BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 40 935—939 (1967)

Preparation of Esters of Phosphoric Acid by the Reaction of Trivalent Phosphorus Compounds with Diethyl Azodicarboxylate in the Presence of Alcohols

Oyo MITSUNOBU,*1 Masaaki YAMADA and Teruaki MUKAIYAMA

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

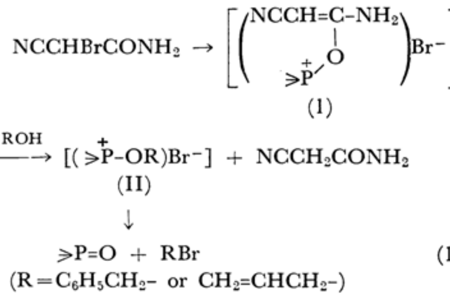
(Received September 28, 1966)

Trivalent phosphorus compounds, phosphine or trialkylphosphites, have been oxidized by means of diethyl azodicarboxylate and either benzyl or allyl alcohol to give the corresponding phosphine oxide or trialkyl phosphates. The reaction was then extended to the phosphorylation of alcohols. When allyl diethyl phosphite was treated with diethyl azodicarboxylate in the presence of an alcohol at room temperature, a corresponding alkyl diethyl phosphate and diethyl *N*-allyl hydrazodicarboxylate were obtained in good yields. On the other hand, when phenol was treated with allyl diethyl phosphite and diethyl azodicarboxylate, diethyl phenyl phosphate, allyl phenyl ether and diethyl hydrazodicarboxylate were obtained. The mechanism of their formation will also be discussed.

The preceding paper[1] describes the oxidation of trivalent phosphorus compounds by means of monobromocyanoacetamide and benzyl alcohol or allyl alcohol. The reaction proceeds *via* the proposed intermediates of an enol phosphonium salt (I) and a quaternary phosphonium salt (II) from which benzyl or allyl bromide is eliminated, resulting in the formation of the oxidized product (Eq. (1)).

[*1] Present address: College of Science and Engineering, Aoyama Gakuin University, Megurisawa-cho, Setagaya-ku, Tokyo.

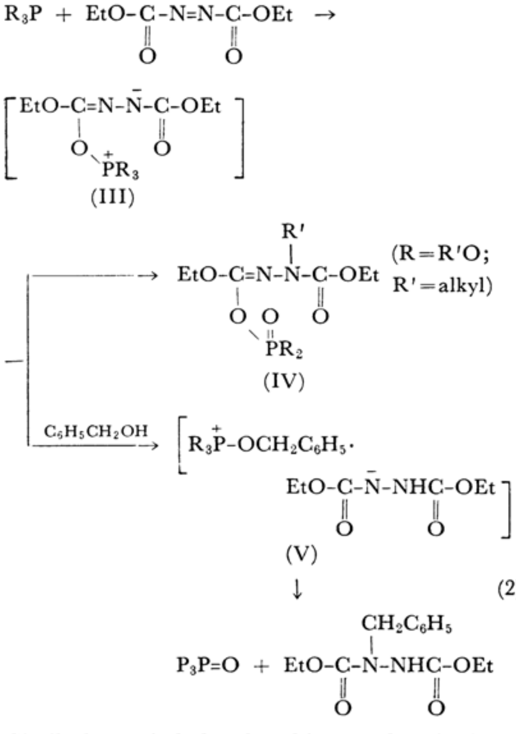
[1] T. Mukaiyama, O. Mitsunobu and T. Obata, *J. Org. Chem.*, **30**, 101 (1965).



(1)

Ginsburg[2] demonstrated that diethyl azodicarboxylate reacts with trialkyl phosphite to give IV *via* imidoyl phosphonium salt (III). Since the phosphonium salt (III) is analogous in structure to I, it may be expected to react with benzyl alcohol to give a second phosphonium salt (V). On the basis of the results reported earlier,[1,3] the formation of trialkyl phosphate may be expected by means of the elimination of diethyl *N*-benzyl hydrazodicarboxylate from V, as is shown below (Eq. (2)).

