A Novel Preparation of Enamine Phosphonates from Ketene *O,N*-, *S,N*-, and *N,N*-Acetals with Diethyl Phosphite

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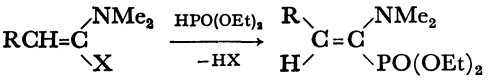
(Received January 22, 1975)

1-Dimethylamino-1-methoxy-1-alkenes (ketene *O,N*-acetals), 1-dimethylamino-1-ethylthio-1-alkenes (ketene *S,N*-acetals) and 1,1-bis(dimethylamino)ethylene (ketene *N,N*-acetal) reacted with diethyl phosphite to give the corresponding (*E*)-diethyl 1-dimethylamino-1-alkenylphosphonates. Although ketene diethylacetal (ketene *O,O*-acetal) reacted with diethyl phosphite to give diethyl 1,1-diethoxy-1-ethylphosphonate, 1,1-bis(ethylthio)-1-alkenes (ketene *S,S*-acetals) did not react with diethyl phosphite.

Enamine phosphonates have been synthesized by Horner's olefination method of tetraethyl dimethylaminomethylenediphosphonate with aldehydes,[1] and also by addition of diethyl phosphite to ynamines.[2] In this paper we wish to report a new method of preparation of enamine phosphonates by the reaction of ketene *O,N*-, *S,N*-, and *N,N*-acetals with diethyl phosphite. The method has the following adventages over the methods described above. The reaction proceeds smoothly under mild conditions, and the procedure is quite simple.

Results and Discussion

Ketene *O,N*- (Ia—c), *S,N*- (IIa—c), and *N,N*-acetals (III) reacted exothermally with diethyl phosphite at room temperature to give the corresponding enamine phosphonates (Va—c) in 50—80% yields (Table 1), according to the following scheme.



(1)

Ia R=H X=OMe — Va R=H
b R=Me X=OMe — b R=Me
c R=Et X=OMe — c R=Et
IIa R=H X=SEt
b R=Me X=SEt
c R=Et X=SEt
III R=H X=NMe_2

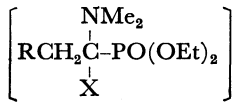
The structures of Va—c were identified by elemental analysis and NMR, mass, and IR spectral data. NMR spectra indicate that the enamine phosphonates obtained by this method are only *E*-isomer. The PCCH coupling constant of Vb and Vc was observed to be 13.5 Hz, which is the same as that reported by Schindler and Plöger.[2a]

TABLE 1. ENAMINE PHOSPHONATES FROM KETENE O,N-, S,N-, AND N,N- ACETALS WITH DIETHYL PHOSPHITE

Ketene Acetal	Product	Bp (°C)/ mmHg	Yield (%)
Ia(R=H, X=OMe)	Va(R=H)	92—94/1	75
Ib(R=Me, X=OMe)	Vb(R=Me)	114—115/5	58
Ic(R=Et, X=OMe)	Vc(R=Et)	116—123/6	47
IIa(R=H, X=SEt)	Va(R=H)		54
IIb(R=Me, X=SEt)	Vb(R=Me)		77
IIc(R=Et, X=SEt)	Vc(R=Et)		81
III(R=H, X=NMe_2)	Va(R=H)		55

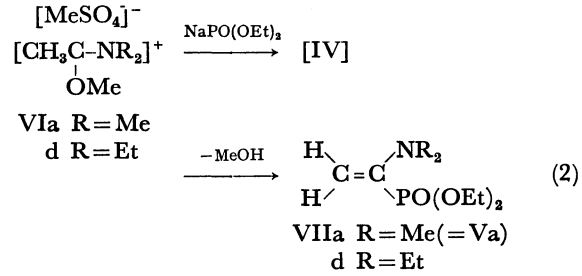
The reaction was carried out without solvent at 60—80 °C for 0.5—1 hr.

Since the compounds (I, II, and III) are the analog of enamine or ketene acetal, it is expected that β-carbon of I, II, and III would exhibit a strong nucleophilic character due to the conjugation of the double bond with electron donor groups.[3] Thus, it seems reasonable to speculate that an intermediate(IV) was formed by addition of diethyl phosphite to the C=C double bond of I, II, or III, although our attempt to isolate IV was unsuccessful. Enamine phosphonate (V) would be produced immediately by the elimination of HX from IV.



