphosphine (131 mg, 0.5 mmol) was added at room temperature with vigorous stirring. After stirring for 2 hr, the amount of III formed was determined by UV absorption after separation with paper chromatography. Yield 70%.

P¹,P²-*Bis(*p-*nitrophenyl) Pyrophosphate*: To a solution of *p*-nitrophenyl dihydrogen phosphate (220 mg, 1 mmol) and 2, 2′-dipyridyl disulfide (165 mg, 0.75 mmol) in anhydrous pyridine 5 m*l*, triphenylphosphine (197 mg, 0.75 mmol) was added with vigorous stirring at room temperature. After 2 hr, the amount of II formed was determined by the method mentioned above. Yield 91%.

Paper chromatography was carried out by the desending technique on Toyo Roshi No. 50 paper using isopropyl alcohol-concentrated ammonium hydroxyde-water (7 : 1 : 2 (v/v)). In this solvent, *p*-nitrophenyl dihydrogen phosphate has R_F 0.3, ($\lambda_{max}^{H_2O}$ 310 mμ, $\varepsilon=0.96\times10^4$), P¹,P²-bis(*p*-nitrophenyl) pyrophosphate R_F 0.65, ($\lambda_{max}^{H_2O}$ 288 mμ, $\varepsilon=1.95\times10^4$), *n*-butyl *p*-nitrphenyl phosphate R_F 0.80, ($\lambda_{max}^{H_2O}$ 290 mμ, $\varepsilon=10^4$), benzyl *p*-nitrphenyl phosphate R_F 0.80, ($\lambda_{max}^{H_2O}$ 290 mμ, $\varepsilon=1.05\times10^4$), *p*-nitrophenyl phosphoroanilidate R_F 0.82, ($\lambda_{max}^{H_2O}$ 291 mμ, $\varepsilon=10^4$), *p*-nitrophenyl phosphorobenzylamidate R_F 0.79, ($\lambda_{max}^{H_2O}$ 289 mμ, $\varepsilon=1.05\times10^4$) and *p*-nitrophenyl phosphoromorpholidate R_F 0.83, ($\lambda_{max}^{H_2O}$ 289 mμ, $\varepsilon=10^4$).

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4) M. Smith, J. G. Moffatt, and H. G. Khorana, *J. Amer. Chem. Soc.*, **80**, 6204 (1958).

5) R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, **1958**, 3610.

6) H. Kubota and T. Akita, *Yakugaku Zasshi* **81**, 511 (1961).

7) W. T. Caldusell and E. C. Kornfeld, *J. Amer. Chem. Soc.*, **64**, 1695 (1942).

8) C. Rath and L. L. Ware, *J. Chem. Soc.*, **1958**, 1853.