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Selective Synthesis of the Geometrical Isomers of *O,O*-Diethyl *O*-1-(*N*-methoxyimino)ethylphosphorothioate and a New Thiono-Thiolo Rearrangement Reaction

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Condensation of *O,O*-diethyl phosphorochloridothioate with *N*-methoxyacetamide in the presence of a base gave selectively the geometrical isomers of *O,O*-diethyl *O*-1-(*N*-methoxyimino)ethylphosphorothioate which on heating rearranged to the corresponding thiolo isomers having P-S-C=N linkage.

A number of organophosphates containing alkoxyimino moiety in the molecules have been claimed as insecticides without any information on the geometrical isomers regarding the C=N bond.[1] Our interest in examining the geometry-biological activity relationships of alkoxyiminoalkyl phosphates has led us to develop a selective method for preparing the geometrical isomers. We describe here the results of a preliminary study including a new thiono-thiolo rearrangement reaction.

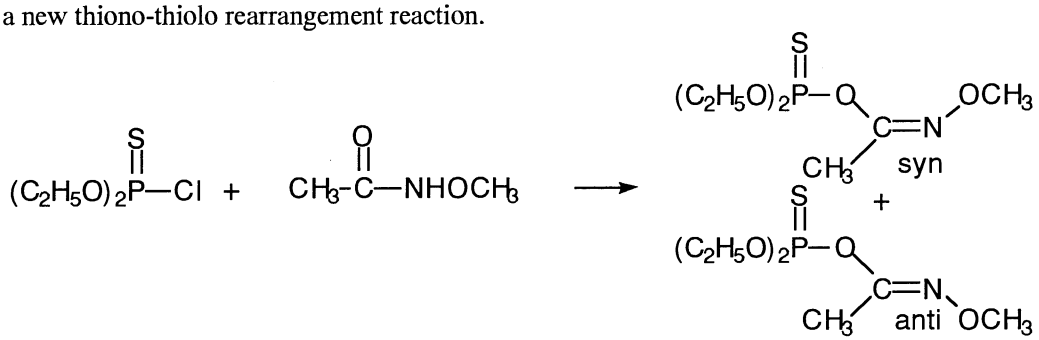


Table 1 shows the results on the condensation of *O,O*-diethyl phosphorochloridothioate with *N*-methoxyacetamide in the presence of a base leading to *O,O*-diethyl *O*-1-(*N*-methoxyimino)ethyl phosphorothioate. Among several bases examined, NaH and CaO provided reaction conditions which almost exclusively afforded the *anti* isomer, while K_2CO_3 gave a (15 : 85) mixture of *syn/anti* isomers. On the other hand, the coexistence of a catalytic amount of CuCl under two phase transfer condition led to the selective formation of *syn* isomer. By-

production of a highly toxic substance, *O,O,O',O'*-tetraethyl dithiopyrophosphate, was effectively reduced by the use of $NaHCO_3$ as the base.

Table 1. Selective Synthesis of the Geometrical Isomers[a)]

No.	Base	Solvent	Yield%	*syn*	*anti*
1	NaH	THF	90	1	99
2	CaO	MIBK	95	1	99
3	K_2CO_3	MIBK	80	15	85
4	$NaHCO_3$/CuCl	Toluene/H_2O	93	99	1
5	NaOH/CuCl	Toluene/H_2O	80[b)]	99	1

a) The *syn/anti* ratio was determined by means of HPLC analysis. b) *O,O,O',O'*-Tetraethyl dithiopyrophosphate was obtained in 12% yield as a by-product.

