A Selective Phosphorylation by Means of α-Bromocyanoacetamides and Trialkyl Phosphites

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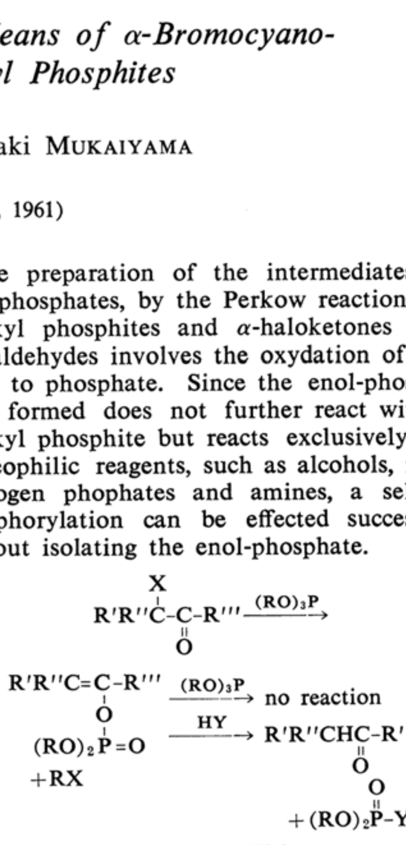
Phosphorylation by means of ketene dimer, ethyl vinyl ether, tetraethyl pyrophosphite and diethylphosphorochloridite has been described in a preceding paper¹⁾.

The well-known methods of phosphorylation by means of dehydrating reagents mostly consist of the initial formation of enol-phosphate by the addition of a monohydrogen or a dihydrogen phosphate to the organic dehydrating reagents with a triple or a cummulated double bond, such as carbodiimides[2)], acetylenic ethers[3)] and trichloroacetonitrile[4)], followed by alcoholysis or phosphorolysis. However, except in the case of trichloroacetonitrile, the isolation of an intermediate adduct, enol-phosphate, was not possible, with the result that the coupling of two different phosphates invariably produced a mixture of the two symmetrical pyrophosphates, together with the unsymmetrical product. The formation of undesirable symmetrical pyrophosphates is attributed to the fact that phosphates used in the phosphorylation react more rapidly with the enol-phosphates than with the dehydrating reagent, thereby causing the formation of symmetrical pyrophosphates. Therefore, the enol-phosphate must be isolated in advance if a selective phosphorylation is to take place.

The preparation of the intermediates, the enol-phosphates, by the Perkow reaction from trialkyl phosphites and α-haloketones or α-haloaldehydes involves the oxydation of phosphite to phosphate. Since the enol-phosphate thus formed does not further react with the trialkyl phosphite but reacts exclusively with nucleophilic reagents, such as alcohols, monohydrogen phophates and amines, a selective phosphorylation can be effected successfully without isolating the enol-phosphate.



$$\mathrm{R'R''\overset{X}{\overset{|}{C}}-\underset{\underset{O}{\|}}{C}-R'''} \xrightarrow{(RO)_3P}$$

$$\begin{array}{l} \mathrm{R'R''C{=}\underset{\underset{\underset{(RO)_2\overset{|}{P}{=}O}{O}}{|}}{C}-R'''} \\ \mathrm{+RX} \end{array} \begin{array}{l} \xrightarrow{(RO)_3P} \text{no reaction} \\ \xrightarrow{HY} \mathrm{R'R''CH\underset{\underset{O}{\|}}{C}-R'''} \\ \qquad\qquad \mathrm{+(RO)_2\overset{\overset{O}{\|}}{P}-Y} \end{array}$$

X : Halogen
HY : Nucleophilic reagent

Most of the enol-phosphates obtained by the Perkow reaction[5)], however, are not suitable for the purpose of phosphorylation because they are prepared under severe conditions or are sluggish toward nucleophilic reagents, except in the case of a ketene acylal reported by Cramer[6)]. The low reactivity of enol-phosphates

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[1)] T. Mukaiyama, T. Hata and O. Mitsunobu, *J. Org. Chem.* **27**, 1815 (1962).

[2)] H. G. Khorana and A. R. Todd, *J. Chem. Soc.*, **1953**, 2257.

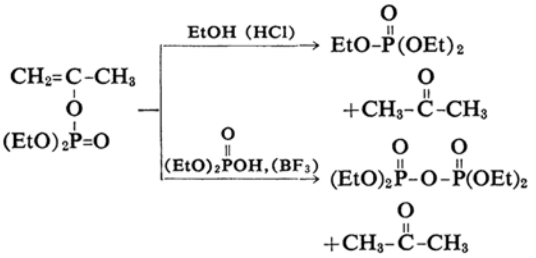
[3)] J. F. Arens and T. Doornbos, *Rec. trav. chim.*, **74**, 79 (1955)

[4)] F. Cramer and G. Weimann, *Chem. & Ind.*, **1960**, 46.