When triphenyl phosphine was allowed to react with diethyl azodicarboxylate in the presence of benzyl alcohol at room temperature, triphenyl phosphine oxide (95%) and diethyl *N*-benzyl hydrazodicarboxylate (70%) were obtained (Eq. (2), $R=C_6H_5$).

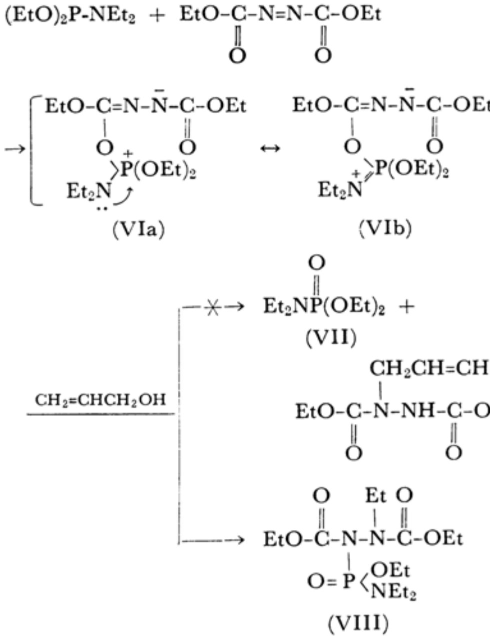


(2)

Similarly, triethyl phosphite and tri-*n*-butyl phosphite were oxidized to give triethyl phosphate and tri-*n*-butyl phosphate in 79% and 91% yields respectively (Eq. (2); $R=C_2H_5O$ or C_4H_9O). In both cases, however, the structures of the higher boiling materials thus obtained have not yet been confirmed.

Allyl alcohol could also be used in place of benzyl alcohol in the above reaction. Namely, when triphenyl phosphine, triethyl phosphite, or tri-*n*-butyl phosphite was treated with diethyl azodicarboxylate in the presence of allyl alcohol, the corresponding oxidized product, triphenyl phosphine oxide, triethyl phosphate, or tri-*n*-butyl phosphate, was obtained in a good yield. The results are summarized in Table 1.

Contrary to the case of the oxidation of trialkyl phosphite, diethyl *N*-diethylphosphoroamidite gave no corresponding oxidized product, diethyl *N*-diethylphosphoroamidate (VII), but diethyl *N*-(ethyl diethylamino)phosphoryl *N′*-ethyl hydrazodicarboxylate (VIII) was obtained in a 75% yield (Eq. (3)). This result may be explained as follows. The positive charge of the initially formed imidoyl phosphonium salt (VI) is not localized on the phosphorus atom, but also resides partially on the nitrogen atom (VIa, b). Therefore, the nucleophilic attack of the allyloxy anion on the phosphorus atom became slower than the migration of the ethyl group, and VIII was primarilly formed (Eq. (3)).



(3)

Next, the reaction was extended to the phosphorylation of alcohol, with the assumption that allyloxy phosphonium salt (IX) would be formed by the reaction of diethyl allyl phosphite with diethyl azodicarboxylate in the presence of an alcohol. In view of the results obtained earlier,

---

2) V. A. Ginsburg, M. N. Vasil'eva, S. S. Dubov and A. Ya. Yakubovich, *Chem. Abstr.*, **55**, 17477 (1961).

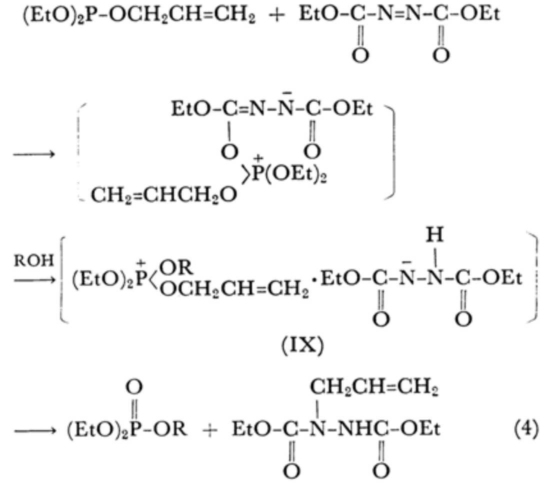
3) O. Mitsunobu, T. Obata and T. Mukaiyama, *J. Org. Chem.*, **30**, 1071 (1965).