Typical procedures are illustrated as follows ;

syn isomer: To a suspension of $NaHCO_3$ (16.8 g) and H_2O (25 g) was added $(n\text{-}C_4H_9)_4NBr$ (2.0 g), CuCl (2.0 g), $CH_3CONHOCH_3$ (9.8 g), and toluene (35 g). To the resulting mixture, $(C_2H_5O)_2P(S)Cl$ (18.9 g) was added dropwise at room temperature while stirring. The mixture was kept at 80 °C for 3 h. After cooling to room temperature the mixture was filtered, washed with water, dried($MgSO_4$), and filtered again. The filtrate was concentrated and the residue was purified by silica gel column chromatography to give 22.5 g of *syn* isomer (93%).

anti isomer: To a solution of $CH_3CONHOCH_3$ (11.6 g) in methyl isobutyl ketone (MIBK) (50 ml) was added CaO (7.3 g). To the mixture, $(C_2H_5O)_2P(S)Cl$ (18.9 g) was added dropwise and the resulting mixture was kept at 80 °C for 7 h. Usual work-up as described above gave 22.8 g of *anti* isomer (95%).

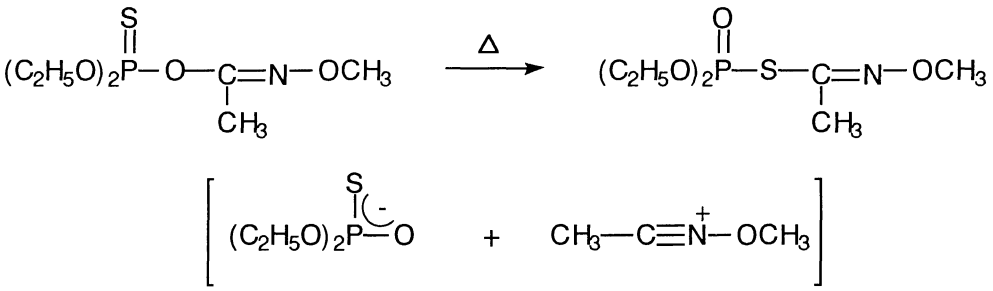
Structures of the products were confirmed on the basis of spectroscopic data and elemental analysis.[2)] The product used CuCl as a catalyst was assigned to be of *syn* isomer, assuming the chelation at two oxygen atoms of an intermediary N-methoxyacetamide anion with copper ion.[3)] Spectral data for the geometrical isomers are reasonable for *syn/anti* isomerism with respect to the C=N bond. However, because of uncertainty of anisotropic effect of P=S group in both ^1H-NMR and ^{13}C-NMR, complete assignment for each isomer was not achieved. The *anti* isomer was two folds as insecticidally active as the *syn* isomer against *Diabrotica undecimpunctata howardi*. It should be added that the *anti*-geometry is essential for increasing the insecticidal activity, as revealed in certain vinyl phosphates.[4)]

On heating at 60 °C for 48 h, both *syn* and *anti* thiono isomers rearranged to the corresponding thiolo isomers consisting of a 1 : 1 mixture of *syn/anti* isomers with respect to the C=N bond. The structure was assigned especially on the basis of P=O and C=N absorptions in its IR spectrum.[5] The addition of a small amount of *O,O*-diethyl hydrogen phosphorothioate to thiono isomers accelerated the production of rearranged thiolo isomers. For instance, the thiolo isomer was obtained as a 1 : 1 mixture of *syn/anti* isomers in 83% yield when *syn* thiono isomer admixed with 1 mol% amount of *O,O*-diethyl hydrogen phosphorothioate was allowed to stand at 25 °C for 8 h. On the other hand, this rearrangement was prevented in the coexistence of a small amount of Michael acceptor as shown in Table 2. Acrolein was the most effective. It thus appears that Michael acceptors act as the agents for trapping the phosphorothioate species generated in the reaction mixture. These finding clearly suggest a rearrangement mechanism involving a dissociation-recombination process.[6]

Table 2. Effects on the Addition of Michael Acceptor[a]

Michael acceptor	Isomerized%
acrolein	0.8
p-benzoquinone	2.5
methyl vinyl ketone	2.6
ethyl acrylate	2.5
acrylonitrile	8.5
none	66.4

a) Ten gram of *syn* or *anti* isomer was kept at 60 °C for 48 h in the presence of Michael acceptor (0.1 g).



The obtained thiolo isomer was much less active against insects than the thiono isomer. A further study on the selective synthesis of related compounds is in progress.

