Phosphorylation by the Use of Diethylphosphorosuccinimidate

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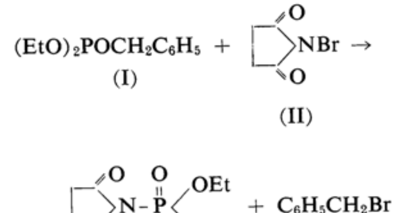
In previous papers,[1,2] it has been shown that the oxidation of various phosphines and phosphites by means of monobromocyanoacetamide and allyl or benzyl alcohol gave the corresponding phosphine oxindes and phosphates in good yields.

It was shown[2] that *N*-bromosuccinimide could also be used successfully in the place of monobromocyanoacetamide in the above reactions. During the course of the experiment, it was found that diethylphosphorosuccinimidate (III) was obtained in a good yield when benzyldiethyl phosphite (I) was treated with an equimolar amount of *N*-bromosuccinimide (II) in the absence of the alcohols (Eq. 1).



(1)

Since diethylphosphorosuccinimidate (III) is a kind of acid anhydride derived from a weak acid and a strong acid, it is expected that its phosphoroimidate bond would be reactive towards active hydrogen compounds, such as alcohols and phenols.

In the present experiment, phosphorylation of alcohols, phenol, and phosphates, by the use of diethylphosphorosuccinimidate was tried.

Contrary to expectation, no reaction was observed when diethylphosphorosuccinimidate was refluxed in a large excess of ethyl alcohol for five hours, and the starting materials were recovered. Further, reactions of diethylphosphorosuccinimidate (III) with alcohols in the presence of several catalysts were tried. Firstly, acid catalysts were employed on the consideration that the phosphoroimidate bond might be activated under acidic conditions. Among the catalysts examined, a protonic acid such as *p*-toluene sulfonic acid was found to be ineffective; while Lewis acids such as boron trifluoride and aluminum trichloride were shown to promote the reaction. In the case of aluminum trichloride, succinimide separated quantitatively, although the yield of alkyldiethyl phosphates (IV) was always lower than that in the case of boron trifluoride. Accordingly, the following reactions were tried with boron trifluoride as catalyst.

For example, when diethylphosphorosuccinimidate (III) was treated with a large excess of ethyl alcohol in the presence of a catalytic amount of boron trifluoride etherate under reflux for five hours, triethyl phosphate (IV, R=Et) was obtained in a 72% yield (Eq. 2). The results of phosphorylation of other alcohols by means of diethylphosphorosuccinimidate in the presence of boron trifluoride are summarized in Table I.

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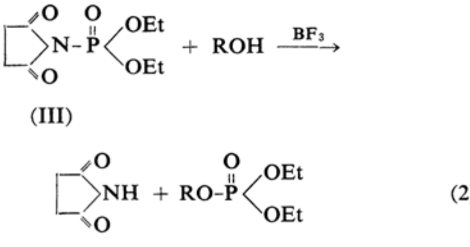
[1] T. Mukaiyama, O. Mitsunobu and T. Obata, *J. Org. Chem.*, **30**, 101 (1965).

[2] T. Mukaiyama, T. Obata and O. Mitsunobu, This Bulletin, **38**, 1088 (1965).

TABLE I. PHOSPHORYLATION OF ALCOHOLS OR PHENOL BY MEANS OF DIETHYLPHOSPHOROSUCCINIMIDATE IN THE PRESENCE OF BORON TRIFLUORIDE

Material	Product		
	Phosphate	Yield, %	B. p., °C/mmHg
EtOH	$EtOP(O)(OEt)_2$	72	98—102/13
n-PrOH	*n*-$PrOP(O)(OEt)_2$	84	104—110/12
i-PrOH	*i*-$PrOP(O)(OEt)_2$	73	98—105/12
n-BuOH	*n*-$BuOP(O)(OEt)_2$	85	120—125/13
C_6H_5OH	$C_6H_5OP(O)(OEt)_2$	34	80—95/0.3



(III)

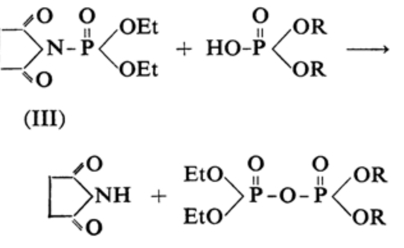
(IV)

(2)

On the other hand, when diethylphosphorosuccinimidate (III) and ethyl alcohol were refluxed in the presence of a catalytic amount of basic catalysts such as sodium or triethyl amine, no reaction was observed and the starting materials were recovered.

In the second place, the reaction of phenol (pK_a=9.9) with diethylphosphorosuccinimidate (III) in the presence of a catalytic amount of boron trifluoride was tried. In this case, diethylphenyl phosphate (IV, R=C_6H_5) was isolated with some difficulty in only a 37% yield from the viscous greenish-black reaction mixture. But when phenol was treated with an equimolar amount of diethylphosphorosuccinimidate in the absence of catalyst, diethylphenyl phosphate was obtained in a 82% yield.

These results suggest that acidic compounds such as phenol are more readily phosphorylated by diethylphosphorosuccinimidate. This suggestion was confirmed by the fact that diethyl and di-*n*-butyl hydrogen phosphates, with pK_a value about 2.1, were easily phosphorylated with diethylphosphorosuccinimidate (III), yielding tetraethyl pyrophosphate and *unsym.* di-*n*-butyl diethyl pyrophosphate (V, R=Et, *n*-Bu), respectively, in high yields (Eq. 3).



(III)

(V)

(3)

In another reaction, preparation of acyl phosphates by the reaction of diethylphosphorosuccinimidate with butyric or valeric acids (pK_a=4.8) was tried. Unexpectedly when the carboxylic of acids and diethylphosphorosuccinimidate were refluxed for five hours in benzene, they did not react at all and the starting materials were recovered.