TABLE 1. OXIDATION OF PHOSPHINE OR PHOSPHITES BY MEANS OF DIETHYL AZODICARBOXYLATE AND EITHER BENZYL ALCOHOL OR ALLYL ALCOHOL

Phosphine or phosphite R_3P R	Alcohol ROH R	Product: Phosphine oxide or phosphate $R_3P{=}O$ R	Yield, %	Diethyl *N*-alkyl hydrazodicarboxylate $EtO\text{-}\underset{\underset{O}{\|}}{C}\text{-}NR\text{-}NH\text{-}\underset{\underset{O}{\|}}{C}\text{-}OEt$ R	Yield, %
C_6H_5	$C_6H_5CH_2$	C_6H_5	95	$C_6C_5CH_2$	70
C_2H_5O	$C_6H_5CH_2$	C_2H_5O	79	$C_6H_5CH_2$	56
n-C_4H_9O	$C_6H_5CH_2$	n-C_4H_9O	91	$C_6H_5CH_2$	52
C_6H_5	$CH_2{=}CHCH_2$	C_6H_5	72	$CH_2{=}CHCH_2$	73
C_2H_5O	$CH_2{=}CHCH_2$	C_2H_5O	82	$CH_2{=}CHCH_2$	84
n-C_4H_9O	$CH_2{=}CHCH_2$	n-C_4H_9O	78*	$CH_2{=}CHCH_2$	78*

* Since tri-*n*-butyl phosphate and diethyl *N*-allyl hydrazodicarboxylate could not be fractionated by distillation, the yields were determined by means of gas chromatography.

the quaternary phosphonium salt (IX) may exclusively decompose into diethyl *N*-allyl hydrazodicarboxylate and alkyl diethyl phosphate, the phosphorylated product (Eq. (4)).



$$(EtO)_2P\text{-}OCH_2CH{=}CH_2 + EtO\text{-}\underset{\underset{O}{\|}}{C}\text{-}N{=}N\text{-}\underset{\underset{O}{\|}}{C}\text{-}OEt$$

$$\longrightarrow \left[\begin{array}{l} EtO\text{-}C{=}N\text{-}\bar{N}\text{-}\underset{\underset{O}{\|}}{C}\text{-}OEt \\ \quad | \\ \quad O \overset{+}{} \rangle P(OEt)_2 \\ CH_2{=}CHCH_2O \end{array}\right]$$

$$\xrightarrow{ROH} \left[(EtO)_2\overset{+}{P}\langle{}^{OR}_{OCH_2CH=CH_2}\cdot EtO\text{-}\underset{\underset{O}{\|}}{C}\text{-}\bar{N}\text{-}\overset{\overset{H}{|}}{N}\text{-}\underset{\underset{O}{\|}}{C}\text{-}OEt\right]$$

(IX)

$$\longrightarrow (EtO)_2\overset{\overset{O}{\|}}{P}\text{-}OR + EtO\text{-}\underset{\underset{O}{\|}}{C}\text{-}\overset{\overset{CH_2CH=CH_2}{|}}{N}\text{-}NH\underset{\underset{O}{\|}}{C}\text{-}OEt \qquad (4)$$

When diethyl azodicarboxylate was treated with allyl diethyl phosphite in the presence of *n*-propyl alcohol at room temperature, diethyl *n*-propyl phosphate and diethyl *N*-allyl hydrazodicarboxylate were obtained in 75% and 92% yields respectively (Eq. (4); R$=n$-C_3H_7), as had been expected. Similarly, ethyl alcohol and isopropyl alcohol were successfully phosphorylated to give triethyl phosphate and diethyl isopropyl phosphate in good yields. The results are summarized in Table 2.

