Phosphorylation of Alcohols by the Use of Benzyldiethyl Phosphite and Monobromocyanoacetamide or *N*-Bromosuccinimide

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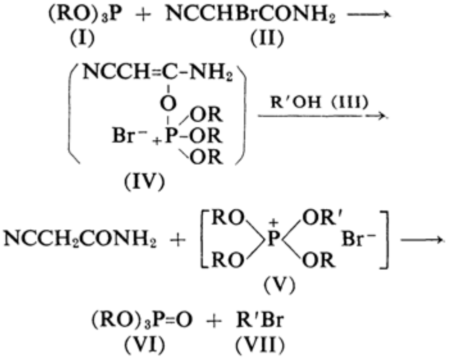
It has been demonstrated in the previous papers[1,2] that various phosphites (I) and phosphines are easily oxidized by means of monobromocyanoacetamides (II) and allyl or benzyl alcohol (III). The reactions are considered to proceed through the formation of reactive quaternary phosphonium salts (V), which in turn decompose to yield the corresponding phosphates (VI) or phosphine oxides and allyl or benzyl bromide (VII) (Eq. 1).

It is to be noted that allyl or benzyl cation which is considered to be stable might preferentially be split off from the quaternary phosphonium salts (V), resulting in the formation of allyl or benzyl bromide (VII) and oxidized products, pentavalent phosphorus compounds (VI).



$$\underset{(I)}{(RO)_3P} + \underset{(II)}{NCCHBrCONH_2} \longrightarrow \underset{(IV)}{\left(\begin{array}{c} NCCH=C-NH_2 \\ | \\ O \\ | \\ Br^- \; {}^+P(OR)_3 \end{array}\right)} \xrightarrow{R'OH\ (III)}$$

$$NCCH_2CONH_2 + \underset{(V)}{\left[(RO)_2\overset{+}{P}(OR')(OR)\ Br^-\right]} \longrightarrow$$

$$\underset{(VI)}{(RO)_3P{=}O} + \underset{(VII)}{R'Br} \qquad (1)$$

In view of the results, it is expected that the successful phosphorylation of alcohols would

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1) T. Mukaiyama, O. Mitsunobu and T. Obata, *J. Org. Chem.*, **30**, 101 (1965).

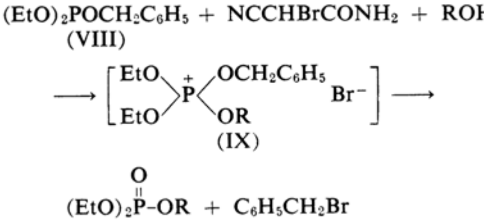
2) O. Mitsunobu, T. Obata and T. Mukaiyama, *J. Org. Chem.*, **30**, 1071 (1965).

TABLE I. REACTION OF MONOBROMOCYANOACETAMIDE WITH BENZYLDIETHYL PHOSPHITE AND ALCOHOLS

Alcohol	Charge ml.	Product		
		Phosphate	Yield, %	B. p., °C/mmHg
Ethanol	2	$EtOP(O)(OEt)_2$	55	84—90/7.3
Ethanol*	2	$EtOP(O)(OEt)_2$	55	87—92/7.3
n-Propanol	2	n-$PrOP(O)(OEt)_2$	37	63—65/0.5
n-Butanol	2	n-$BuOP(O)(OEt)_2$	47	68—75/0.3

* Alcohol was added an hour later to the reaction mixture of monobromocyanoacetamide and benzyldiethyl phosphite at room temperature.

result from the reaction of benzyldiethyl phosphite (VIII) with monobromocyanoacetamide and alcohols through the quaternary phosphonium salts (IX), as is shown in the following Eq. 2.



$$(EtO)_2POCH_2C_6H_5 + NCCHBrCONH_2 + ROH \longrightarrow \left[(EtO)_2\overset{+}{P}(OCH_2C_6H_5)(OR)\ Br^-\right] \longrightarrow (EtO)_2\overset{O}{\overset{\|}{P}}\text{-}OR + C_6H_5CH_2Br \quad (2)$$

(VIII)

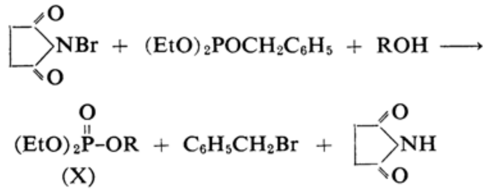
(IX)

Indeed, when benzyldiethyl phosphite (VIII) was treated with monobromocyanoacetamide in the presence of ethyl alcohol in ether at room temperature, triethyl phosphate was obtained in a 55% yield, and both benzyl bromide (84%) and cyanoacetamide (51%) were also isolated (Eq. 2, R=Et). A similar reaction was observed in the case of the other alcohols (see Table I).