(IV)

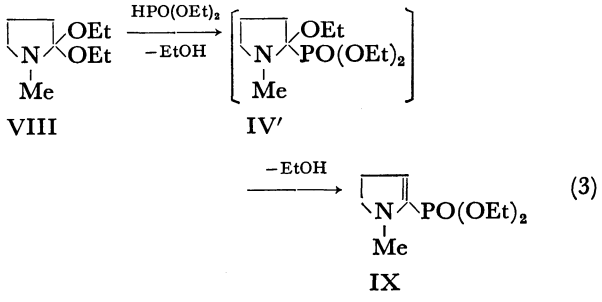
It was found that the adduct (VI) derived from *N,N*-dialkylacetamide and dimethyl sulfate reacted with diethyl phosphite to give VII in 30—40% yields. In this case also, the intermediate (IV) would be formed and undergo elimination of methanol *in situ* to give VII.



(2)

VIa R=Me(=Va)
d R=Et

It is noteworthy that *N*-methylpyrrolidone diethylacetal (VIII) reacted with an excess diethyl phosphite to give the corresponding enamine phosphonate (IX).



(3)

VIII IV′ IX

The reaction process can be explained by considering the intermediate (IV′) which will rapidly loose ethanol *in*

situ and give IX in 60% yield. The product (IX) obtained did not react with another diethyl phosphite, and the excess diethyl phosphite was recovered by distillation *in vacuo*.

In the case of ketene *O,O*-acetal (X), an addition reaction occurred at room temperature. One mole of diethyl phosphite reacted with one mole of X to give diethyl 1,1-diethoxy-1-ethylphosphonate (XI). The structure of XI was confirmed by its NMR spectrum.

$$\underset{\text{X}}{CH_2{=}C(OEt)_2} \xrightarrow{HPO(OEt)_2} \underset{\text{XI}}{CH_3C(OEt)_2PO(OEt)_2} \qquad (4)$$

This seems to be the first example of diethyl phosphite being added to the activated unsaturated system in the absence of a base or free radical initiator.[4] The compound (XI) remained unchanged by refluxing over metallic sodium for 3 hr.

The contribution of dialkylamino group to the β-elimination of HX from the intermediate (IV) might be of great importance.

$$[RCH_2-\overset{\overset{\delta+}{\curvearrowleft}NR_2}{\underset{\underset{\delta-}{\curvearrowleft}X}{C}}-PO(OEt)_2] \qquad \text{IV}$$

Vinyl ethers reacted with diethyl phosphite to give aldehydes, no addition products of vinyl ether and diethyl phosphite being obtained.[5]

Thus, ketene *N,N*-, *O,N*-, and *S,N*-acetals react with diethyl phosphite to form the intermediate (IV, IV') and loose HX from IV or IV'. Ketene *O,O*-acetal is led only to the formation of 1 : 1 adduct (XI). Ketene *S,S*-acetals did not react with diethyl phosphite even under base-catalyzed conditions.

The nucleophilicity of β-carbon of ketene *N,N*-, *O,N*-, *S,N*-, and *O,O*-acetals, vinyl ethers, and ketene *S,S*-acetals decreases in the order given in literature.[3] The order is essentially the same as that obtained for this experiment on the reactivities of these compounds toward diethyl phosphite.

These enamine phosphonates (V, VII, and IX) have good thermal stabilities, but readily react with moisture to decompose to acylphosphonates. The acylphosphonates are further hydrolyzed to acids and diethyl phosphite.[1]

Experimental

All the boiling points are uncorrected. The NMR spectra were obtained at 100 MHz on a JNM-TS-100 spectrometer, with TMS as an internal reference in deuteriochloroform. The mass spectra were obtained on a Hitachi RMU-6 or RMU-7 spectrometer with an indirect inlet. The gas chromatographic analysis were carried out using a Shimadzu GC-3AF on a 1 m×3 mmϕ column packed with 5% SE-30 on Cellite.

Preparation of N,N-*Dialkylacetamide–Dimethyl Sulfate-Adduct (VI).* *N,N*-Dimethylacetamide and dimethyl sulfate-adduct (VIa) was prepared from *N,N*-dimethylacetamide and dimethyl sulfate according to the method of Bredereck *et al.*[6] Unreacted starting material was removed by extraction with dry ether. *N,N*-Diethylacetamide–dimethyl sulfate-adduct (VId) was prepared from the corresponding amide and dimethyl sulfate, in a similar manner.