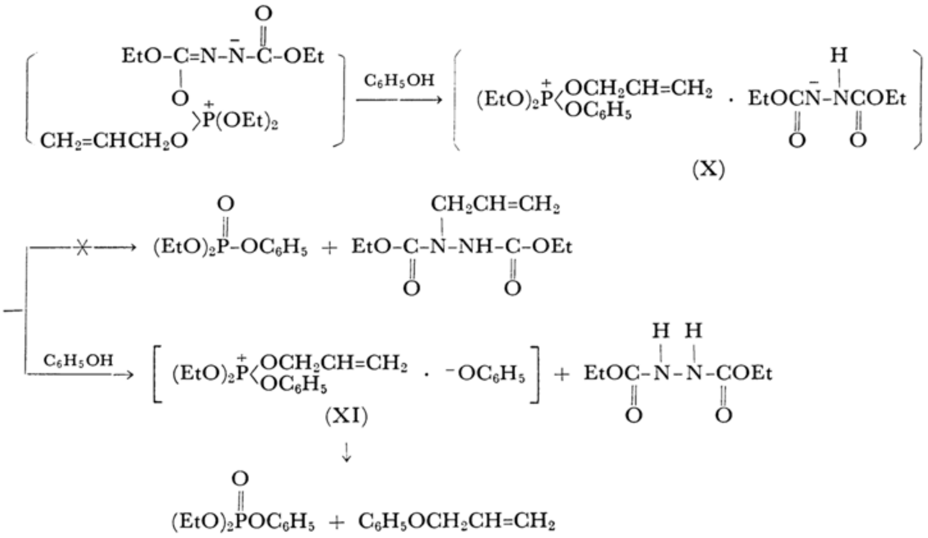
TABLE 2. PHOSPHORYLATION OF ALCOHOLS BY MEANS OF DIETHYL AZODICARBOXYLATE AND ALLYL DIETHYL PHOSPHITE

Alcohol ROH R	Product: Phosphate $RO\overset{\overset{O}{\|}}{P}(OC_2H_5)_2$ R	Bp °C/mmHg	Yield %	Diethyl *N*-allyl hydrazodicarboxylate Yield, %
C_2H_5	C_2H_5	67—70/6	78	94
n-C_3H_7	n-C_3H_7	101—104/9	75	92
i-C_3H_7	i-C_3H_7	75—78/5	62	73

Further, an attempt was made to prepare diethyl phenyl phosphate by the phosphorylation of phenol. When phenol was treated with equimolar amounts of allyl diethyl phosphite and diethyl azodicarboxylate in ether at room temperature, no diethyl *N*-allyl hydrazodicarboxylate was isolated. However, diethyl phenyl phosphate, diethyl hydrazodicarboxylate (42%), and allyl phenyl ether (36%) were obtained. The yields of diethyl phenyl phosphate, diethyl hydrazodicarboxylate, and allyl phenyl ether increased to 87%, 95%, and 73% respectively when two moles of phenol were used in the above reaction. The unexpected formation of diethyl hydrazodicarboxylate and allyl phenyl ether can be explained by assuming the following reaction mechanism.[4] Since the phenoxy anion is more stable than the diethyl hydrazodicarboxylate anion, the quaternary phosphonium salt (X) suffers anion exchange reaction, giving diethoxy allyloxy phenoxy phosphonium phenoxide (XI) and diethyl hydrazodicarboxylate. The intermediate thus formed decomposes into diethyl phenyl phosphate and allyl phenyl ether (Eq. (5)).

---

[4] A similar result has been obtained by Harvey and Jensen. Dibenzoyl ethylene gave dibenzoyl ethane by reacting with triethyl phosphite and phenol. However, no other products were described. R. G. Harvey and E. V. Jensen, *Tetrahedron Letters,* 1801 (1963).