In conclusion, it is noted that phosphorylation alcohols by the use of diethylphosphorosuccinimidate could only be carried out in the presence of certain acid catalysts. On the other hand, more acidic substances such as phenol and dialkyl hydrogen phosphates were readily phosphorylated in quantitative yields even in the absence of catalysts.

Experimental

The melting points and boiling points are uncorrected.

Reagents.—The solvents and alcohols were dried and purified by ordinary procedures. *N*-Bromosuccinimide, and butyric and valeric acids were obtained from a commercial source and purified by recrystallization or distillation. Diethyl hydrogen phosphate[3] and di-*n*-butyl hydrogen phosphate[4] were prepared according to the literature.

Preparation of Diethylphosphorosuccinimidate by the Reaction of *N*-Bromosuccinimide and Benzyldiethyl Phosphite.—Benzyldiethyl 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 the solution had been refluxed for 3 hr., it 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—150°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%.

IR-spectrum in Nujol: 1770, 1725, 1300, 1130, 1030 cm^{-1}.

Diethylphosphorosuccinimidate decomposes when

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[3] A. D. F. Toy, *J. Am. Chem. Soc.*, **70**, 3882 (1948).

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

TABLE II. PHOSPHORYLATION OF PHENOL OR DIALKYL HYDROGEN PHOSPHATES BY MEANS OF DIETHYLPHOSPHOROSUCCINIMIDATE IN THE ABSENCE OF BORON TRIFLUORIDE

Material	Product		
	Phosphate or Pyrophosphate	Yield, %	B. p., °C/mmHg
C_6H_5OH	$C_6H_5OP(O)(OEt)_2$	82	95—105/0.4—0.6
$(EtO)_2P(O)OH$	$(EtO)_2P(O)OP(O)(OEt)_2$	94	115—118/0.3
$(BuO)_2P(O)OH$	$(BuO)_2P(O)OP(O)(OEt)_2$	76	124—125/0.03

heated above 220°C, but prolonged heating at lower temperature (ca. 180—190°C) may at times have the same effect. For this reason, distillation should be carried out under high vacuum, not more than 50 g. being distilled in one operation; care should also be taken as regards the purity of *N*-bromosuccinimide.

Reaction of Diethylphosphorosuccinimidate with Alcohols or Phenol in the Presence of Boron Trifluoride.—To a solution of diethylphosphorosuccinimidate (2.15 g.) in anhydrous *n*-propyl alcohol (2 ml.) was added five drops of boron trifluoride etherate, and the mixture was heated at 100°C for 5 hr. Dry ether (10 ml.) was added to the mixture, which was then allowed to stand at room temperature for some time to permit separation of the resulting succinimide. After separation of the succinimide (1.48 g., 84%), the colorless oil was distilled under reduced pressure and *n*-propyldiethyl phosphate (b. p. 104—110°C/12 mmHg, 1.40 g., 84%) was obtained.

Similarly, triethyl, isopropyldiethyl and *n*-butyldiethyl phosphates were prepared from the reactions of diethylphosphorosuccinimidate with the corresponding alcohols.

In the case of phenol, the reaction mixture turned brown within 30 min. and a small amount of succinimide separated. After heating at 100°C for 5 hr., the resulting viscous greenish-black oil was extracted carefully with several portions of dry ether (20 ml.). The extract was concentrated and diethylphenyl phosphate (b. p. 80—95°C/0.3 mmHg, 0.78 g., 34%) was obtained by distillation. These results are summarized in Table. I

Reaction of Phenol with Diethylphosphorosuccinimidate.—Freshly distilled phenol (1.0 g.) was mixed with diethylphosphorosuccinimidate (2.15 g.), and the mixture was heated at 100°C for 5 hr. When dry ether (10 ml.) was added, white crystalline succinimide (0.74 g., 83%) soon separated. The filtrate was concentrated and distilled under reduced pressure. An 82% yield of diethylphenyl phosphate (b. p. 95—105°C/0.4—0.6 mmHg, 1.58 g.) was obtained.

Reaction of Diethylphosphorosuccinimidate with Diethyl Hydrogen Phosphate, or Di-*n*-butyl Hydrogen Phosphate.—A mixture of equimolar amounts of diethylphosphorosuccinimidate (2.15 g.) and diethyl hydrogen phosphate (1.40 g.) in dry toluene (5 ml.) was heated at 100°C. The reaction took place rapidly. After heating for 5 hr., a quantitative amount of succinimide (870 mg., 97%) precipitated and was filtered off. From the concentrated filtrate, tetraethyl pyrophosphate (b. p. 115—118°C/0.3 mmHg., 2.43 g., 94%) was obtained by fractionation. This compound was identical with an authentic specimen prepared by the procedure given in the literature.[3]

Similarly, *unsym.* diethyl di-*n*-butyl pyrophosphate (b. p. 124—125°C/0.03 mmHg, 2.26 g., 76%) was obtained from di-*n*-butyl hydrogen phosphate (1.76 g.) and diethylphosphorosuccinimidate (1.97 g.). The results are summarized in Table II.

Summary

Phosphorylation of alcohols, phenol, and dialkyl hydrogen phosphates by means of diethylphosphorosuccinimidate has been described. Phorphorylation of alcohols with diethylphosphorosuccinimidate could only be carried out in the presence of certain acid catalysts; while more acidic compounds such as phenol and dialkyl hydrogen phosphates were readily phosphorylated to give the corresponding phosphate and *sym.*- or *unsym.*-pyrophosphate in quantitative yields even in the absence of catalysts.

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