[5)] J. F. Allen and O. H. Johnson, *J. Am. Chem. Soc.*, **77**, 2871 (1955).

[6)] F. Cramer and K. G. Gärtner, *Chem. Ber.*, **91**, 704 (1958).

toward alcohols and monohydrogen phosphates has been demonstrated. The reaction of diethyl isopropenyl phosphate, an example of enol-phosphates, with ethanol could not be observed even when they were heated for 2 hr. at 150°C. However, when they were treated in the presence of a catalytic amount of hydrogen chloride for 12 hr. at 100°C, they gave a 55% yield of triethyl phosphate. Similarly, a 55% yield of tetraethyl pyrophosphate was obtained by heating the above enol-phosphate with diethyl hydrogen phosphate in the presence of a catalytic amount of boron trifluoride for an hour at 100°C.



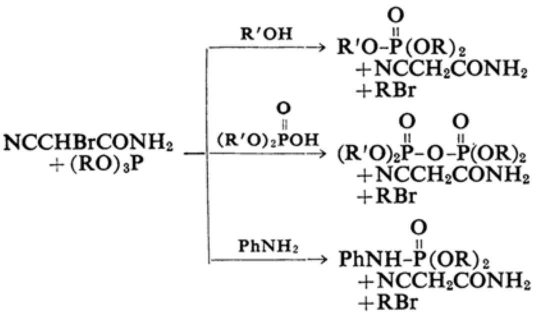
$$CH_2{=}\underset{\underset{(EtO)_2P=O}{|}}{\underset{O}{\underset{|}{C}}}{-}CH_3 \xrightarrow{EtOH\ (HCl)} EtO{-}\overset{\overset{O}{\|}}{P}(OEt)_2 + CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH_3$$

$$\xrightarrow{(EtO)_2\overset{\overset{O}{\|}}{P}OH,\ (BF_3)} (EtO)_2\overset{\overset{O}{\|}}{P}{-}O{-}\overset{\overset{O}{\|}}{P}(OEt)_2 + CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH_3$$

However, one of the enol-phosphates which are reactive toward nucleophilic reagents can be prepared from monobromocyanoacetamide and trialkyl phosphites, as will be described below.

When a solution of 1 mol. of monobromocyanoacetamide and 1 mol. of either an alcohol, a monohydrogen phosphate or aniline in ether was treated with a solution of 1 mol. of trialkyl phophite at −50°C, the reaction started instantly, cyanoacetamide soon separated from the solution, and the corresponding phosphate, pyrophosphate or phosphoramidate was obtained in a high yield, along with an alkyl bromide, as is shown in the following:

$NCCHBrCONH_2 + (RO)_3P$



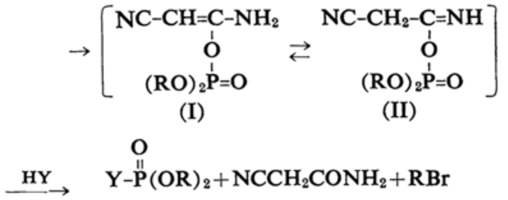
$$NCCHBrCONH_2 + (RO)_3P \xrightarrow{R'OH} R'O{-}\overset{\overset{O}{\|}}{P}(OR)_2 + NCCH_2CONH_2 + RBr$$

$$\xrightarrow{(R'O)_2\overset{\overset{O}{\|}}{P}OH} (R'O)_2\overset{\overset{O}{\|}}{P}{-}O{-}\overset{\overset{O}{\|}}{P}(OR)_2 + NCCH_2CONH_2 + RBr$$

$$\xrightarrow{PhNH_2} PhNH{-}\overset{\overset{O}{\|}}{P}(OR)_2 + NCCH_2CONH_2 + RBr$$

The reactions seem to proceed through the initial formation of the enol-phosphate as a result of the interaction of monobromocyanoacetamide with trialkyl phosphite, followed by the attack of nucleophilic reagents to form phosphates, pyrophosphates and phosphoramidate.