In the above reaction, the initially formed enol quaternary phosphonium salt (IV) is assumed to be rather stable, because there is no noticeable difference in the yield of phosphate even when ethyl alcohol was added an hour later to the reaction mixture of benzyldiethyl phosphite and monobromocyanoacetamide.

In the second experiment, phosphorylation of alcohols by the use of benzyldiethyl phosphite and *N*-bromosuccinimide was tried under the assumption that the reaction may proceed through an enol phosphonium salt[3] analogous to that of monobromocyanoacetamide (Eq. 3).

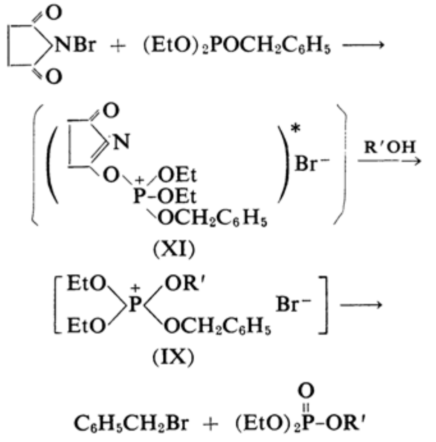
When benzyldiethyl phosphite was added to a suspension of equimolar amounts of *N*-bromosuccinimide and ethyl alcohol in ether, triethyl phosphate (X, R=Et) was obtained in a 61% yield along with benzyl bromide (85%) and succinimide (72%), as expected (Eq. 3); *n*-propyl and *n*-butyl alcohols were also phosphorylated to the corresponding alkyldiethyl phosphates (X, $R=C_3H_7$, C_4H_9) in yields of 60% and 31%, respectively (see Table II).



(X)

(3)

Contrary to the case of monobromocyanoacetamide, when ethyl alcohol was added an hour later to the reaction mixture of *N*-bromosuccinimide and benzyldiethyl phosphite, triethyl phosphate could not be isolated, and diethylphosphorosuccinimidate (XIII) was obtained in a quantitative yield by fractionation. In this case, the unstable quaternary phosphonium salt (XI) may decompose spontaneously, yielding benzyl bromide and imidoyl phosphate



(XI)

(IX)

(4)

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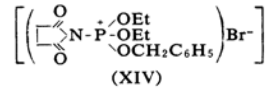
[3] S. Trippett, *J. Chem. Soc.*, **1962**, 2337.

* Two alternative structures, the *O*-phosphonium salt (XI) or the *N*-phosphonium salt (XIV), are conceivable for the structure of this quaternary phosphonium salt.



(XIV)

The *O*-phosphonium form (XI) is preferred to the *N*-phosphonium form (XIV) in this case, by analogy with the case of the monobromocyanoacetamide. But recent investigation supports the latter structure on the basis of a NMR spectrum (A. K. Tsolis et al., *Tetrahedron Letters*, **1964**, 3217).

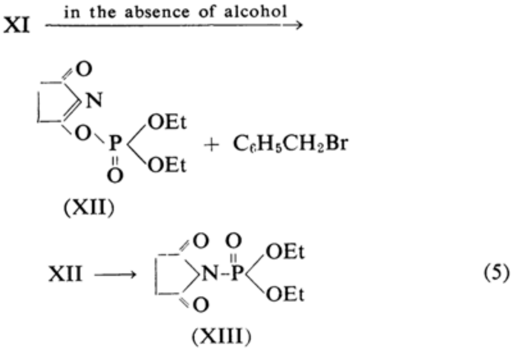
TABLE II. REACTION OF *N*-BROMOSUCCINIMIDE WITH BENZYLDIETHYL PHOSPHITE AND ALCOHOLS

Alcohol	Charge ml.	Product		
		Phosphate	Yield, %	B. p., °C/mmHg
Ethanol	2	$EtOP(O)(OEt)_2$	61	105—108/27
n-Propanol	1.5	n-$PrOP(O)(OEt)_2$	60	107—108/7
n-Butanol	1.5	n-$BuOP(O)(OEt)_2$	31	65—67/0.65

(XII), which is considered to rearrange rapidly to a more stable diethylphosphorosuccinimidate (XIII) (Eq. 5).

Whereas, the diethylphosphorosuccinimidate (XIII) did not react with alcohols at all even when they were refluxed for five hours; the starting materials were recovered.

From these results, it may be stated that imidoyl phosphonium salt (XI) is a necessary intermediate for the reactive quaternary phosphonium salt (IX), from which alkyl-diethyl phosphate may be produced by the elimination of benzyl bromide (Eq. 4).



Experimental

All boiling points are uncorrected.

Reagents.—Benzyldiethyl phosphite was prepared by the transesterification of triethyl phosphite with benzyl alcohol.[4] Monobromocyanoacetamide[5] and *N*-bromosuccinimide[6] were prepared by the procedures given in the literature. Alcohols and solvents used were dried and distilled by the ordinary procedures.

