1,3-Dipolar Cycloaddition of Diethyl Nitromethylphosphonate, via the Nitrile Oxide, to Alkenes and 1-Alkynes. A Convenient One-Pot Synthesis of 3-Diethoxyphosphoryl-4,5-dihydroisoxazoles and 3-Diethoxyphosphorylisoxazoles

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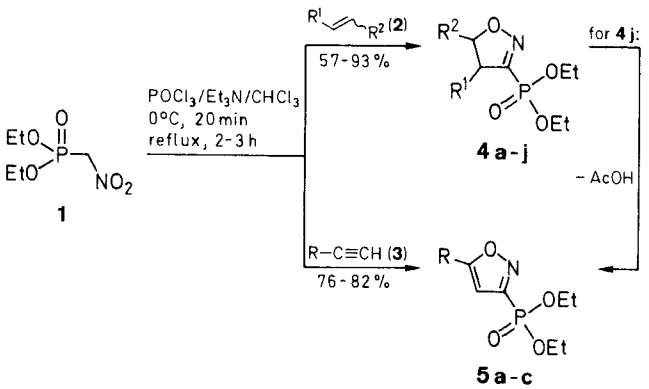
The one-pot reaction of diethyl nitromethylphosphonate with alkenes or 1-alkynes in the presence of phosphoryl chloride and triethylamine leads to 3-diethoxyphosphoryl-substituted 4,5-dihydroisoxazoles or isoxazoles, respectively, in good yields.

1,3-Dipolar cycloaddition[1] of nitrile oxides, nitrones, and silyl nitronates with alkenes and alkynes leads to the formation of isoxazoles, 4,5-dihydroisoxazoles, or tetrahydroisoxazoles in high yield. In the light of recent developments, these products are versatile intermediates for organic syntheses.[2] Their synthetic versatility originates from their potentiality as synthetic equivalents of 1,3-diketones, β-hydroxy ketones, γ-amino alcohols, α,β-unsaturated ketones, and related compounds.[3] The use of functionalized 1,3-dipoles in cycloaddition reactions leads to cycloadducts with additional functionalities, thus broadening the scope of the application of 1,3-dipolar compounds in organic synthesis. Only few reports on the preparation of phosphorus-functionalized 1,3-dipoles and some synthetic applications of their cycloadducts have appeared. *N*-Glycosyl-*C*-dialkoxyphosphorylnitrones have been prepared by the reaction of dialkyl phosphites with the *N*-glycosylnitrone, followed by oxidation with *p*-benzoquinone.[4] Diethoxyphosphoryl-substituted cyclic nitrones were similarly prepared,[5] and (diethoxyphosphoryl)acetonitrile oxide was prepared by bromination-dehydrobromination of *N*-[2-(diethoxyphosphoryl)ethylidene]hydroxylamine.[6] 3- and 5-(Diphenylphosphinylmethyl)isoxazoles were prepared by some modified methods.[7] However, the hitherto reported synthetic methods suffer from a limited scope for the preparation of phosphorus-functionalized 1,3-dipoles and their cycloadducts because of the difficult availability of the starting materials and due to tedious procedures.

We report herein a convenient method for the synthesis of phosphorus-functionalized 4,5-dihydroisoxazoles and isoxazoles, which consists of the one-pot reaction of diethyl nitromethylphosphonate[8] **(1)** with alkenes **2** or 1-alkynes **3**, respectively, in the presence of phosphoryl chloride and triethylamine.

The reaction of diethyl nitromethylphosphonate **(1)** with alkenes **2** or 1-alkynes **3**, phosphoryl chloride, and triethylamine in refluxing chloroform appeared to be complete within 2–3 hours (TLC control). In all cases, the products **4** or **5** were obtained in good yield (Table 1). In



2, 4	R^1	R^2	2, 4	R^1	R^2
a	H	Ph	f	H	CH_2OCO_2Et
b	H	*n*-C_5H_{11}	g	H	CH_2Br
c	H	*n*-C_6H_{13}	h	$-(CH_2)_4-$	
d	H	$COCH_3$	i	CO_2Et	CO_2Et(*trans*)
e	H	CO_2Et	j	H	$OCOCH_3$