References

1) Reports appear in the patent literature. For example, see U.S. Patent, 3760041 (Bayer, 1973); U.S. Patent, 4443439 (Hokko, 1984); U.S. Patent, 4473562 (Chevron, 1984); U.S. Patent, 4940699 (Sumitomo, 1990).

2) *syn* Isomer: n_D 1.4665; IR (film) 2992 (m), 2944 (m), 2914 (m), 1659 (m, C=N), 1446 (m), 1377 (m), 1260 (s), 1188 (m), 1164 (m), 1068 (s), 1023 (s), 972 (s), 888 (m), 825 (s), 780 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.30 (6H, t, J=6 Hz), 2 .00 (3H, s), 3.72 (3H, s), 3.90 - 4.45 (4H, m); ^{13}C-NMR ($CDCl_3$) δ = 14.24 (d, Jcp = 4.2 Hz), 15.81 (d, Jcp = 7.6 Hz), 62.08, 65.07 (d, Jcp = 5.5 Hz), 155.71 (d, Jcp = 8.3 Hz); ^{31}P-NMR ($CDCl_3$) δ = 60.40; Anal. Found: C, 34.70; H, 6.65; N, 5.92; P, 12.50; S, 13.40%. Calcd for $C_7H_{16}NO_4PS$: C, 34.84; H, 6.70; N, 5.81; P, 12.84; S, 13.29%. *anti* Isomer: n_D 1.4640; IR (film) 2986 (m), 2938 (m), 2860 (m), 1659 (m, C=N), 1467 (m), 1443 (m), 1386 (s), 1254 (s), 1188 (m), 1164 (m), 1023 (s), 975 (s), 972 (s), 903 (s), 825 (s), 753 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.35 (6H, t, J = 6 Hz), 2.05 (3H, d, J = 2 Hz), 3.75 (3H, s), 3.90 - 4.45 (4H, m); ^{13}C-NMR ($CDCl_3$) δ = 15.81 (d, Jcp = 7.6 Hz), 17.71, 61.83, 65.00 (d, Jcp = 5.5 Hz), 145.01 (d, Jcp = 9.0 Hz); ^{31}P-NMR ($CDCl_3$) δ = 58.60; Anal. Found: C, 34.65; H, 6.91; N, 5.70; P, 12.60; S, 13.05%. Calcd for $C_7H_{16}NO_4PS$: C, 34.84; H, 6.70; N, 5.81; P, 12.84; S,13.29%.

3) M. Eto, "Organophosphorus Pesticides: Organic and Biological Chemistry," CRC Press, Cleveland (1974), p. 42.

4) For example, see J. E. Casida, *Science*, **122**, 597 (1955); A. R. Stiles, C. H. Reilly, G. R. Polland, C. H. Tieman, L. F. Ward, Jr., D. D. Phillips, S. B. Soloway, and R. R. Whetstone, *J. Org. Chem.*, **26**, 3960 (1961).

5) Thiolo isomer: n_D 1.4739; IR (film) 2992 (m), 2948 (m), 2916 (m), 1590 (w, C=N), 1444 (m), 1394 (m), 1370 (m), 1264 (s, P=O), 1162 (m), 1100 (m), 1036 (s, P-O-C), 1014 (s), 978 (s), 902 (m), 882 (m), 792 (m), 748 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.30 (6H, t, J = 6 Hz), 2.15 and 2.25 (each 1.5 H, CH_3, *syn/anti* mixture), 3.80 (3H, s, CH_3O), 3.85 - 4.85 (4H, m); MS *m/z* 241 (M^+), 210, 154, 125, 72, 43; Anal. Found: C, 34.95; H, 6.80; N, 5.66; P, 12.70; S, 13.35%. Calcd for $C_7H_{16}NO_4PS$: C, 34.84; H, 6.70; N, 5.81; P, 12.84; S, 13.29%.

6) K. E. DeBruin, S. M. Schelble, and E. E. Boros, *Phosphorus, Sulfur and Silicon*, **75**, 151 (1993).

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