(5)

Experimental

Diethyl azodicarboxylate[5] and allyl diethyl phosphite[6] were prepared by the procedures in the literature. Triphenyl phosphine, triethyl phosphite, and tri-*n*-butyl phosphite were commercial products and were purified by recrystallization or redistillation. The solvents and alcohols were purified and dried by ordinary procedures.

Reaction of Triphenyl Phosphine with Diethyl Azodicarboxylate and Benzyl Alcohol. A solution of diethyl azodicarboxylate (5.22 g, 0.03 mol) in 20 m*l* of ether was added, drop by drop, to a solution of triphenyl phosphine (7.86 g, 0.03 mol) and benzyl alcohol (3.24 g, 0.03 mol) in 30 m*l* of ether at room temperature with vigorous stirring. The reaction soon started, with a liberation of heat. After the reaction mixture had been kept standing for two days at room temperature, the triphenyl phosphine oxide (6.20 g, 74.3%, mp 148—150°C) was removed by filtration. The filtrate was distilled to give diethyl *N*-benzyl hydrazodicarboxylate (5.55 g, 69.6%, bp 140—145°C/4 mmHg; an analytical sample was obtained by redistillation, bp 125—127°C/0.06 mmHg, n_D^{22} 1.5066).

Found: C, 58.61; H, 6.83; N, 10.55%. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52%.

From the residue of the distillation, triphenyl phosphine oxide (1.77 g, 21.2%; recrystallization from carbon tetrachloride gave mp 153—155°C) was obtained.

Reaction of Tri-*n*-butyl Phosphite with Diethyl Azodicarboxylate and Benzyl Alcohol. A solution of tri-*n*-butyl phosphite (7.50 g, 0.03 mol) in 15 m*l* of tetrahydrofuran was added, drop by drop, to a solution of diethyl azodicarboxylate (5.22 g, 0.03 mol) and benzyl alcohol (3.24 g, 0.03 mol) in 25 m*l* of tetrahydrofuran at room temperature with vigorous stirring. The solution was then kept standing for two days at room temperature. After the solvent had been removed, the residue was distilled to give tri-*n*-butyl phosphate (7.29 g, 91.4%, bp 103—112°C/0.2 mmHg. Redistillation gave bp 84—90°C/0.08 mmHg, n_D^{18} 1.4263), diethyl *N*-benzyl hydrazodicarboxylate (4.17 g, 52.2%, bp 137—142°C/0.14 mmHg), and higher boiling substance (2.06 g, bp 165—193°C/0.12 mmHg).

Reaction of Triphenyl Phosphine with Diethyl Azodicarboxylate and Allyl Alcohol. A solution of diethyl azodicarboxylate (5.22 g, 0.03 mol) in 10 m*l* of ether was added, drop by drop, to a solution of triphenyl phosphine (7.86 g, 0.03 mol) and allyl alcohol (2 m*l*) in 20 m*l* of ether at room temperature with vigorous stirring. The reaction soon started, with a liberation of heat; a white precipitate appeared. After the mixture had been kept standing overnight at room temperature, the triphenyl phosphine oxide (6.03 g, 72.4%, mp 150—151°C) was removed by filtration. From the filtrate, diethyl *N*-allyl hydrazodicarboxylate (4.75 g, 73.2%, bp 115—120°C/4 mmHg) was obtained by distillation. Redistillation gave an analytical sample, bp 119—122°C/4 mmHg.

Found: C, 50.19; H, 7.53; N, 12.74%. Calcd for $C_9H_{16}O_4N_2$: C, 49.99; H, 7.46; N, 12.96%.