Preparation of Ketene O,N-*Acetals (I).* 1-Dimethylamino-1-methoxyethylene (Ia) was prepared from IVa and sodium methoxide in methanol by the method of Bredereck *et al.*,[7] except that the mixture of Ia and *N,N*-dimethylacetamide dimethyl acetal was refluxed over sodium instead of calcium in order to purify the product (Ia). Yield 81%, bp 104 °C. (lit,[7] bp 104—105 °C). 1-Dimethylamino-1-methoxy-1-propylene (Ib) was prepared from *N,N*-dimethylpropionamide-dimethyl sulfate-adduct and sodium methoxide. The product, bp 117—118 °C, was obtained in 34% yield. (lit,[7] bp 117—120 °C). In a similar manner, 1-dimethylamino-1-methoxy-1-butene (Ic) was obtained in 30% yield, bp 128—136 °C.

Preparation of Ketene S,N-*Acetals (II).* 1-Dimethylamino-1-ethylthioethylene (IIa) was prepared from *N,N*-dimethyl-*S*-ethylthioacetamidium iodide and sodium ethylmercaptide in dry ether by the method of Mukaiyama *et al.*[8] The product was obtained in 72% yield, bp 58—59 °C/20 mmHg. (lit,[8] bp 58—59 °C/21 mmHg). In a similar manner, compounds IIb and IIc were obtained, respectively. 1-Dimethylamino-1-ethylthio-1-propylene (IIb); yield 58%, bp 68—71 °C/24 mmHg. 1-Dimethylamino-1-ethylthio-1-butene (IIc); yield 85%, bp 70—71 °C/17 mmHg. The purity of these compounds was confirmed by gas chromatography.

Preparation of Ketene N,N-*Acetal (III).* This was prepared from tetramethylacetamidinium methyl sulfate and sodium hydride by the method of Bredereck *et al.*[7] Yield 11%, bp 115—118 °C. (lit,[7] bp 115 °C).

Preparation of N-*Methylpyrrolidone Diethylacetal (VIII).* This acetal was prepared from *N*-methylpyrrolidone–dimethyl sulfate-adduct and sodium ethoxide by the method described above.[7] Yield 46%, bp 67 °C/12 mmHg. (lit,[7] bp 57—58 °C/10 mmHg). This acetal did not loose one mole of ethanol, even under reflux over metallic sodium for several hours.

Preparation of Ketene S,S-*Acetals.* These were prepared by pyrolysis of ethyl orthothioester in the presence of potassium bisulfate by the method of Volger and Arens.[9] 1,1-Bis(ethylthio)ethylene was obtained in 43% yield, bp 75 °C/12 mmHg. (lit,[9] bp 80—81 °C/17 mmHg). 1,1-Bis(ethylthio)-1-propylene was obtained in 70% yield, bp 79 °C/12 mmHg. (lit,[9] bp 60—60.2 °C/4 mmHg).

Preparation of Ketene O,O-*Acetal (X).* This was obtained from α-bromoacetaldehyde diethyl acetal by treatment with potassium *t*-butoxide.[10] Yield 40%, bp 82—84 °C/200 mmHg. (lit,[10] bp 83—86 °C/200 mmHg).

Reaction of Ketene O,N-*Acetals (I) with Diethyl Phosphite.* To 30 g (217 mmol) of diethyl phosphite in a flask equipped with a reflux condenser was added 22 g (106 mmol) of Ia at room temperature. An exothermic reaction took place and the temperature was raised to 60—80 °C. The methanol produced as the by-product was refluxed. The mixture was kept at 60—80 °C for 0.5 hr. After removal of the alcohol by means of an aspirator, the residue was distilled and purified by redistillation *in vacuo*. This was confirmed to be (*E*)-diethyl 1-dimethylaminovinylphosphonate (Va). Yield 34 g (75.4%), bp 92—94 °C/1 mmHg. IR; 1250 cm^{-1} (P=O). Mass; *m/e* (relative intensity) 207 (M^+, 17.5) 178 (16.3) 150 (17.5) 71 (93.8) 70 (100). NMR; δ 1.32 (t, 6H, $-OCH_2\underline{CH_3}$) 2.72 (s, 6H, $-NMe_2$) 3.65 (d, 1H, $^{H=P}$, J_{PCCH}=11.2 Hz) 4.03 (d-q, 4H, $-O\underline{CH_2}CH_3$) 4.75 (d, 1H, $^{H=P}$, J_{PCCH}=15.8 Hz). Found: C, 46.42; H, 8.66; N, 6.67%. Calcd for $C_8H_{18}NPO_3$: C, 46.33; H, 8.76; N, 6.78%.