$NCCHBrCONH_2 + (RO)_3P$



$$\rightarrow \left[NC{-}CH{=}\underset{\underset{(RO)_2P=O}{|}}{\underset{O}{\underset{|}{C}}}{-}NH_2 \rightleftarrows NC{-}CH_2{-}\underset{\underset{(RO)_2P=O}{|}}{\underset{O}{\underset{|}{C}}}{=}NH \right]$$

(I) (II)

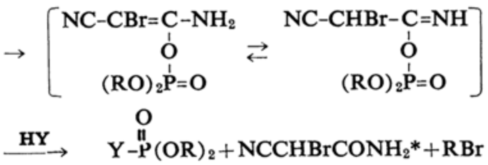
$$\xrightarrow{HY} Y{-}\overset{\overset{O}{\|}}{P}(OR)_2 + NCCH_2CONH_2 + RBr$$

HY : Alcohol, monohydrogen phosphate or aniline

It is reasonable to postulate that the enol-phosphate (I), which possesses an amino group attached to its carbon-carbon double bond, is capable of existing in both the amine I and imine II forms. The phosphorylation probably proceeds as a result of the contribution of the imine form II rather than the amine form I which existed in equilibrium. It has been shown that when *N*, *N*-diethyl monobromocyanoacetamide, which does not exist as the imine form, was treated with triethyl phosphite and ethanol, not triethyl phosphate but a tar product was produced. As phosphorylation proceeds, the imine II is continually removed from the equilibrium by an irreversible phosphorylation, and eventually the amine I is transformed through the imine intermediate II into cyanoacetamide.

Similarly, when a solution of 0.5 mol. of dibromocyanoacetamide was used in place of the 1 mol. of monobromocyanoacetamide, the corresponding phosphates, pyrophosphate and phosphoramidate were obtained in good yields.

$NCCBr_2CONH_2 + (RO)_3P$



$$\rightarrow \left[NC{-}CBr{=}\underset{\underset{(RO)_2P=O}{|}}{\underset{O}{\underset{|}{C}}}{-}NH_2 \rightleftarrows NC{-}CHBr{-}\underset{\underset{(RO)_2P=O}{|}}{\underset{O}{\underset{|}{C}}}{=}NH \right]$$

$$\xrightarrow{HY} Y{-}\overset{\overset{O}{\|}}{P}(OR)_2 + NCCHBrCONH_2{}^{*} + RBr$$

HY : Alcohol, monohydrogen phosphate or aniline

* Monobromocyanoacetamide further reacts with trialkyl phosphite through the former equation.

In addition, a new method for the preparation of monobromocyanoacetamide was found. When a solution of dibromocyanoacetamide and cyanoacetamide was treated in the presence of a catalytic amount of boron trifluoride, monobromocyanoacetamide was obtained in a yield 74% of the theoretical one. This is a simpler treatment and produces a higher yield than those hitherto reported in the literature[7].

$$NCCBr_2CONH_2 + NCCH_2CONH_2 \xrightarrow{BF_3} 2\,NCCHBrCONH_2$$

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[7] B. M. Gupta and J. F. Thorpe, *J. Chem. Soc.*, **121**, 1902 (1922).

Experimental

Reaction of Diethyl Isopropenyl Phosphate with Ethanol.—A mixture of diethyl isopropenyl phosphate (1.94 g.), ethanol (0.55 g.) and 2 drops of concentrated hydrochloric acid was heated for 12 hr. at 100°C. The mixture was then distilled under reduced pressure to give triethyl phosphate (1.0 g., 55%), b. p., 67∼69°C/1.2 mmHg., along with acetone and ethyl bromide.

Reaction of Diethyl Isopropenyl Phosphate with Diethyl Hydrogen Phosphate.—A mixture of diethyl isopropenyl phosphate (1.94 g.), diethyl hydrogen phosphate (1.54 g.) and 2 drops of boron trifluoride etherate was heated at 100°C for an hour. Diethyl isopropenyl phosphate (1.0 g.) was recovered, and tetraethyl pyrophosphate (1.6 g., 55%), b. p., 132∼∼135°C/0.8 mmHg., was obtained.

Monobromocyanoacetamide.—A solution of dibromocyanoacetamide (24.2 g.) and cyanoacetamide (8.4 g.) in 150 ml. of ethanol, in the presence of 10 drops of boron trifluoride etherate was refluxed for 5 hr. After removal of the ethanol, a large amount of white precipitate was separated, washed with benzene, and recrystallized from benzene; monobromocyanoacetamide (24 g., 74%), m. p., 116 117°C, was obtained.

Reactions of Alcohols, Phenol or Diethyl Hydrogen Phosphate with Monobromocyanoacetamide and Trialkyl Phosphites.—*Ethanol.*—To a solution of ethanol (0.28 g.) and monobromocyanoacetamide (1.0 g.) in dry ether (90 ml.) was added, drop by drop a solution of triethyl phosphite (1.0 g.) in dry ether (10 ml.) at -50°C. A white precipitate, cyanoacetamide, soon separated; the solution was kept for an additional hour at room temperature and was then filtered. After removal of the ether and ethyl bromide, triethyl phosphate (1.0 g., 91%), b. p., 65∼67°C/1 mmHg., was obtained.