3, 5	R
a	H
b	*n*-C_4H_9
c	*n*-C_5H_{11}

Table 1. Compounds **4–6** Prepared

Dipolarophile	Refluxing Time (h)	Product[a]	Yield[b] (%)	Molecular Formula[c]
2a	2	**4a**	76	$C_{13}H_{19}NO_4P$ (283.3)
2b	3	**4b**	78	$C_{12}H_{24}NO_4P$ (277.3)
2c	3	**4c**	80	$C_{13}H_{26}NO_4P$ (291.3)
2d	4[d]	**4d**	73	$C_9H_{16}NO_5P$ (249.2)
2e	2	**4e**	93	$C_{10}H_{18}NO_6P$ (279.2)
2f	2	**4f**	77	$C_{11}H_{20}NO_7P$ (309.3)
2g	3	**4g**	57	$C_8H_{15}BrNO_4P$ (300.1)
2h	3	**4h**	58	$C_{11}H_{20}NO_4P$ (261.3)
2i	2	**4i**	82	$C_{13}H_{22}NO_8P$ (351.3)
2j	2	**4j** (+ **5a**)	30[e] (50)	$C_9H_{16}NO_6P$ (265.2)
2j	6	**5a**	76	$C_7H_{12}NO_4P$ (205.2)
3b	3	**5b**	82	$C_{11}H_{20}NO_4P$ (261.3)
3c	3	**5c**	79	$C_{12}H_{22}NO_4P$ (275.3)
–	2	**6**	20	$C_{10}H_{20}N_2O_8P_2$ (358.2)

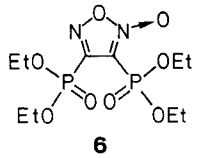
[a] All products were obtained as oils. Purity was checked by HPLC; the 4-substituted isomer was not detected.
[b] Yields of isolated products purified by column chromatography.
[c] Satisfactory microanalyses: C ± 0.27, H ± 0.27, N ± 0.31, P ± 0.25.
[d] Reaction was carried out at 40°C.
[e] Simultaneously **5a** (formed from **4j**) was obtained in 50% yield.

Table 2. Spectral Data of Compounds **4–6**

Compound	IR (liquid film) ν (cm^{-1})	^{1}H-NMR (CCl_4/TMS) δ, J (Hz)
4a	1580, 1270, 1160, 1040, 800, 770	1.30 (t, 6H, J = 7, $2OCH_2C\underline{H}_3$), 3.3 (m, 2H, 4-H), 4.23 (qd, 4H, J = 7, 10, $2OC\underline{H}_2$), 5.60 (t, 1H, J = 10, 11, 5-H), 7.30 (s, $5H_{arom}$)
4b	1575, 1280, 1260, 1160, 800	0.90 (t, 3H, J = 2, CH_3), 1.6 (m, 14H, $2OCH_2C\underline{H}_3 + 4CH_2$), 3.0 (m, 2H, 4-H), 4.26 (qd, 4H, J = 7, 10, $2OC\underline{H}_2$), 4.60 (m, 1H, 5-H)
4c	1575, 1290, 1260, 1160, 1015, 800	0.90 (t, 3H, J = 2, CH_3), 1.6 (m, 16H, $2OCH_2C\underline{H}_3 + 5CH_2$), 3.0 (m, 2H, 4-H), 4.26 (qd, 4H, J = 7, 10, $2OC\underline{H}_2$), 4.60 (m, 1H, 5-H)
4d	1725, 1500, 1260, 1160, 1020, 800	1.30 (t, 6H, J = 7, $2OCH_2C\underline{H}_3$), 2.10 (s, 3H, $COCH_3$), 3.40 (d, J = 8, 4-H), 4.20 (qd, 4H, J = 7, 10, $2OC\underline{H}_2$), 4.90 (t, 1H, J = 8, 5-H)
4e	1740, 1580, 1200, 1160, 1020, 800	1.30 (t, 9H, J = 7, $3OCH_2C\underline{H}_3$), 3.46 (d, 2H, J = 10, 4-H), 4.26 (qd, 6H, J = 7, 10, $3OC\underline{H}_2$), 5.06 (t, 1H, J = 10, 5-H)
4f	1760, 1580, 1280, 1160, 1020, 800	1.30 (t, 9H, J = 7, $3OCH_2C\underline{H}_3$), 3.0 (m, 2H, 4-H), 4.2 (m, 8H, $4OC\underline{H}_2$), 4.95 (m, 1H, 5-H)
4g	1580, 1260, 1160, 1020 (br), 800, 660	1.36 (t, 6H, J = 7, $2OCH_2C\underline{H}_3$), 3.0 (m, 2H, 4-H), 3.5 (m, 2H, CH_2Br), 4.20 (qd, 4H, J = 7, 10, $2OC\underline{H}_2$), 4.9 (m, 1H, 5-H)
4h	1560, 1280, 1160, 1020 (br), 800	1.5 (m, 14H, $2OCH_2C\underline{H}_3 + 4CH_2$), 3.0 (m, 1H, 4-H), 4.2 (m, 5H, $2OCH_2$ + 5-H)
4i	1740, 1570, 1260 (br), 1160, 1020 (br), 795	1.35 (t, 12H, J = 7, $4OCH_2C\underline{H}_3$), 4.2 (m, 9H, $4OCH_2$ + 4-H), 5.23 (d, 1H, J = 7, 5-H)
4j	1765, 1580, 1280, 1160, 1020 (br), 800	1.30 (t, 6H, J = 7, $2OCH_2C\underline{H}_3$), 2.00 (s, 3H, $COCH_3$), 3.2 (m, 2H, 4-H), 4.20 (qd, 4H, J = 7, 10, $2OC\underline{H}_2$), 6.5 (dd, 1H, J = 2, 6, 5-H)
5a	1580, 1530, 1280 (br), 1160, 1020 (br), 795	1.36 (t, 6H, J = 7, $2OCH_2C\underline{H}_3$), 4.25 (qd, 4H, J = 7, 10, $2OC\underline{H}_2$), 6.50 (s, 1H, 4-H), 8.60 (s, 1H, 5-H)
5b	1580, 1265, 1160, 1020, 800	1.05 (t, 3H, J = 2, CH_3), 1.30 (t, 6H, J = 7, $2OCH_2C\underline{H}_3$), 1.6 (m, 4H, $2CH_2$), 3.00 (t, 2H, J = 6, $=CCH_2$), 4.26 (qd, 4H, J = 7, 10, $2OC\underline{H}_2$), 6.40 (s, 1H, 4-H)
5c	1580, 1265, 1160, 1020, 800	1.00 (t, 3H, J = 2, CH_3), 1.30 (t, 6H, J = 7, $2OCH_2C\underline{H}_3$), 1.6 (m, 6H, $3CH_2$), 3.00 (t, 2H, J = 6, $=CCH_2$), 4.25 (qd, 4H, J = 7, 10, $2OC\underline{H}_2$), 6.50 (s, 1H, 4-H)
6[a]	1630, 1600, 1240 (br), 1160, 1020, 800	1.36 (dt, 12H, J = 7, $4OCH_2CH_3$), 4.25 (qd, 8H, J = 7, 10, $4OC\underline{H}_2$)