Reaction of Monobromocyanoacetamide with Benzyldiethyl Phosphite and Alcohols.—To a vigorously stirred suspension of monobromocyanoacetamide (1.63 g., 0.01 mol.) in ethyl alcohol (2 ml.) and ether (20 ml.), an ethereal solution (10 ml.) of benzyldiethyl phosphite (2.28 g., 0.01 mol.) was added drop by drop over a period of 10 min., at room temperature. A white precipitate of cyanoacetamide, soon separated. After the addition was completed, the mixture was stirred at room temperature for 2 hr. and then allowed to stand overnight. Cyanoacetamide (m. p. 110—116°C, 430 mg., 51%) was removed by filtratain. The filtrate was concentrated under reduced pressure, and the resulting oil was treated with dry ether (10 ml.) to remove the residual cyanoacetamide. After concentration, the solution was distilled under reduced pressure, yielding benzyl bromide (b. p. 65—75°C/7.3 mmHg, 1.43 g., 84%) and triethyl phosphate (b. p. 84—90°C/7.3 mmHg, 1.00 g., 55%).

Similarly, *n*-propyldiethyl and *n*-butyldiethyl phosphates were prepared from monobromocyanoacetamide, benzyldiethyl phosphite and the corresponding alcohols. The physical constants of these compounds together with the yields obtained are summarized in Table I.

When ethyl alcohol was added an hour later to the mixture of monobromocyanoacetamide and benzyldiethylphosphite at room temperature, 55% of triethyl phosphate was also obtained via the same procedure as in the above reaction.

Reaction of *N*-Bromosuccinimide with Benzyldiethyl Phosphite and Alcohols.—A solution of benzyldiethyl phosphite (2.28 g., 0.01 mol.) in 10 ml. of dry ether was added drop by drop with vigorous stirring to a suspension of *N*-bromosuccinimide (1.78 g., 0.01 mol.) in 1.5 ml. of anhydrous *n*-propyl alcohol and ether (15 ml.). The temperature was controlled at about −40°C by cooling in an ethanol - dry ice bath. After addition was completed, the mixture was stirred for an additional 30 min., and allowed to warm slowly to room temperature. After being stirred for an additional 2 hr., the mixture was concentrated under reduced pressure, and the resulting pale yellow oil was treated with dry ether (2 ml.) at −20°C to separate the succinimide. The white crystalline succinimide (m. p. 124—126°C, 770 mg., 78%) was filtered off and the filtrate was concentrated and distilled. Benzyl bromide (b. p. 75—78°C/7 mmHg, 1.37 g., 80%) and *n*-propyldiethyl phosphate (b. p. 107—108°C/7 mmHg, 1.17 g., 60%) were obtained. The distillation residue was filtered and washed with 5 ml. of ether yielding crude succinimide (m. p. 115—118°C, 180 mg., 18%).

In a similar fashion, ethanol and *n*-butyl alcohol were phosphorylated, yielding triethyl phosphate and *n*-butyldiethyl phosphate. These results are summarized in Table II.

Reaction of *N*-Bromosuccinimide with Benzyldiethyl Phosphite in the Absence of Alcohol.—Benzyl diethyl phosphite (25.0 g., 0.11 mol.) was added drop by drop to a suspension of *N*-bromosuccinimide (17.8 g., 0.1 mol.) in dry ether (150 ml.) over a period of 20 min., at room temperature. After refluxing for an additional 3 hr., the solution

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[4] F. W. Hoffmann, R. J. Ess and R. P. Usinger, Jr., *J. Am. Chem. Soc.*, **78**, 5817 (1956).

[5] T. Hata and T. Mukaiyama, This Bulletin, **35**, 1106 (1962).

[6] E. Campaingne and B. F. Tullar, "Organic Syntheses," **33**, 96 (1953).

was concentrated and distilled under reduced pressure; benzyl bromide (b. p. 80—83°C/15 mmHg, 5.1 g., 88%) and diethylphosphorosuccinimidate (b. p. 140—155°C/0.03 mmHg, 19.3 g., 82%) were obtained. Redistillation gave white crystalline diethylphosphorosuccinimidate (m. p. 60—62°C, b. p. 145—150°C/0.03 mmHg, 15.3 g., 65%). Found: N, 6.10. Calcd. for $C_8H_{14}O_5NP$: N, 5.96%.

Summary

The phosphorylation of alcohols with benzyldiethyl phosphite and monobromocyanoacetamide has been investigated. By this method, the corresponding alkyldiethyl phosphates were obtained in fairly good yields along with benzyl bromide and cyanoacetamide. Similarly, it has been established that *N*-bromosuccinimide can be successfully used in the place of monobromocyanoacetamide in the above phosphorylation.

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