In a similar fashion, other alcohols, phenol and diethyl hydrogen phosphate gave the corresponding phosphates or pyrophosphates. The results of the phosphorylation of alcohols, phenol and diethyl hydrogen phosphate by means of monobromocyanoacetamide and trialkyl phosphites are summarized in Tables I and II.

Reactions of Ethanol, Phenol or Diethyl Hydrogen Phoshate with Dibromocyanoacetamide and Triethyl Phosphite.— *Ethanol.*— To a solution of ethanol (0.9 g.) and dibromocyanoacetamide (2.4 g.) in dry ether (30 ml.) was added, drop by drop a solution of triethyl phosphite (3.3 g.) in dry ether (10 ml.) at -50°C. A white precipitate, cyanoacetamide, soon separated; the solution was kept for

TABLE I. PHOSPHORYLATION OF ALCOHOLS AND PHENOL BY MEANS OF MONOBROMOCYANOACETAMIDE AND TRIETHYL PHOSPHITE

Alcohol	Charge g.	Product			
		Phosphate			Cyanoacetamide
			Yield %	B. p. °C/mmHg	Yield %
Methanol	2.20	Methyl diethyl-	77	102∼104/25	93
Ethanol	0.28	Triethyl-	91	65∼67/1	88
n-Propanol	0.37	*n*-Propyl diethyl-	85	73∼74/0.8	82
Phenol	0.58	Phenyl diethyl-	72	103∼120/1	94

TABLE II. PHOSPHORYLATION OF DIETHYL HYDROGEN PHOSPHATE BY MEANS OF MONOBROMOCYANOACETAMIDE AND TRIALKYL PHOSPHITES

Phosphite	Charge g.	Product			
		Pyrophosphate			Cyanoacetamide
			Yield %	B. p. °C/mmHg	Yield %
Trimethyl-	0.76	*unsym*-Dimethyl diethyl-	92	100∼106/0.004	87
Triethyl-	0.93	Tetraethyl-	94	135∼136/1	98
Tri-*n*-butyl-	1.55	*unsym*-Diethyl di-*n*-butyl-	96	114∼118/0.02	85

TABLE III. PHOSPHORYLATION OF ETHANOL, PHENOL AND DIETHYL HYDROGEN PHOSPHATE BY MEANS OF DIBROMOCYANOACETAMIDE AND TRIETHYL PHOSPHITE

Reagent	Charge g.	Product			
		Phosphate			Cyanoacetamide
			Yield %	B. p. °C/mmHg	Yield %
Ethanol	0.90	Triethyl-	72	94∼95/11∼12	96
Phenol	1.88	Phenyl diethyl-	57	103∼123/1	94
Diethyl hydrogen phosphate	3.08	Tetraethyl pyro-	60	134∼136/1	84

an additional 2 hr. and was then worked up in the usual manner, producing cyanoacetamide (0.5 g., 96%), m. p., 120°C, and triethyl phosphate (2.6 g., 72%), b. p., 94∼95°C/11∼12 mmHg.

In a similar fashion, phenol and diethyl hydrogen phosphate gave phenyl diethyl phosphate and tetraethyl pyrophosphate respectively. The results of the phosphorylation of these compounds are summarized in Table III.

Reactions of Mono- or Dibromocyanocetamide with Aniline and Triethyl Phosphite.—*Monobromocyanoacetamide*.—To a solution of monobromocyanoacetamide (1.0 g.) in dry ether (90 ml.) was added, drop by drop, a solution of aniline (0.57 g.) and triethyl phosphite (1.0 g.) in dry ether (10 ml.) at −50°C. A white precipitate, cyanoacetamide, (0.51 g., 98%) was filtered off. After removal of the ether and ethyl bromide, diethyl *N*-phenylphosphoramidate (1.3 g., 93%) was obtained and recrystallized from benzene, m. p. and mixed m. p., 94∼96°C.

Dibromocyanoacetamide.—When dibromocyanoacetamide (1.5 g.) was used in place of monobromocyanoacetamide (1.0 g.), diethyl *N*-phenylphosphoramidate (1.3 g., 93%) was obtained.

Summary

A method of selective phosphorylation by means of α-bromocyanoacetamides and trialkyl phosphites was devised. In this method, various phosphates, pyrophosphates and phosphoramidate were obtained in excellent yields under mild conditions without isolating the intermediate, enol-phosphate.

The use of dibromocyanoacetamide in place of monobromocyanoacetamide produced the same results, the yields being, however, less.

A new method for the preparation of monobromocyanoacetamide was also described.

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