[a] MS: m/z = 359 ($M^+ + 1$, 13.87%), 244 (100), 183 (58.75), 137 (14).

the reaction with vinyl acetate **(2j)**, the initially formed cycloadduct **4j** was converted to 3-(diethoxyphosphoryl)isoxazole **(5a)** via elimination of acetic acid. In the reaction with diethyl fumarate **(2i)**, the *trans* product **4i** was obtained. The conformation of **4i** was determined by comparison of the proton coupling constant between 4-H and 5-H with the ^{1}H-NMR data of similar 4,5-dihydroisoxazoles.[9]



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It is conceivable that in this reaction the 1,3-dipole is the *in situ* formed nitrile oxide,[10] because the nitrile oxide dimer, bis(diethoxyphosphoryl)furoxan **(6)**, was obtained in the absence of a scavenger. The reaction with monosubstituted ethylenes (1-alkenes) and acetylenes (1-alkynes) shows high regioselectivity and gives only the 5-substituted derivative. The frontier-orbital theory provides a satisfactory explanation of the regioselectivity.[11] The structures of the products were established by microanalyses, IR and ^{1}H-NMR spectrometry (Tables 1, 2).

Further studies on the application of the phosphorus-functionalized 4,5-dihydroisoxazoles **4** and isoxazoles **5** in organic synthesis are in progress.

Diethyl nitromethylphosphonate **(1)** was synthesized according to Lit.[8] Phosphoryl chloride was purified by distillation prior to use. Triethylamine and $CHCl_3$ were dried by standard methods. All dipolarophiles were of commercial grade. IR spectra were recorded on a Shimadzu-440 Infrared spectrophotometer, ^{1}H-NMR spectra on a Varian EM 360 L (60 MHz) spectrometer.

3-Diethoxyphosphoryl-4,5-dihydroisoxazoles 4 and 3-Diethoxyphosphorylisoxazoles 5; General Procedure:

To a stirred solution of diethyl nitromethylphosphonate (**1**; 0.98 g, 5 mmol), the alkene **2** or 1-alkyne **3** (6 mmol) and Et_3N (2.1 g, 20 mmol) in $CHCl_3$ (20 mL) at 0 °C is added a solution of $POCl_3$ (0.5 mL, 5.5 mmol) in $CHCl_3$ (1 mL). After 20 min, the mixture is refluxed for 2–3 h (TLC control), then evaporated under reduced pressure. To the residue is added H_2O (10 mL) and this mixture is extracted with EtOAc (3 × 10 mL) and dried (Na_2SO_4). The solvent is removed and the remaining product is subjected to column chromatography on silica gel using successive portions of EtOAc/petroleum ether (gradient 70:30 → 30:70) as eluent.

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