In a similar manner, Ib and Ic reacted with diethyl phos-

phite to give the corresponding enamine phosphonates (Vb and Vc), respectively.

(*E*)-Diethyl 1-dimethylamino-1-propenylphosphonate (Vb) from Ib with diethyl phosphite; Yield 58%, bp 114—115 °C/5 mmHg. IR; 1250 cm^{-1} (P=O). Mass; *m/e* (relative intensity) 211 (M^+, 17.1) 206 (7.6) 192 (12.4) 164 (19.0) 84 (100) 68 (61.9). NMR; δ 1.34 (t, 6H, $-OCH_2C\underline{H}_3$) 1.82 (d-d, 3H, C-Me) 2.60 (s, 3H, N-Me) 2.63 (s, 3H, N-Me) 4.08 (d-q, 4H, $-OC\underline{H}_2CH_3$) 6.23 (d-q, 1H, $_{H=P}$, J_{PCCH}=13.5 Hz). Found: C, 48.91; H, 9.26; N, 6.43%. Calcd for $C_9H_{20}NPO_3$: C, 48.87; H, 9.05; N, 6.33%.

(*E*)-Diethyl 1-dimethylamino-1-butenylphosphonate (Vc) from Ic with diethyl phosphite; Yield 47%, bp 116—123 °C/6 mmHg. IR; 1250 cm^{-1} (P=O). Mass; *m/e* (relative intensity) 235 (M^+, 18.3) 206 (20.1) 178 (17.5) 98 (78.6) 82 (100). NMR; δ 1.02 (t, 3H, $C-CH_2C\underline{H}_3$) 1.33 (t, 6H, $-OCH_2C\underline{H}_3$) 2.30 (q-d-d, 2H, $C-C\underline{H}_2CH_3$) 2.60 (s, 3H, N-Me) 2.62 (s, 3H, N-Me) 4.07 (d-q, 4H, $-OC\underline{H}_2CH_3$) 6.08 (d-t, 1H, $_{H=P}$, J_{PCCH}=13.5 Hz). Found: C, 51.10; N, 9.91; N, 6.04%. Calcd for $C_{10}H_{22}NPO_3$: C, 51.06; H, 9.36; N, 5.96%.

Reaction of Ketene S,N-*Acetals (II) with Diethyl Phosphite.* To 9 g (65 mmol) of diethyl phosphite in a flask equipped with a reflux condenser was added 5 g (38.2 mmol) of IIa at room temperature. The reaction occurring exothermally, the mixture was maintained at 60—80 °C for 0.5 hr. After removal of ethanethiol by distillation at atmospheric pressure, the residue was distilled *in vacuo*. The product (4.3 g) obtained was identified by gas chromatography to be the same compound as (*E*)-diethyl 1-dimethylaminovinylphosphonate (Va), obtained by the reaction of Ia and diethyl phosphite. Yield 54%.

In a similar manner, IIb and IIc reacted with diethyl phosphite to give the corresponding enamine phosphonates (Vb and Vc), respectively.

(*E*)-Diethyl 1-dimethylamino-1-propenylphosphonate (Vb) from IIb with diethyl phosphite; Yield 77%.

(*E*)-Diethyl 1-dimethylamino-1-butenylphosphonate (Vc) from IIc with diethyl phosphite; Yield 81%.

Reaction of Ketene N,N-*Acetal (III) with Diethyl Phosphite.* To 3 g (21.7 mmol) of diethyl phosphite was added 2.5 g (21.9 mmol) of III at room temperature. The mixture was heated at 60—80 °C for 1 hr. After removal of dimethylamine produced as the by-product, the residue was distilled to give 2.5 g (12.1 mmol) of Va. Yield 54.5%, bp 73—74 °C/0.1 mmHg.