Reaction of Tri-*n*-butyl Phosphite with Diethyl Azodicarboxylate and Allyl Alcohol. A solution of diethyl azodicarboxylate (5.22 g, 0.03 mol) in 10 m*l* of ether was added, drop by drop, to a solution of tri-*n*-butyl phosphite (7.50 g, 0.03 mol) and allyl alcohol (2 m*l*) in 20 m*l* of ether with vigorous stirring at room temperature. After the solution had then been kept standing overnight at room temperature, two fractions, A (11.25 g, bp 56—122°C/3 mmHg) and B (1.95 g, bp 116—152°C/0.2 mmHg), were obtained by distillation. A was redistilled (bp 110—122°C/3 mmHg), compared with authentic specimens by gas chromatography, and thus proved to be a mixture of tri-*n*-butyl phosphate and diethyl *N*-allyl hydrazodicarboxylate (the ratio was about 1 : 1).

Phosphorylation of Ethanol by Means of Allyl Diethyl Phosphite and Diethyl Azodicarboxylate. A solution of diethylazodicarboxylate (1.74 g, 0.01 mol) in 5 m*l* of ether was added, drop by drop, to a solution of allyl diethyl phosphite (1.78 g, 0.01 mol) and ethanol (1 m*l*) in 10 m*l* of ether at room temperature with vigorous stirring. After the solution had been kept

---

[5] N. Robjohn, "Organic Syntheses," Coll. Vol. III, p. 375 (1955).

[6] A. N. Pudvik and I. M. Aladzheva, *Chem. Abstr.*, **60**, 1788 (1964).

standing overnight at room temperature, triethyl phosphate (1.42 g, 78.0%, bp 62—68°C/3—4 mmHg. Redistillation gave bp 67—70°C/6 mmHg) and diethyl *N*-allyl hydrazodicarboxylate (2.03 g, 94%, bp 113—128°C/3 mmHg. Redistillation gave bp 126—131°C/6 mmHg) were obtained by fractionation.

Similarly, *n*-propyl diethyl phosphate and isopropyl diethyl phosphate were obtained in 74.5% and 61.7% yields respectively.

Reaction of Allyl Diethyl Phosphite with Phenol and Diethyl Azodicarboxylate. A solution of allyl diethyl phosphite (5.34 g, 0.03 mol) in 6 m*l* of ether was added, drop by drop, to a solution of diethyl azodicarboxylate (5.22 g, 0.03 mol) and phenol (5.64 g, 0.06 mol) in 25 m*l* of ether at room temperature with vigorous stirring. The reaction soon started, with a liberation of heat, a white precipitate appeared. After the mixture had been kept standing overnight at room temperature, a nearly quantitative yield of diethyl hydrazodicarboxylate (mp 128—130°C) was removed by filtration. From the filtrate, allyl phenyl ether (2.92 g, 72.5%, bp 78—84°C/18—21 mmHg. Redistillation gave an analytical sample, bp 76—79°C/18—19 mmHg Found: C, 79.33; H, 7.44%) and diethyl phenyl phosphate (6.00 g, 87%, bp 113—137°C/3 mmHg. Redistillation gave an analytical sample, bp 137—139°C/4 mmHg. Found: C, 52.23; H, 6.90%) were obtained by fractionation.

Reaction of Diethyl *N*-Diethylphosphoroamidite with Diethyl Azodicarboxylate and Allyl Alcohol. A solution of diethyl azodicarboxylate (1.74 g, 0.01 mol) in 5 m*l* of ether was added, drop by drop, to a solution of diethyl *N*-diethylphosphoroamidite (1.93 g, 0.01 mol) and allyl alcohol (1.5 m*l*) in 10 m*l* of ether with vigorous stirring at room temperature. The reaction soon started, with a liberation of heat. After the reaction mixture had been kept standing overnight at room temperature, diethyl *N*-(ethyl *N*-diethylamino)-phosphoryl *N'*-diethyl hydrazodicarboxylate (2.75 g, 75.0%, bp 146—156°C/3 mmHg) was obtained by fractionation. Redistillation gave an analytical sample, bp 139—143°C/0.06 mmHg.

Found: N, 11.68%. Calcd for $C_{14}H_{30}N_3O_6P$: N, 11.44%.

The authors wish to express their hearty thanks to members of Analytical Room, this Laboratory, for microanalyses.