Reaction of N-*Methylpyrrolidone Diethylacetal (VIII) with Diethyl Phosphite.* To 10 g (74.1 mmol) of VIII was added 8 g (60.0 mmol) of diethyl phosphite at room temperature. A moderate exothermic reaction occurred and the reaction temperature was kept at 60—80 °C for 0.5 hr. After removal of the ethanol produced as a by-product by means of an aspirator, the residue was distilled *in vacuo*. Recovered was 1.5 g (11.1 mmol) of *N*-methylpyrrolidone diethyl acetal (VIII), bp 37—39 °C/10^{-1} mmHg. Obtained was 8.2 g of the fraction boiling at 50—75 °C/10^{-3} mmHg. This fraction was redistilled to isolate 6 g (27.4 mmol) of IX, yield 60%, bp 62—65 °C/10^{-3} mmHg. When 2 moles of diethyl phosphite was added to 1 mole of IX, the latter was completely consumed, but 1 mole of diethyl phosphite remained unchanged at the end of the reaction. IR; 1250 cm^{-1} (P=O). Mass; *m/e* (relative intensity) 219 (M^+, 24.1) 162 (42.21) 146 (30.1) 144 (30.1) 111 (22.9) 82 (100). NMR; δ 1.13 (t, 6H, $-OCH_2C\underline{H}_3$) 2.2—3.0 (m, 2H, ring protons) 2.68 (s, 3H, N-Me) 3.0—3.3 (m, 2H, ring protons) 4.12 (d-q, 4H, $-OC\underline{H}_2CH_3$) 5.66 (d-t, 1H, $_{H=P}$, J_{PCCH}=7.5 Hz). Found: C, 49.3; H, 8.7; N, 6.7%. Calcd for $C_9H_{18}NPO_3$: C, 49.3; H, 8.3; N, 6.4%.

Reaction of VI with Sodium Diethyl Phosphite. Sixteen grams (100 mmol) of sodium diethyl phosphite in 30 ml of diethyl phosphite was added dropwise to 21.3 g (100 mmol) of VIa at room temperature. The mixture was vigorously stirred and heated at 60—80 °C for 2 hr. On distillation, 6 g (29 mmol) of VIIa was obtained. Yield 29%. This was identified by gas chromatography to be the same as diethyl 1-dimethylaminovinylphosphonate (Va).

In a similar manner, the reaction of VId with sodium diethyl phosphite was carried out. After the reaction, a hundred milliliter of ether was added to the mixture and the precipitates were separated. On distillation of the ether solution, diethyl 1-diethylaminovinylphosphonate (VIId) was obtained in 38.3% yield, bp 85—87 °C/0.5 mmHg. IR; 1225 cm^{-1} (P=O). Mass; *m/e* (relative intensity) 235 (M^+, 19.4) 230 (18.3) 206 (18.3) 192 (24.7) 178 (20.4) 164 (29.0) 136 (18.2) 99 (36.6) 98 (72.0) 72 (53.8) 70 (100). NMR; δ 1.04 (t, 6H, $-NCH_2C\underline{H}_3$) 1.32 (t, 6H, $-OCH_2C\underline{H}_3$) 3.18 (q, 4H, $-NC\underline{H}_2CH_3$) 3.72 (d, 1H, $_{H=P}$, J_{PCCH}=11.2 Hz) 4.08 (d-q, 4H, $-OC\underline{H}_2CH_3$) 4.83 (d, 1H, $_{H=P}$, J_{PCCH}=15.8 Hz). Found: C, 51.05; H, 8.92; N, 5.34%. Calcd for $C_{10}H_{22}NPO_3$: C, 51.06; H, 9.43; N, 5.95%.

Reaction of Ketene O,O-*Acetal with Diethyl Phosphite.* To 18.6 g (51.7 mmol) of diethyl phosphite was added 2 g (17.2 mmol) of X at room temperature. A moderate exothermic reaction occurred and the reaction temperature was maintained at 60 °C for 1 hr. On distillation, 1.6 g (6.3 mmol) of XI was obtained in 36.5% yield, bp 67—69 °C/10^{-2} mmHg. (lit,[5] bp 75—77 °C/0.04 mmHg). Mass; *m/e* (relative intensity) 209 (M^+-OEt, 9.5) 181 (14.3) 117 (90.5) 89 (76.2) 61 (100). NMR; δ 1.21 (t, 6H, $C-OCH_2C\underline{H}_3$) 1.35 (t, 6H, $P-OCH_2C\underline{H}_3$) 1.54 (d, 2H, P-C-Me, J_{PCCH}=12 Hz) 3.68 (q, 4H, $C-OC\underline{H}_2CH_3$) 4.20 (d-q, 4H, $P-OC\underline{H}_2CH_3$).

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